Type 2 Diabetes in the Elderly: Challenges in a Unique Patient Population

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Abstract

In the older patient population, rates of Type 2 Diabetes (T2D) and obesity are reaching epidemic proportions. In fact, older patients will soon constitute the majority of patients with T2D in most developed countries. The higher prevalence of T2D in older individuals is seen in both men and women and across racial and ethnic groups. However, certain ethnic groups are disproportionately affected and successful strategies must account for these fundamental differences. T2D in old age is associated with traditional diabetes-associated complications including micro- and macro vascular disease, but is also closely related to numerous other comorbidities including cognitive impairment, urinary incontinence, sarcopenia, and increased fall risk. An overall state of chronic inflammation and dysregulated immune system may underlie these increased risks; yet our understanding of immunometabolism during the aging process remains incomplete. In addition, optimal recognition and treatment of diabetes in the elderly is hampered by a lack of relevant, high-quality studies, as the majority of clinical trial data establishing risk profiles, glycemic targets, and therapeutic interventions for T2D are not applicable for large segments of the older patient population. Simply acknowledging this gap is inadequate. We need strong evidence-based data upon which to successfully identify diabetic patients and then intervene in ways that are targeted to specific individuals within a heterogeneous group of elderly patients with T2D.

Keywords

Type 2 Diabetes Mellitus; Obesity; Elderly

Introduction

In the last decade alone, the percentage of adults over the age of 65 in the United States (U.S.) has increased by 18%, and by the year 2030 one in five Americans will be 65 years or older [1]. In fact, the fastest growing segment of the population are those > 85 years old.
which currently represent 1.5% of the population but will account for ~5% of the population by 2050 [2]. This demographic shift has dramatic implications on the social and economic structure of both public and private sectors and will place unprecedented demands on our healthcare system. More than 80% of those over 65 experience multiple chronic conditions, including Type 2 Diabetes (T2D), accounting for over 95% of their total healthcare costs [3]. The prevalence of T2D has escalated over the last several decades as our population has progressively become older and heavier. Obesity rates have increased nearly two-fold from 1990 to 2010 [4]. Obesity increases the risk of numerous chronic conditions [5] and is a principal cause of both insulin resistance (IR) and diminished beta (β)-cell function, the two major factors involved in the pathogenesis of T2D [6]. Accordingly, the rate of T2D has substantially increased in older adults [7] and remains a major cause of excess morbidity and mortality [8]. From 1980 through 2014, the rate of diagnosed diabetes in the U.S. population increased more than 120% for those 65–74 years old (9.7% to 21.5%) and ≥75 years old (8.6% to 19.2%) [2]. In 2011, the rate of diagnosed diabetes among people aged 65–74 was more than 13 times that of people younger than 45 years of age. The rates of diagnosed T2D are even higher in long-term care residents, with upwards of 1/3 affected [9]. In the coming decades, people ≥65 years old will constitute the majority of diabetic patients in the U.S. and most other developed countries. These findings necessitate a greater focus on individualized care in the obese patient population and underscore the need for new guidelines and therapeutic strategies in the management of obesity and T2D in older patients.

Older adults with T2D face the same spectrum of micro vascular (retinopathy, nephropathy, neuropathy) and macro vascular (cardioand cerebrovascular) complications as younger patients. T2D in older adults leads to excess morbidity and mortality that is greater than their non-diabetic counterparts [8]. However, the older diabetic patient population with T2D poses unique challenges as they are also at high risk for polypharmacy, functional decline, cognitive impairment, depression, urinary incontinence, and falls, among other diabetes-related comorbidities. In addition, older adults with T2D are a heterogeneous patient population with disparate functional capacity, living accommodations, comorbid conditions, and life expectancy. Unfortunately, there is a paucity of evidence-based data to guide clinical decision making in many segments of the older diabetic patient population. Therefore, it is imperative to develop sound evidence-based strategies tailored to limit diabetic complications and mortality, yet maintain meaningful quality of life during the aging process.

**Manuscript Text**

**Definition of elderly and old age**

There is currently no universally accepted age threshold to define the terms “elderly” or “old age.” Most developed countries adhere to the chronologic age of either 60 or 65 years old as the definition of an older or elderly individual, mainly as a construct equivalent to the traditional age of retirement [10]. However, this is not universally accepted, has continuously evolved over time, and is considered arbitrary in different geographic regions where “biologic” age is not always synonymous with “chronologic” age [11,12]. In addition,
the definition of older may be better be delineated not by age, but by an individual’s active contribution to society or other socially constructed indicators [13]. For instance, the World Health Organization (WHO) has proposed a working definition for older persons to be above the age of 50 years old in the African subcontinent, a value which combines age and social/cultural/functional markers of aging [14]. While we realize the important limitations of a standardized definition, for the purposes of this review we will adhere to the definition of elderly or old age as > 65 years old (unless otherwise noted), but will make all attempts to highlight subdivisions in this age demographic based on functional status, geographic location, and other socio-cultural factors such as race and ethnicity when data is available.

**Demographics of T2D in aging**

The higher prevalence of T2D in older individuals is seen in both men and women and across racial and ethnic groups [2]. However, certain ethnic groups are disproportionately affected and successful strategies to combat obesity and T2D must account for these critical differences.

African-Americans (AAs) in the U.S. have among the highest prevalence rates of obesity and T2D [15]. They are also at higher risk for the development of cardiovascular disease (CVD), critical sequelae of diabetes and the major cause of diabetes-related mortality [16,17]. As a consequence, AAs have a 1.3 times greater risk of nonfatal stroke, a 1.8 times greater risk of fatal stroke, and a 1.5 times greater risk of CV mortality compared to Caucasians [18,19]. These ethnic disparities are most pronounced in AA females. Diabetes affects 38.2% of AA women between the ages of 65–74 [2] and a staggering 58.6% are obese [15]. The prevalence of hypertension (HTN) in AA women is also particularly high at 44.0% [19]. In AAs, both T2D and HTN are robust predictors of CVD [20]. CVD develops approximately 5 years earlier and AAs have higher mortality rates when compared to Caucasians of a similar age [21]. AAs are also more prone to diabetes-related complications and are at greater risk of developing progressive chronic kidney disease (CKD) and end stage renal disease (ESRD) compared with other racial groups [22].

Hispanic/Latino Americans are also at greater risk for T2D and diabetes-related cardiometabolic abnormalities. ESRD is more likely to be present in Hispanics/Latinos [23] and they have higher rates of non-traumatic amputation compared to Caucasians [24]. Hispanic/Latinos residing in the U.S. currently comprise 16% of the population, but the U.S. Census Bureau estimates that this will increase to one in three Americans by 2050. It is important to recognize that Hispanic/Latinos are a heterogeneous population and are comprised of diverse subgroups including Puerto Ricans, Mexicans, Cubans, and Central and South Americans. Critical differences in diabetes prevalence by subgroup can therefore be masked by combining all Hispanic/Latino individuals into a single group. In fact, data from the recent Hispanic Community Health Study/Study of Latinos (HCHS/SOL) indicates considerable diversity among Hispanic/Latino subgroups in diabetes prevalence, as well as differences in the rates of diabetes awareness, glycemic control and health insurance status [25]. In the HCHS/SOL, the prevalence of total diabetes (both diagnosed and undiagnosed) among all Hispanic/Latino groups was 16.9% for both men and women, compared to 10.2% for non-Hispanic whites. However, when examining Hispanic/Latino groups individually,
T2D prevalence varied from 18.3% in those of Mexican descent to 10.2% in those of South American descent. In between these extremes, 18.1% of individuals of Dominican and Puerto Rican descent; 17.7% of those of Central American descent; and 13.4% of individuals of Cuban descent living in the U.S. had T2D. Significant predictors of T2D included longer duration of U.S. residency, less education and lower income. In addition, the authors noted substandard glycemic control (52% of patients) and high rates of uninsured (47.9%) within the Hispanic/Latino community [25]. As with other ethnic groups, the prevalence of T2D in Hispanic/Latinos increases dramatically with advancing age. While 2.6% of men and 2.9% of women 18 to 29 years old have diabetes, greater than 50% of women and 48.6% of men 70–74 years old are affected. This enlarging group of older Hispanics/Latinos with T2D will present unique challenges to our healthcare system.

Asian countries have also experienced an alarming increase in the rate of diabetes. The heavily populated nations of China and India now have the largest number of diabetics in the world, and by the year 2030 the Asian continent is projected to have the highest global proportion of diabetics in the world [26]. The prevalence of diabetes in China has increased from 1% in 1980 to 9.7% in 2010 [27] and adult obesity rates now exceed 30% [28]. The increases in T2D and obesity in Asian countries have been attributed to numerous factors: readily available fast food, sedentary lifestyle, poor urban planning, academic pursuits, changes in mode of transportation, differences in body composition, and factors related to diabetes pathogenesis, among others [29]. In addition, Asians are typically diagnosed with diabetes at younger ages compared to other ethnicities. For instance, men residing in China and Korea on average develop diabetes approximately 3 years earlier than Caucasian men [2,30]. Ethnic Asians typically have excess visceral adipose tissue (VAT) at lower BMI levels, [31] which is associated with increased hepatic fatty acid lipid flux, altered adipokines, non-alcoholic fatty liver disease (NAFLD), and hepatic insulin resistance [32]. Asian individuals also have greater insulin secretory defects, either from reduced β-cell mass and/or functional impairment in pancreatic β-cells, [33,34] and those with prediabetes have marked reductions in β-cell function with minimal insulin resistance [35]. This predominance of β-cell dysfunction over insulin resistance may be genetically determined [36,37]. Asian individuals are at higher risk of developing diabetes-related microvascular complications and CVD compared to Caucasians [28,38–40]. Interestingly, Asians also appear to have a differential efficacy response to some diabetes medications, with greater glycemic lowering effects with acarbose, glucagon-like peptide-1 (GLP-1) receptor agonists, and Dipeptidyl peptidase-IV (DPP-IV) inhibitors compared to other ethnicities [41,42].

In the U.S., Asian-Americans and Native Hawaiians and other Pacific Islanders (NHPIs) are fast growing minority populations who are at higher risk for T2D than Caucasians [43–45]. State-based data from the CDC Behavioral Risk Factor Surveillance System (BRFSS) from 2011–2014 indicates that the age-adjusted prevalence of T2D in NHPIs is as high as 19.1% in the state of California and among Asians as high as 15.3% in New York state [2]. On average NHPIs have higher rates of obesity and are less educated than Asians (both independent predictors of T2D); however, both ethnic groups are disproportionately affected by high rates of obesity and physical inactivity [43,45]. These trends extend to the elderly population. In Asian-American males the prevalence of diabetes rises from 1.3% in those 0–44 years old to 22.5% in those 65–74 years old and in Asian-American females the increase
is 1.4% to 29.4% [2]. Asian-Americans and NHPIs are more likely to have diabetic nephropathy and ESRD and NPHPIs carry the highest risk of non-traumatic amputation of all ethnic groups [23,24].

The above findings mandate a more ethnic-conscious approach to diabetes management extending throughout the lifespan. Given the average earlier age of diabetes diagnosis in Asians and NHPIs, these ethnicities should be targeted earlier in life with implementable and successful preventative strategies to reduce obesity and diabetes risk and limit diabetes-related complications in old age. There is clear evidence that intensive treatment of T2D early in the course of the disease has a substantial “legacy” effect in preventing long-term complications [46] even if glycemic control deteriorates over time (although ethnic-specific data is currently lacking). As Asians and NHPIs age, practitioners must be acutely aware of the duration of their diabetes, which may be more prolonged in these ethnic groups, and tailor glycemic targets and interventions appropriately. In NHPIs, an effective educational strategy may be prudent given their average lack of education compared to other ethnic groups. In those individuals of AA, Asian, and Hispanic/Latino descent, a culturally appropriate lifestyle intervention to reduce obesity is likely to be effective, with Asians targeted at lower BMI levels than other ethnic groups. One study, in fact, indicated that AAs and Hispanics were more likely to follow exercise recommendations from a healthcare professional than other ethnic groups [47]. Promoting de-acculturation which advocates eating more fresh foods from their native country and less “Western” style foods has also been successful with Mexican-Americans [48–50]. In the AA community, a culturally-sensitive community-based combined lifestyle and pharmacologic approach should be undertaken, as with lifestyle alone 40–50% of prediabetic subjects still progress to T2D, while pharmacologic intervention is uniformly more successful (reviewed in [51]). These lifestyle interventions must be culture-appropriate, as a cross-sectional analysis of the 2007 SHIELD US survey showed that despite a similar percentage of respondents from different racial groups receiving exercise recommendations from a healthcare professional, there were large racial differences in the actual implementation of these recommendations [47].

In summary, the rising prevalence of T2D in the elderly spans all racial/ethnic groups. Identifying, recognizing, and then implementing culturally-specific interventions is paramount to good clinical care. In addition, translational research is required that is focused on epidemiological, phenotypic and genetic differences between racial/ethnic groups and their differential responses to treatment within the context of varied socioeconomic environments.

**Pathogenesis of T2D in the elderly**

There are many potential etiologic reasons for the increase in T2D prevalence with advancing age. These include lifestyle and cultural factors (obesity and sedentary lifestyle), [52,53] potential age-related changes in insulin action and secretion, [54] inflammatory and hormonal dysregulation, [55,56] genetic factors, [57] changes in sleep pattern, [58,59]
increased oxidative stress, and increased use of medications that increase hyperglycemic propensity. A number of different organ systems and tissues are therefore affected during the aging process with profound ramifications on diabetes risk (Figure 1).

Obesity is an important cause of both insulin resistance (IR) and impaired beta (β)-cell function, the two major factors leading to T2D, and the risk of developing poor glycemic control increases linearly with body mass index (BMI) [63, 64]. In those ≥65 years old, obesity rates have increased from 23.6% in 1990 to 39.6% in 2010. The close positive association of BMI with T2D risk, insulin dependence, and macrovascular and microvascular complications was recently shown in a continuous longitudinal survey of Medicare beneficiaries from 1991–2010 [65]. In this analysis, the risk of T2D in older patients was three-fold higher in those with morbid obesity (BMI ≥40 kg.m⁻²) compared to normal weight individuals, insulin-dependence was five times higher, and the risks of CVD, cerebrovascular disease, renal, and ocular complications were 1.5 to 4 times greater. The obesity epidemic is largely due to excess caloric intake and/or sedentary lifestyle [66] in the presence of genetic susceptibility [67]. Compared to other age groups, older adults are the most sedentary [68]. On average, older adults spend upwards of 80% of their time awake doing sedentary activities [68, 69]. A systematic review of 24 studies reported at least a moderate degree of evidence for a direct relationship between sedentary behavior, BMI and the metabolic syndrome in adults > 60 years old [70]. Greater sedentary time was also associated with increased all-cause mortality.

Despite the increased prevalence of T2D in older adults, the fundamental effects of the aging process itself on insulin sensitivity remain relatively unexplored, with the limited available data supporting divergent conclusions. Insulin resistance is broadly defined as a subnormal biological response to normal insulin concentrations, but in clinical practice typically refers to a subnormal glucose response [71]. It manifests as the inability of insulin to adequately stimulate peripheral tissue (mainly skeletal muscle) glucose uptake and suppress hepatic glucose production. Although some studies have reported that older patients have increased insulin resistance [72–75], others have found that aging does not per se cause significant insulin resistance [76, 77]. These discrepant results may be related to differences in physical activity level and body composition among study populations [78].

Aging is associated with a progressive decline in muscle mass, quality, and strength with resultant weakness and declining mobility that can culminate in the syndromes of sarcopenia and/or frailty [79]. Of note, prominent risk factors for sarcopenia include both obesity and insulin resistance [80], and insulin sensitizing agents significantly reduce loss of fat free mass in obese insulin resistant subjects [81]. A direct causal relationship between insulin resistance and sarcopenia however is uncertain. In some obese individuals, muscle mass is much lower than expected, a condition termed ‘sarcopenic obesity’. This syndrome is accompanied by changes in muscle fiber type [82], fatty infiltration [83], and reduced muscle strength [84]. These changes are at least partly attributable to inflammatory mediators and resultant lipotoxicity [85, 86]. On a cellular metabolic level, common obesity-associated derangements in mitochondrial function, endoplasmic reticulum (ER) stress, lipid deposition, and stress-related pathways appear to converge in both insulin resistance and...
sarcopenia [87,88], but the capacity for glucose utilization remains an undetermined component of the sarcopenia syndrome. Whether increased adiposity and loss of muscle mass (as evident in ‘sarcopenic obesity’) provide a complete explanation for any observed age-related increases in insulin resistance is unclear. However, even when study populations are matched for physical activity level and percent lean body mass, results have not been consistent. Older individuals evaluated by the hyperinsulinemic-euglycemic clamp, the gold standard for assessment of insulin sensitivity, may or may not have reduced peripheral glucose uptake [89,90].

Along with changes to skeletal muscle mass, the aging liver undergoes many changes: reduction in blood supply of ~1% per year, number of liver cells and elasticity along with a reduced capacity for metabolic function and detoxification. The ability of insulin to suppress hepatic glucose production (i.e. hepatic insulin sensitivity) in elderly subjects has been evaluated in a small number of studies mainly involving healthy, normal weight patients [72,91,92]. Again, these publications have yielded contradictory results with studies showing greater [91], no difference [92], or less [91] insulin-mediated suppression of hepatic glucose production in the older patient population. Of note, comparison studies of overweight/obese, younger versus older patients, following weight loss by any method have not been performed and represent a significant gap in our understanding of weight loss interventions in older adults.

Changes to pancreatic morphology with aging were first noted in the 1970’s [93]. Cellular senescence of pancreatic β-cells has since been implicated in the pathogenesis of T2D. The aging pancreas exhibits definite defects in β-cell mass [94], as β-cell proliferation is reduced in aging humans [95,96]. Whether this translates into a decline in β-cell function is controversial. In humans, disorderly insulin release, a decrease in insulin pulse amplitudes, and decreased response to glucose oscillations as well as alterations in insulin clearance have all been observed [97], which may be related to a loss of pancreatic β-cell GLUT2 expression in humans [98] as well as differences in β-cell glucose oxidation [99]. However, in a study of young (ages 23–25) vs. older (ages 64–66) adults, the older patients had greater defects in insulin secretion only in the presence of impaired glucose tolerance or frank T2D. This suggests that there may not be a strict decline in β-cell function with aging, but this decrement may manifest solely in those with existing dysregulation of glucose homeostasis.

Aging is a biological process that is characterized by a decline in basic metabolic processes. According to the free radical theory of aging, reactive oxygen species (ROS) can elicit damage to cellular proteins, nucleic acids, and lipids and ultimately lead to age-related organ dysfunction [100]. ROS produced by the mitochondrial respiratory chain damage mitochondrial proteins, lipids and DNA, and accumulated insults during a lifespan lead to a decline in the bioenergetic function of mitochondria [101]. Experimental evidence indicates that oxidative stress is an important mechanism for the development of not only T2D, but also the metabolic syndrome, CVD, and nonalcoholic steatohepatitis (NASH) [102–108]. The role of oxidative stress in T2D is rapidly evolving. As a direct result of the activation of the oxidative stress cascade, insulin signaling is disrupted through serine phosphorylation of insulin receptor substrate (IRS) proteins [109]. In addition, ROS can directly affect systemic inflammation and the expression of the anti-inflammatory factor adiponectin, as plasma

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markers of oxidative stress correlate negatively with circulating adiponectin levels [110]. We have previously shown that older compared to younger mice fed a high-fat diet (HFD) have reduced glucose tolerance, advanced atherosclerosis, and pathologic changes resembling human non-alcoholic steatohepatitis (NASH) largely due to excess oxidative stress and generation of ROS with loss of antioxidant enzyme capacity, and that this effect can be reversed by insulin sensitizing agents [111]. These results indicate that chronic overproduction of redox signaling pathways, leading to excess oxidative stress and ROS generation may contribute to cell aging and act as an important mediator in dysglycemia.

To summarize, the pathogenesis of T2D in the elderly is multifactorial. The obesity epidemic is a major contributing factor to the rising prevalence of T2D, as excess adiposity is associated with insulin resistance and inadequate β-cell function. It is unclear; however, if aging has an independent effect on these two major factors and whether changes to muscle composition resulting in ‘sarcopenic obesity’ is a major driver of dysregulated metabolism. While it is clear that important changes to numerous organs (including skeletal muscle, pancreas, liver) and adipose tissue occur with aging, their relative contributions to the rising prevalence of T2D in elderly patients remains uncertain. Most importantly, well-designed trials of weight loss specifically in the older patient population will shed light on the benefits and drawbacks of intervening in this vulnerable group.

‘Inflammaging’ and T2D in the elderly

Obesity and its associated comorbidities (including T2D, CVD, NAFLD/NASH, and cognitive impairment) promote a state of chronic low-grade inflammation detected both systemically and within specific tissues [112] and is now recognized as a major cause of decreased insulin sensitivity and T2D [113]. Activation of proinflammatory pathways leads to the secretion of numerous cytokines [114] which induce changes in gene expression that can directly impair insulin signaling and glucose uptake [115]. Aging is the most prominent risk factor for a myriad of obesity-related chronic diseases including T2D, Alzheimer’s disease, frailty and sarcopenia, CVD, fatty liver and steatohepatitis, and certain forms of cancer. A common feature that links these age-related conditions is chronic inflammation, a process that has been termed ‘Inflammaging’ [116,117]. Individuals over the age of 65 have increased serum levels of multiple pro-inflammatory factors including interleukin (IL)-6, IL-1β and IL-18 and tumor necrosis factor-α (TNF-alpha) [118,119]. Although a complete discussion of the role of inflammation in the aging process and its contribution to age-related declines is beyond the scope of this review (see the comprehensive review by Goldberg, et al. [56]), inflammatory pathway activation has been observed in all insulin target tissues/organs, including adipose [120], liver [121], brain [122], kidney [123], intestine [124], pancreas [125] and skeletal muscle [126,127], underscoring the global role of inflammation in driving the pathogenesis of T2D [113,128].

Acting as the body’s primary long-term energy reservoir, adipose tissue (AT) is now recognized as the largest endocrine organ, secreting over fifty metabolically-active adipokines, cytokines, and chemokines [129]. In fact, the early stages of systemic inflammatory gene expression are selectively induced in AT, rather than liver and skeletal muscle [130]. Weight gain occurs when caloric intake exceeds energy expenditure, resulting
in adipose tissue expansion to accommodate increased energy storage demands. In obesity, excessive expansion substantially alters adipose tissue histology and function. As adipocytes enlarge, some become apoptotic and are surrounded by macrophages to form crown-like structures, a hallmark of adipose inflammation [131]. Interactions among adipocytes and adipose immune cells at different stages of this process enhance pro-inflammatory and suppress anti-inflammatory immune cell accumulation and production of metabolically-active mediators.

A comprehensive, balanced system of pro- and anti-inflammatory mediators and immune cells is required to maintain normal adipose storage, endocrine function, and systemic insulin action, all critical to whole body metabolism [132]. Recent, transformative animal studies highlight the importance of several immune cells in maintaining lean adipose tissue, creating a shifting paradigm in obesity research. Lean AT is populated predominantly by alternatively-activated macrophages (AAMacs), eosinophils, type 2 innate lymphoid cells (ILC2s), invariant natural killer T (iNKT) cells, and CD4+ Type 2 helper (T\textsubscript{h}2) and regulatory T (T\textsubscript{reg}) cells that contribute to a cytokine-associated type 2 anti-inflammatory axis (Figure 2). Eosinophil-derived interleukin (IL)-4 promotes the differentiation and maintenance of T\textsubscript{h}2s, T\textsubscript{reg}s, and AAMacs. Accordingly, eosinophil deficiency leads to high-fat diet (HFD)-induced insulin resistance, while IL-4 deficient mice are rescued in proportion to the number of adoptively-transferred wild-type eosinophils entering into adipose tissue [133]. IL-33 and IL-25 also rapidly activate ILC2s [134] to produce IL-13 and IL-5 that further promote adipose tissue eosinophil and M2 ATM accumulation, and lead to activation of iNKTs [136,137]. Adoptive transfer of iNKTs into obese mice induces weight loss and improves glucose tolerance in a cytokine-dependent manner [138]. Thus, a newly defined ILC2-eosinophil-NKT axis helps maintain lean mice AT metabolic homeostasis; but this axis has yet to be explored in humans.

In obesity, the immunologic milieu of adipose tissue shifts from a cytokine-associated type 2 anti-inflammatory to a type 1 proinflammatory environment. In this context, the normal architecture, energy storage, and endocrine activities of adipocytes are profoundly altered as they accumulate triglycerides and become hypertrophic. In fact, adipocytes may initiate the cascade of adipose tissue inflammation, as they link storage capacity and endocrine function and are the predominant source of adiponectin, leptin, and other key mediators [139]. Leptin has multiple pro-inflammatory effects and increases soon after exposure to nutrient excess. Leptin stimulates production of pro-inflammatory IL-1, IL-6, IL-12, and tumor necrosis factor alpha (TNF\textalpha) by innate immune cells, and directly increases CD4+ T\textsubscript{h}1 polarization and inhibits T\textsubscript{reg} proliferation. Both leptin and MHCII expression promote T\textsubscript{h}1 cell polarization and activation, since adipose inflammation is markedly attenuated in both leptin- and MHCII-deficient obese mice [140]. The effects are also opposed by IL-4 and −10 from T\textsubscript{h}2 and T\textsubscript{reg} cells [141].

Emerging evidence highlights the importance of T\textsubscript{reg}s in defining the immunologic milieu of lean and obese AT. In the lean state, the stability of T\textsubscript{reg}s is enhanced by IL-10 [142], a potent adipocyte-derived anti-inflammatory cytokine that is also produced by anti-inflammatory macrophages and T lymphocytes. Furthermore, adiponectin decreases MHCII expression which is required by antigen presenting cells (APCs) to increase T\textsubscript{reg} abundance.
Surprisingly, Tregs comprise 50% of CD4+ adipose resident T cells (ARTs) in VAT of lean mice, but decline to about 15% of the CD4+ ART population in obesity [143]. Adipose tissue Tregs also regulate systemic insulin action and strongly inhibit pro-inflammatory responses of other T cell subtypes. Insulin-sensitizing PPARγ ligands increase adipose Treg content, while Treg-specific PPARγ deficiency impairs ligand-induced insulin sensitivity [144]. Adoptive transfer of Tregs to obese, insulin-resistant mice improves insulin action, underscoring the role of Tregs in insulin sensitivity [145]. In fact, we found remarkably high Treg levels (50% of CD4+ARTs) in HFD-fed mice lacking MHCII in their adipocytes (aMHCII−/− mice) that explained their improved insulin sensitivity, suggesting that adipocyte MHCII activity regulates Treg abundance and function [140]. In humans we found not only that adipocyte MHCII up-regulation occurs in obesity [140], but expression of adipose tissue Treg markers decrease, and expression of Tß1 markers and IFNγ increases [145–147]. Of relevance to the aging process, the VAT Treg pool decreases with advancing age in animal models [143]. This finding has yet to be replicated in humans and a subsequent study demonstrated that mice deficient in AT Tregs are protected against age-associated insulin resistance [148]. If confirmed, the decrease in Tregs may be due to reduced IL-33 [149]. Recently, IL-33 was identified as an indispensable factor for the development and maintenance of VAT Tregs, since genetic ablation of IL-33 or its receptor severely reduces adipose Treg abundance [150]. IL-33 thus has important actions on both Tregs and ILC2s, and has emerged as a central regulator of cells that limits inflammation in lean AT. Therefore, further human studies are needed to clarify the role of Tregs in human aging and determine whether these immunometabolic AT changes contribute to higher rates of T2D during the human aging process.

Complications of T2D in the elderly

A number of complications and geriatric syndromes are more common in patients with T2D. The risk of nephropathy is doubled. T2D also accelerates CVD [151,152], the primary cause of mortality in T2D patients. In fact, 65% of diabetics die from heart disease or stroke. The risks of retinopathy and macular degeneration (the two primary causes of blindness) are both higher in the diabetic population. Depression is independently associated with poor glycemic control [153]. Disabilities in activities of daily living (ADL’s) are 1.5 times more likely with T2D. Older diabetics also have a twofold inability to climb stairs and an increased risk of falling. Even prediabetes, which is present in > 50% of those > 75 years old, may be associated with increased mortality and CV events based on a small number of studies [154,155]. Polypharmacy is an important risk in this patient population and this risk is increasing over time. In a longitudinal study of community-dwelling adults 62–85 years old, concurrent use of > 5 prescription medications increased from 30.6% to 35.8% over the periods of 2005–2006 to 2010–2011 [156]. Over 15% of older adults in 2010–2011 were deemed to be at risk for a major drug-drug interaction compared to 8.4% in 2005–2006.

With an aging population, there has been an alarming increase in the prevalence of cognitive dysfunction including dementia. Dementia now affects 6–10% of those over the age of 65, 30–50% of those over the age of 95, and nearly 70% in those over the age of 95, making it a leading public health concern. The metabolic syndrome (including central obesity) has been associated with the risk of cognitive decline, overall dementia and vascular dementia [157].
The presence of insulin resistance (IR), in itself, has been linked to an increased risk of mild cognitive impairment (MCI) [158] and the degree of IR negatively correlates with tests of cognitive function and brain preservation by imaging [159]. Insulin has direct effects on the brain; affects the production, degradation and clearance of β-amyloid leading to plaque deposition [160] and plays a pivotal role in the phosphorylation of tau to form neurofibrillary tangles, which are implicated in Alzheimer-associated dementia [161]. In addition, insulin and hyperglycemia have direct effects on the vasculature, increasing the risk of vascular cognitive impairment and vascular dementia. A recent meta-analysis demonstrated significant improvement in memory and executive function after weight loss [162]. No other recently published study examined the post-surgical impact of bariatric surgery on cognition using a neuropsychometric test battery but was performed in middle-aged subjects. Gunstad, et al. analyzed data from 109 bariatric surgery patients (mean age 44.7 years old) and 41 obese controls at baseline and at 12 week follow-up (with results now extending out to 3 years) [163]. Compared to controls, surgical patients had improved memory performance and executive function, raising the possibility that large-scale weight loss with bariatric surgery may have a protective effect on cognition in older obese individuals; a critical yet untested outcome measure.

**Glycemic targets for T2D in older patients**

There are few studies specifically addressing optimal glycemic goals in older patients. The vast majority of the available data derives from younger and middle-aged Type 2 diabetic patients and may not necessarily be applicable to older patients. Most of the large randomized control trials that form the basis of our current understanding on preventing diabetic complications were not designed to evaluate those > 75 years old and do not take functional status into account. For instance, the United Kingdom Prospective Diabetes Study (UKPDS) [46] excluded patients > 65 years old and the ACCORD [164], VADT [165] and ADVANCE [166] trials excluded those > 80 years old. The American Diabetes Association (ADA) Consensus Development Conference on Diabetes and Older Adults in 2012 admitted that “There are essentially no directly applicable clinical trial data on glucose control for large segments of the older diabetic patient population” [167,168]. Neither the ADA nor the U.S. Department of Veteran Affairs and the U.S. Department of Defenses (VA/DOD) guidelines specifically mention age and there is no attempt to discriminate based on decade of life [169]. In fact, one of the major obstacles in determining therapeutic options in an older patient group is the lack of glycemic targets based on varying age and comorbid subgroups. We recognize that subdividing older patients by age may a useful component in establishing such targets, but the literature is devoid of studies using this approach (although they may indirectly utilize age grouping as a criterion by taking into account life expectancy), and this approach is somewhat limited by the extreme differences in functional status, body composition, comorbidities, etc. that exist in older patients of the same chronologic age.

Elderly individuals with T2D fall generally into two predominant categories: those who acquire the condition in middle age and those who acquire T2D later in life (i.e. middle-aged onset diabetes and elderly- onset diabetes) [170]. The vast majority of older patients with T2D are middle-aged onset and these patients suffer a greater burden of microvascular
disease and are at higher risk for inferior glycemic control [171,172]. Despite these differences, however, the limited evidence that underlies our current treatment approaches does not take diabetes duration into account. In addition, although macrovascular disease appears to be related to age at diabetes onset, it is unclear if this is an important factor for the development of CVD [172]. Overall glycemic control may also be a mitigating factor of diabetes duration in determining all-cause mortality, as one study showed that elderly-onset diabetes was only associated with higher mortality if the initial glycated hemoglobin (HgbA1c) was ≥7.5% [173].

In determining glycemic targets in older patients, it is important to devise strategies that not only limit hyperglycemia which can increase complication risk, lead to dehydration, and create vision and cognitive changes which can increase fall risk; but also limit hypoglycemia which can also increase the risk of CVD [174], cognitive impairment [175] and falls. In addition, adding anti-diabetic medications can contribute to polypharmacy. Most of the available proposed guidelines are ultimately based upon an individual’s overall health and projected life expectancy [168,176]. Since studies have demonstrated that ~8 years are required before the benefits of improved glycemic control are reflected in decreased microvascular complications, a frail, older patient with < 10 year projected life expectancy who is at risk for CVD disease may benefit from less stringent control that avoids hypoglycemia (i.e. HgBA1c < 8%). In contrast, a fit, older patient with > 10 year life expectancy without complications would benefit from more stringent control (i.e. HgBA1c < 7.0%). A patient with advanced complications and/or life expectancy < 5 years may require even less stringent targets (i.e. HgbA1c 8–9%). A general framework for glycemic targets as proposed by the ADA can be seen in table 1. These broad recommendations, however, could certainly be refined by future well-designed trials directly applicable to specific segments of the older adult population.

In summary, the lack of available evidence-based guidelines for large segments of the elderly diabetic population is a major impediment to providing optimal clinical care. Large, randomized trials specifically in older adults are necessary to better refine an individual’s glycemic control targets and to tailor treatment accordingly. In addition, trials of older patients with certain phenotypic characteristics and specific comorbidities must be performed to ascertain if the results found in younger adults can be properly translated to elderly patients.

**Treatment of T2D in the elderly**

The treatment of T2D in older patients must be individualized not only to ensure effectiveness, but to maximize patient safety and quality of life. Guiding principles before deciding on a treatment regimen should include an assessment of multiple factors: patient risk for atherosclerotic disease and diabetes-related comorbidities, medication history, functional status to determine if the patient is able to independently manage his/her T2D, presence of depression and/or cognitive impairment, history of urinary incontinence and/or falls, severe hypoglycemia or attenuated awareness of hypoglycemia, and duration of diabetes, among others. Treatment options generally fall into 3 categories.
Lifestyle modification: The effectiveness of standard lifestyle intervention in weight management and glycemic control has been largely unsuccessful due to poor patient adherence and long-term sustainability. In the UKPDS, for example, all patients were advised to follow a low calorie, low fat, high complex carbohydrate diet in addition to regular physical exercise as recommended by the ADA [177]. After three years, only 3% of those in the lifestyle intervention group had achieved and maintained the desired fasting blood glucose concentration below 108 mg/dL. Sustained weight loss has also been difficult to achieve with health care provider dietary and physical activity advice. As an example, a meta-analysis of behavior intervention (diet and exercise recommendations) trials failed to show significant weight loss compared to controls [178]. In contrast, a well-designed and more intensive lifestyle intervention has been shown to be an effective weight loss strategy and improve glucose homeostasis [179]. Data from the recent multicenter Look AHEAD (Action for Health in Diabetes) trial found that intensive lifestyle intervention (initial weekly meetings to discuss reduced-calorie 1200–1800 kcal diet, use of meal replacements, decreased fat intake to < 30% of total daily calories and instructions for moderate-intensity physical activity of ≥175 minutes/week) resulted in greater weight loss and decrease in HgbA1c compared with standard diabetes support and education [179]. However, the average age of the participants in the Look AHEAD study was 58.6 years old.

Despite the above findings, there is evidence that older patients can respond positively to lifestyle interventions, and age should not in itself be a deterrent to improving one’s lifestyle. In the Diabetes Prevention Program (DPP), those > 60 years old had the largest improvement in glycemic control, largely due to greater adherence compared to younger participants [180]. The lifestyle intervention in the DPP consisted of a weight loss goal of 7% initial body weight in the first 6 months accomplished by: 1) a physical activity expenditure goal of > 700 kcal/week through at least 150 minutes of moderate intensity activity combined with 75 minutes of strength training per week, and 2) dietary modification that subtracted 500–1,000 kcal from daily caloric intake and limited fat consumption to 25% or total calories [181]. Older adults with T2D may benefit from caloric restriction and increased physical activity with even a modest weight loss goal of 5% [168]. In an RCT tailoring nutrition to the individual’s medical, lifestyle, and personal factors called Medical Nutrition Therapy (MNT), the intervention group had greater improvements in fasting glucose and HgBA1c levels [182].

The effect of differing dietary macronutrient composition on metabolism and glycemic control in younger versus older individuals is largely unknown. The American Diabetes Association (ADA) recommends both nutrition therapy and exercise as nonpharmaceutical cornerstones in the management of T2DM. The American Heart Association (AHA) also recommends a dietary macronutrient composition of 45–65% carbohydrate, ≤20% protein and 25–35% fat with reduction in saturated and Tran’s fats [183]. Despite these recommendations, beneficial effects in both diabetic and non-diabetic subjects, including improved glycemic control and greater weight loss, have been observed by increasing dietary protein and lowering carbohydrate intake [184–190]. Data from a series of studies conducted in adults without T2DM found that, compared with high-carbohydrate low-calorie diet therapy, high-protein/low carbohydrate low-calorie diet therapy caused a greater
loss of body fat and preservation of fat-free mass [191,192], greater improvements in lipid profile [193,194], more favorable postprandial glucose and insulin responses [195] and greater improvements in insulin sensitivity and β-cell function [196]. Data from several studies conducted in patients with T2DM have found specific benefits of low-calorie diets that contain increased protein and decreased carbohydrate than low-calorie diets with higher carbohydrate content, including a protein-mediated increase in insulin secretion [197] and greater decreases in body weight, HgbA1c and use of diabetes medications [198]. These studies, however, were all conducted in young to middle-aged adults. In healthy subjects, an increased protein intake of up to 30% does not adversely affect renal function [199,200], however the EURODIAB IDDM Complications study showed that Type 1 diabetics who consumed > 20% of their calories from protein had higher albumin excretion rates [201]. Short-term studies (< 12 month duration) in Type 2 Diabetics have yet to replicate the adverse effects of increasing protein intake on nephropathy [202–204] but longer-term studies are needed and current guidelines do not distinguish by patient age. Older adults with T2D, in particular, are at risk for greater loss of muscle strength compared to younger patients and may benefit from increased protein intake, but studies are limited. The metabolic effects of altering dietary composition in an elderly population and their role in preserving lean mass, especially muscle mass, is thus relatively unknown and requires further investigation.

The effect of differing exercise regimens and diet on cognitive function in older individuals and their relationship to metabolic improvements remains controversial. There is clear evidence that physical activity can contribute to healthy aging and reduce morbidity and mortality [205,206]. There is also strong evidence that moderate-to-high levels of physical activity (mainly by increasing cardiorespiratory fitness) may delay and/or prevent the onset of cognitive decline [207–209]. Yet there are only a limited number of studies, with small population sizes, addressing the effect of exercise in tertiary prevention of cognitive decline in those with existing dementia [210,211]. Research on the effect of dietary modification to prevent cognitive decline is also in its infancy and the benefits of changing macronutrient content is oftentimes difficult to separate from their effects on associated comorbidities such as obesity, diabetes, and CVD [212].

One of the major limitations in our current knowledge is the lack of established guidelines and evidence-based studies for exercise and diet in older patients with T2D. In general, adults between the ages of 18 and 64 years old are recommend by the Centers for Disease Control (CDC) to engage in 150 minutes of moderate-intensity or 75 minutes of vigorous-intensity aerobic activity per week combined with muscle-strengthening activities on ≥ 2 days of the work (working all major muscle groups). These same guidelines advise older adults to increase their activity to 300 minutes of moderate-intensity or 150 minutes of vigorous-intensity exercise per week combined with muscle training activities [213]. However, recommendations specific for an older type 2 diabetic patient are lacking. The ADA, for instance, endorses a similar amount of exercise in diabetics as the CDC does for the general population aged 18 to 64, but provides no specific exercise recommendations in those over the age of 65 [214]. In addition, the ADA has very generalized guidelines for dietary caloric content and macronutrient composition in Type 2 Diabetics, does not set an
ideal percentage of calories from carbohydrates, protein, or fat, and does not dictate specific recommendations based on patient age [214].

**Drug therapy for T2D in older patients:** There is a paucity of data related to specific drug therapy in older patients with T2D [215]. All types of oral and injectable diabetes medications (Table 2) can theoretically be used in patients > 65 years old, although the therapy must be individualized based on functional status, hypoglycemic risk and awareness, and presence/absence of comorbidities [168]. In older patients, a major consideration is selecting therapeutic agents that limit hypoglycemia in the setting of an age-related decline in renal function and/or frank chronic kidney disease. Hypoglycemia in older individuals is associated with significant morbidities leading to both physical and cognitive dysfunction, and recurrent hospital admissions due to frequent hypoglycemia are associated with further deterioration in patients’ general health that can eventually lead to frailty and disability [216]. Patients with dementia are four times more likely to be admitted for hypoglycemia episodes compared to those with normal cognition [217]. Severe hypoglycemia can result in acute vascular complications including stroke, heart failure and arrhythmia [218]. In addition, the brain is dependent on glucose and is exquisitely vulnerable to the effect of hypoglycemia. After a single hypoglycemia event, cognitive changes occur, and recurrent hypoglycemia leads to a graded increased risk of dementia with each subsequent hypoglycemic episode [175]. Given that the risk of hypoglycemia is also increased by 3–4 folds in obesity, the inter-relationship between T2D, obesity, cognitive dysfunction and hypoglycemia during aging must be given consideration in determining a safe treatment regimen.

According to the most recent ADA guidelines, metformin (a biguanide) is considered first-line therapy in T2D [219]. Given its low hypoglycemic risk profile and low cost, metformin may also be beneficial in older adults. However, limitations to its use include side effects (predominantly gastrointestinal), weight loss which may preclude its use in frail patients, and a small risk of lactic acidosis in patients with renal dysfunction. Sulfonylureas are also cost-effective, but are limited by hypoglycemia that may be problematic for older patients, especially those with reduced glomerular filtration capacity or poor appetites. The shorter duration glipizide and the glinides (repaglinide and nateglinide) may be preferable in this scenario; but overall the risk of prolonged hypoglycemia with all sulfonylureas and glinides makes their use largely inadvisable in the elderly population. Alpha-glucosidase inhibitors such as acarbose specifically target post-prandial hyperglycemia and have low hypoglycemia risk; however, gastrointestinal side effects, frequent dosing, and relatively low efficacy may limit their applicability in some older patients. Thiazolidinediones (pioglitazone and rosiglitazone) improve sensitivity to insulin predominantly by binding to the PPARγ receptor. However, they have been associated with weight gain, edema, heart failure, bone fractures, and bladder cancer, precluding their use in certain older adults. Dipeptidyl peptidase-IV (DPP-4) inhibitors (sitagliptin, linagliptin, saxagliptin, and alogliptin) preferentially target post-prandial hyperglycemia, carry limited hypoglycemic potential, and are generally well tolerated. This suggests that they may be useful for older patients; but applicable prospective studies are limited. A recent retrospective observational study focused on the safety and tolerability of the DPP-4 inhibitors in type 2 diabetics aged 65 years and
older. Researchers reviewed the medical records of 431 patients with type 2 diabetes (mean age of 74 years) and demonstrated a trend towards less mild hypoglycemia among those taking DPP-4 inhibitors as compared to those taking non-DPP-4 inhibitors (3% vs. 8%, p = 0.062). Additionally, patients on DPP-4 inhibitors showed a reduction in HgBA1c from approximately 8.3% to 7.4%, consistent with previous literature in younger subjects. Among patients receiving DPP-4 inhibitors identified in this study, most patients were taking sitagliptin (74.3%), followed by vildagliptin (21.8%) and saxagliptin (3.9%) [220]. A systematic review of 18 articles and 3 presentations of studies of DPP-4 inhibitors administered as monotherapy or in combination with metformin, a thiazolidinedione, glimepiride, glibenclamide, or insulin to elderly patients (generally defined as ≥65 years of age) with T2D, showed significant HgBA1c reductions with addition of DPP-4 medications that ranged from ~0.7% (baseline HgBA1c 7.8%) to 1.2% (baseline HgBA1c 8.3). In addition, no significant differences were noted in the HgBA1c-lowering effects of these agents between elderly and younger patients. Less information about the incidence of hypoglycemia or weight gain in elderly patients was reported, but the available results suggest that the risk of hypoglycemia with DPP-4 inhibitors was not significantly different from that of placebo and that these agents were weight neutral (weight change of ≤0.9 kg) [221]. Glucagon-like peptide-1 (GLP-1) receptor agonists (twice daily exenatide, once daily liraglutide, once weekly exenatide XR, dulaglutide, and albiglutide) are also useful in preventing post-prandial hyperglycemia and impart low hypoglycemic risk. They can promote weight loss, and at higher doses, liraglutide is approved for weight reduction independent of diabetes status. However, they can cause nausea, promote weight loss, and are injectable therapies and thus may not be ideal for frail patients or those with vision, sensory or hearing impairment. Both the DPP-4 and GLP-1 receptor agonists also require dose reductions with kidney dysfunction and are largely unstudied with coexistent hepatic impairment. Sodium-glucose co-transporter-2 (SGLT2) inhibitors (canagliflozin, empagliflozin, and dapagliflozin) are newer oral diabetes medications, but there experience in older adults is unknown. Their use may also be limited by side effects (dehydration, increased thirst, polyuria), increased risk of genital and urinary tract infections and reduced effectiveness in patients with preexisting kidney disease.

Insulin therapy can be used successfully in select older adults with T2D, and generally have similar efficacy and hypoglycemia risk compared to younger patients. The biggest limitation is the potential for hypoglycemia and this risk must carefully be assessed in an individual older patient. A 12 month study of insulin either through multiple daily injections (MDI) or an insulin pump, demonstrated that healthy, functional adults with a mean age of 66 years old could maintain an HgBA1c of 7% with a low occurrence of hypoglycemia [222]. A separate study demonstrated that long-acting insulin in older patients (mean age 69 years old) with T2D did not increase the risk of hypoglycemia compared to younger patients [223]. However, patients with much comorbidity were excluded from these trials and there is limited data in patients > 75 years old. In addition, vision impairment and limited manual dexterity may be barriers to insulin therapy compliance for some older adults.

**Bariatric surgery as a treatment modality in obese older patients:** Nearly half of adult patients with T2D fail to achieve adequate glycemic control with medication and
lifestyle modifications alone. In contrast, marked weight loss following bariatric surgery (BS) often results in complete remission of T2D [224]. Conventional bariatric surgery procedures include Roux-en-Y gastric bypass (RYGB), laparoscopic adjustable gastric banding (LAGB), laparoscopic sleeve gastrectomy (SG), biliopancreatic diversion (BPD) and biliopancreatic diversion with duodenal switch (BPD-DS). Currently, the three most popular bariatric surgical procedures performed in the United States and worldwide are the RYGB, SG and LAGB procedures [225]. Eligibility criteria for bariatric surgery have been expanded from the original NIH Consensus Conferences of 1991 to include individuals up to 60 years of age [226,227]. Although the majority of outcome data related to BS derives from studies of young and middle-aged patients, there has been a discernable increase in the number of older patients undergoing BS [228–231], especially laparoscopic SG. This increase is likely related to the perceived safety and effectiveness of the SG procedure, with shorter operating times, abbreviated hospital stays, substantial weight loss and remission of comorbidities [232,233].

Despite the increasing popularity of BS, aging is an important negative predictor of diabetes remission following BS [234]. However, BS can still be successful in older obese patients. Retrospective data of operations, mainly performed by laparoscopy, have shown that older obese adults undergoing bariatric surgery have more baseline co-morbidities and require more medications than younger subjects, but lose clinically significant amounts of weight and have a significant reduction in co-morbidities post-surgery [228–231]. A recent systematic review of RYGB in the elderly (> 65 years old) that included eight primary studies of over 1800 patients showed that the mean excess weight loss at study endpoint was 66.2%, mean 30 day mortality was 0.14%, and total complication rate was 21.1% [235,236]. Based on these results it was determined that RYGB is effective in producing marked weight loss in patients over the age of 65 with an acceptable safety profile. However, the effect of age on BS-induced changes in insulin sensitivity and β-cell function are currently unknown and further studies on the metabolic improvements and limitations of BS in older patients are certainly warranted.

Conclusions

The number of elderly individuals in the U.S. is growing. Within this rapidly expanding demographic, the rates of T2D and obesity are reaching epidemic proportions. Patients > 65 years old will soon constitute the majority of patients with T2D in most developed countries including the U.S. T2D in old age carries an increased risk of the traditional diabetes-associated complications including microvascular and macrovascular disease, but also age-related comorbidities including cognitive impairment, urinary incontinence, sarcopenia, and increased falls. An overall state of chronic inflammation and dysregulated immunometabolism may underlie these increased risks. Unfortunately, a majority of the clinical trial data related to risk profiles, glycemic targets, and therapeutic interventions for T2D are not applicable for large segments of the older patient population. Recognition of this knowledge gap is not adequate. We need strong evidence-based data upon which to successfully intervene in a heterogeneous group of elderly patients with T2D. In order to truly recognize, understand and ultimately treat metabolic disease in older individuals, we must first address several substantial limitations in our fundamental understanding of T2D.
pathogenesis and treatment during the aging process. These include: 1) the effect of race/ethnicity and socio-economic factors on diabetes and obesity risk during the aging process, 2) the effect of aging on insulin release and action and the roles of frailty and sarcopenia, 3) the effects of obesity and immunometabolism on healthy aging and the relative importance of weight loss interventions, 4) the effect of age on diabetic complications and comorbidities, and 5) the differential effects of the aging process on therapeutic responses and treatment options. Most importantly, evidence-based data from studies in younger diabetic patients need to either be validated or refuted in older patients to truly individualize diabetic care and ultimately improve patient outcomes.

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References

References

1. (2012) A Profile of Older Americans: 2012. US Department of Health and Human Services.
2. CDC. Centers for Disease Control and Prevention. Vol 2016.
3. Wolff JL, Starfield B, Anderson G (2002) Prevalence, expenditures, and complications of multiple chronic conditions in the elderly. Arch Intern Med 162: 2269–2276. [PubMed: 12418941]
4. Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, et al. (2006) Prevalence of overweight and obesity in the United States, 1999–2004. JAMA 295: 1549–1555. [PubMed: 16595758]
5. Guh DP, Zhang W, Bansback N, Amarsi Z, Birmingham CL, et al. (2009) The incidence of co-morbidities related to obesity and overweight: a systematic review and meta-analysis. BMC Public Health 9: 88. [PubMed: 19320986]
6. DeFronzo RA (2004) Pathogenesis of type 2 diabetes mellitus. Med Clin North Am 88: 787–835. [PubMed: 15308380]
7. Cowie CC, Rust KF, Ford ES, Eberhardt MS, Byrd-Holt DD, et al. (2009) Full accounting of diabetes and pre-diabetes in the U.S. population in 1988–1994 and 2005–2006. Diabetes Care 32: 287–294. [PubMed: 19017771]
8. Bethel MA, Sloan FA, Belsky D, Feinglos MN (2007) Longitudinal incidence and prevalence of adverse outcomes of diabetes mellitus in elderly patients. Arch Intern Med 167: 921–927. [PubMed: 17502533]
9. Dybicz SB, Thompson S, Molotsky S, Stuart B (2011) Prevalence of diabetes and the burden of comorbid conditions among elderly nursing home residents. Am J Geriatr Pharmacother 9: 212–223. [PubMed: 21659006]
10. Roebuck J (1979) When does old age begin? The Evolution of the English definition. Journal of Social History 12: 416–428.
11. Thane P (1978) The muddled history of retiring at 60 and 65. New Society 45: 234–236.
12. Glascock A (1980) A holocutural analysis of old age. Comparative Social Research 3: 331–332.
13. Gorman M (1999) Development and the rights of older people in The ageing and development report: poverty, independence and the worlds’ older people, Vol. 1 (ed. Randel J) 3–21 (Earthscan Publications Ltd, London, 1999).

J Geriatr Med Gerontol. Author manuscript; available in PMC 2019 November 05.
14. World Health Organization Definition of an older or elderly person. Proposed Working Definition of an Older Person in Africa for the MDS Project.

15. Ogden CL, Carroll MD, Kit BK, Flegal KM (2014) Prevalence of childhood and adult obesity in the United States, 2011–2012. JAMA 311: 806–814. [PubMed: 24570244]

16. Garcia MJ, McNamara PM, Gordon T, Kannel WB (1974) Morbidity and mortality in diabetics in the Framingham population. Sixteen year follow-up study. Diabetes 23: 105–111. [PubMed: 4359625]

17. Harris MI (1998) Diabetes in America: epidemiology and scope of the problem. Diabetes Care 21: C11–14. [PubMed: 9850480]

18. Lackland DT (2015) Clinical Hypertension in High Risk African Americans.

19. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, et al. (2014) Heart disease and stroke statistics—2014 update: a report from the American Heart Association. Circulation 129: e28–e292. [PubMed: 24352519]

20. Clark LT, Ferdinand KC, Flack JM, Gavin JR 3rd, Hall WD, et al. (2001) Coronary heart disease in African Americans. Heart Dis 3: 97–108. [PubMed: 11975778]

21. Gillum RF (1996) The epidemiology of cardiovascular disease in black Americans. N Engl J Med 335: 1597–1599. [PubMed: 8900959]

22. Clark F, Azen SP, Zemke R, Jackson J, Carlson M, et al. (1997) Occupational therapy for independent-living older adults. A randomized controlled trial. JAMA 278: 1321–1326. [PubMed: 9343462]

23. Young BA, Maynard C, Boyko EJ (2003) Racial differences in diabetic nephropathy, cardiovascular disease, and mortality in a national population of veterans. Diabetes Care 26: 2392–2399. [PubMed: 12882868]

24. Young BA, Maynard C, Reiber G, Boyko EJ (2003) Effects of ethnicity and nephropathy on lower-extremity amputation risk among diabetic veterans. Diabetes Care 26: 495–501. [PubMed: 12547888]

25. Schneiderman N, Llabre M, Cowie CC, Barnhart J, Carnethon M, et al. (2014) Prevalence of diabetes among Hispanics/Latinos from diverse backgrounds: the Hispanic Community Health Study/Study of Latinos (HCHS/SOL). Diabetes Care 37: 2233–2239. [PubMed: 25061138]

26. (2015) Federation ID IDF Diabetes Atlas (7th edition).

27. Yang SH, Dou KF, Song WJ (2010) Prevalence of diabetes among men and women in China. N Engl J Med 362: 2425–2426.

28. Kim JH, Kim DJ, Jang HC, Choi SH (2011) Epidemiology of micro- and macrovascular complications of type 2 diabetes in Korea. Diabetes Metab J 35: 571–577. [PubMed: 22247898]

29. Bar-Or O, Foreyt J, Bouchard C, Brownell KD, Dietz WH, et al. (1998) Physical activity, genetic, and nutritional considerations in childhood weight management. Med Sci Sports Exerc 30: 2–10. [PubMed: 9475638]

30. Chiu M, Austin PC, Manuel DG, Shah BR, Tu JV (2011) Deriving ethnic-specific BMI cutoff points for assessing diabetes risk. Diabetes Care 34: 1741–1748. [PubMed: 21680722]

31. Deurenberg P, Yap M, van Staveren WA (1998) Body mass index and percent body fat: a meta analysis among different ethnic groups. Int J Obes Relat Metab Disord 22: 1164–1171. [PubMed: 9877251]

32. Unger RH, Clark GO, Scherer PE, Orci L (2010) Lipid homeostasis, lipotoxicity and the metabolic syndrome. Biochim Biophys Acta 1801: 209–214. [PubMed: 19948243]

33. Yoon KH, Ko SH, Cho JH, Lee JM, Ahn YB, et al. (2003) Selective beta-cell loss and alpha-cell expansion in patients with type 2 diabetes mellitus in Korea. J Clin Endocrinol Metab 88: 2300–2308. [PubMed: 12727989]

34. Rattarasarn C, Soonthornpan S, Leelawattana R, Setasuban W (2006) Decreased insulin secretion but not insulin sensitivity in normal glucose tolerant Thai subjects. Diabetes Care 29: 742–743. [PubMed: 16505544]

35. Taniguchi A, Nagasaki S, Fukushima M, Sakai M, Nagata I, et al. (2000) Assessment of insulin sensitivity and insulin secretion from the oral glucose tolerance test in nonobese Japanese type 2 diabetic patients: comparison with minimal-model approach. Diabetes Care 23: 1439–1440. [PubMed: 10977053]
36. Kato N, Loh M, Takeuchi F, Verweij N, Wang X, et al. (2015) Trans-ancestry genome-wide association study identifies 12 genetic loci influencing blood pressure and implicates a role for DNA methylation. Nat Genet 47: 1282–1293. [PubMed: 26390057]

37. Okada Y, Sim X, Go MJ, Wu JY, Gu D, et al. (2012) Meta-analysis identifies multiple loci associated with kidney function-related traits in east Asian populations. Nat Genet 44: 904–909. [PubMed: 22797727]

38. Parving HH, Lewis JB, Ravid M, Remuzzi G, Hunsicker LG, et al. (2006) Prevalence and risk factors for microalbuminuria in a referred cohort of type II diabetic patients: a global perspective. Kidney Int 69: 2057–2063. [PubMed: 16612330]

39. Liu J, Hong Y, D’Agostino RB Sr, Wu Z, Wang W, et al. (2004) Predictive value for the Chinese population of the Framingham CHD risk assessment tool compared with the Chinese Multi-Provincial Cohort Study. JAMA 291: 2591–2599. [PubMed: 15173150]

40. Woodward M, Zhang X, Barzi F, Pan W, Ueshima H, et al. (2003) The effects of diabetes on the risks of major cardiovascular diseases and death in the Asia-Pacific region. Diabetes Care 26: 360–366. [PubMed: 12547863]

41. Weng J, Soegondo S, Schnell O, Sheu WH, Grzeszczak W, et al. (2015) Efficacy of acarbose in different geographical regions of the world: analysis of a real-life database. Diabetes Metab Res Rev 31: 155–167. [PubMed: 25044702]

42. Gamble JM, Clarke A, Myers KJ, Agnew MD, Hatch K, et al. (2015) Incretin-based medications for type 2 diabetes: an overview of reviews. Diabetes Obes Metab 17: 649–658. [PubMed: 25772666]

43. McNeely MJ, Boyko EJ (2004) Type 2 diabetes prevalence in Asian Americans: results of a national health survey. Diabetes Care 27: 66–69. [PubMed: 14693968]

44. Karter AJ, Schillinger D, Adams AS, Moffet HH, Liu J, et al. (2013) Elevated rates of diabetes in Pacific Islanders and Asian subgroups: The Diabetes Study of Northern California (DISTANCE). Diabetes Care 36: 574–579. [PubMed: 23069837]

45. Lee JW, Brancati FL, Yeh HC (2011) Trends in the prevalence of type 2 diabetes in Asians versus whites: results from the United States National Health Interview Survey, 1997–2008. Diabetes Care 34: 353–357. [PubMed: 21216863]

46. (1998) Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet 352: 837–853. [PubMed: 9742976]

47. Gavin JR 3rd, Fox KM, Grandy S (2011) Race/Ethnicity and gender differences in health intentions and behaviors regarding exercise and diet for adults with type 2 diabetes: a cross-sectional analysis. BMC Public Health 11: 533. [PubMed: 21729303]

48. Gordon-Larsen P, Harris KM, Ward DS, Popkin BM, National Longitudinal Study of Adolescent Health (2003) Acculturation and overweight-related behaviors among Hispanic immigrants to the US: the National Longitudinal Study of Adolescent Health. Soc Sci Med 57: 2023–2034. [PubMed: 14512234]

49. Batis C, Hernandez-Barrera L, Barquera S, Rivera JA, Popkin BM (2011) Food acculturation drives dietary differences among Mexicans, Mexican Americans, and Non-Hispanic Whites. J Nutr 141: 1898–1906. [PubMed: 21880951]

50. Satia-Abouta J, Patterson RE, Neuhauser ML, Elder J (2002) Dietary acculturation: applications to nutrition research and dietetics. J Am Diet Assoc 102: 1105–1118. [PubMed: 12171455]

51. DeFronzo RA, Abdul-Ghani M (2011) Type 2 diabetes can be prevented with early pharmacological intervention. Diabetes Care 34: S202–209. [PubMed: 21525456]

52. Narayan KM, Boyle JP, Thompson TJ, Gregg EW, Williamson DF (2007) Effect of BMI on lifetime risk for diabetes in the U.S. Diabetes Care 30: 1562–1566. [PubMed: 17372155]

53. Han TS, Tajar A, Lean ME (2011) Obesity and weight management in the elderly. Br Med Bul 97: 169–196.

54. Gong Z, Muzumdar RH (2012) Pancreatic function, type 2 diabetes, and metabolism in aging. International journal of endocrinology.

55. Dandona P, Dhindsa S (2011) Update: Hypogonadotrophic hypogonadism in type 2 diabetes and obesity. J Clin Endocrinol Metab 96: 2643–2651. [PubMed: 21896895]
56. Goldberg EL, Dixit VD (2015) Drivers of age-related inflammation and strategies for healthspan extension. Immunological reviews 265: 63–74. [PubMed: 25879284]

57. Lyssenko V, Laakso M (2013) Genetic screening for the risk of type 2 diabetes: worthless or valuable? Diabetes Care 36: S120–126. [PubMed: 23882036]

58. Hublin C, Lehtovirta M, Partinen M, Koskenvuo M, Kaprio J (2016) Napping and the risk of type 2 diabetes: a population-based prospective study. Sleep medicine 17: 144–148. [PubMed: 26847990]

59. Lam KB, Jiang CQ, Thomas GN, Arora T, Zhang WS, et al. (2010) Napping is associated with increased risk of type 2 diabetes: the Guangzhou Biobank Cohort Study. Sleep 33: 402–407. [PubMed: 20337199]

60. Bonomini F, Rodella LF, Rezzani R (2015) Metabolic syndrome, aging and involvement of oxidative stress. Aging Dis 6: 109–120. [PubMed: 25821639]

61. Leslie WS, Hankey CR, Lean ME (2007) Weight gain as an adverse effect of some commonly prescribed drugs: a systematic review. QJM 100: 395–404. [PubMed: 17566010]

62. Pandit MK, Burke J, Gustafson AB, Minocha A, Peiris AN (1993) Drug-induced disorders of glucose tolerance. Ann Intern Med 118: 529–539. [PubMed: 8442624]

63. Colditz GA, Willett WC, Rotnitzky A, Manson JE (1995) Weight gain as a risk factor for clinical diabetes mellitus in women. Ann Intern Med 122: 481–486. [PubMed: 7872581]

64. Chan JM, Rimm EB, Colditz GA, Stampfer MJ, Willett WC (1994) Obesity, fat distribution, and weight gain as risk factors for clinical diabetes in men. Diabetes Care 17: 961–969. [PubMed: 7988316]

65. Gray N, Picone G, Sloan F, Yashkin A (2015) Relation between BMI and diabetes mellitus and its complications among US older adults. South Med J 108: 29–36. [PubMed: 25580754]

66. (2000) Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Health Organization technical report series 894.

67. Ravussin E, Bogardus C (2000) Energy balance and weight regulation: genetics versus environment. Br J Nutr 83: S17–20. [PubMed: 10889787]

68. Davis MG, Fox KR, Hillsdon M, Sharp DJ, Coulson JC, et al. (2011) Objectively measured physical activity in a diverse sample of older urban UK adults. Med Sci Sports Exerc 43: 647–654. [PubMed: 20689449]

69. Matthews CE, Chen KY, Freedson PS, Buchowski MS, Beech BM, et al. (2008) Amount of time spent in sedentary behaviors in the United States, 2003–2004. Am J Epidemiol 167: 875–881. [PubMed: 18303006]

70. de Rezende LF, Rey-Lopez JP, Matsudo VK, do Carmo Luiz O (2014) Sedentary behavior and health outcomes among older adults: a systematic review. BMC Public Health 14: 333. [PubMed: 24712381]

71. Moller DE, Flier JS (1991) Insulin resistance--mechanisms, syndromes, and implications. N Engl J Med 325: 938–948. [PubMed: 1881419]

72. Broughton DL, James OW, Alberti KG, Taylor R (1991) Peripheral and hepatic insulin sensitivity in healthy elderly human subjects. Eur J Clin Invest 21: 13–21. [PubMed: 1907550]

73. Paolisso G, Scheen A, Lefebvre P (1995) Glucose handling, diabetes and ageing. Horm Res 43: 52–57. [PubMed: 7721262]

74. Ryan AS (2000) Insulin resistance with aging: effects of diet and exercise. Sports Med 30: 327–346. [PubMed: 11103847]

75. Broughton DL, Taylor R (1991) Review: deterioration of glucose tolerance with age: the role of insulin resistance. Age Ageing 20: 221–225. [PubMed: 1853796]

76. Ferrannini E, Vichi S, Beck-Nielsen H, Laakso M, Paolisso G, et al. (1996) Insulin action and age. European Group for the Study of Insulin Resistance (EGIR). Diabetes 45: 947–953. [PubMed: 8666147]

77. Imbeault P, Prins JB, Stolic M, Russell AW, O’Moore-Sullivan T, Despres JP, et al. (2003) Aging per se does not influence glucose homeostasis: in vivo and in vitro evidence. Diabetes Care 26: 480–484. [PubMed: 12547885]

78. Scheen AJ (2005) Diabetes mellitus in the elderly: insulin resistance and/or impaired insulin secretion? Diabetes Metab 31: 5S27–5S34. [PubMed: 16415763]
79. Ryall JG, Schertzer JD, Lynch GS (2008) Cellular and molecular mechanisms underlying age-related skeletal muscle wasting and weakness. Biogerontology 9: 213–228. [PubMed: 18299960]

80. Stenholm S, Harris Tamara B, Rantanen Taina, Visser Marjolein, Kritchevsky Stephen B., et al. (2008) Sarcopenic obesity: definition, cause and consequences. Curr Opin Clin Nutr Metab Care 11: 693–700. [PubMed: 18827572]

81. Lee CG, Boyko EJ, Barrett-Connor E, Miljkovic I, Hoffman AR, et al. (2011) Insulin sensitizers may attenuate lean mass loss in older men with diabetes. Diabetes Care 34: 2381–2386. [PubMed: 21926282]

82. Tanner CJ, Barakat HA, Dohm GL, Pories WJ, MacDonald KG, et al. (2002) Muscle fiber type is associated with obesity and weight loss. Am J Physiol Endocrinol Metab 282: E1191–1196. [PubMed: 12006347]

83. Delmonico MJ, Harris TB, Visser M, Park SW, Conroy MB, et al. (2009) Longitudinal study of muscle strength, quality, and adipose tissue infiltration. Am J Clin Nutr 90: 1579–1585. [PubMed: 19864405]

84. Lafortuna CL, Maffioletti NA, Agosti F, Sartorio A (2005) Gender variations of body composition, muscle strength and power output in morbid obesity. Int J Obes (Lond) 29: 833–841. [PubMed: 15917862]

85. Bruce CR, Hoy AJ, Turner N, Watt MJ, Allen TL, et al. (2009). Overexpression of carnitine palmitoyltransferase-1 in skeletal muscle is sufficient to enhance fatty acid oxidation and improve high-fat diet-induced insulin resistance. Diabetes 58: 550–558. [PubMed: 19073774]

86. Ussher JR, Koves TR, Cadete VJ, Zhang L, Jaswal JS, Swyrd SJ, et al. (2010) Inhibition of de novo ceramide synthesis reverses diet-induced insulin resistance and enhances whole-body oxygen consumption. Diabetes 59: 2453–2464. [PubMed: 20522596]

87. Shulman GI (2000) Cellular mechanisms of insulin resistance. J Clin Invest 106: 171–176. [PubMed: 10903330]

88. Zembron-Lacny A, Dziubek W, Rogowski L, Skorupka E, Dabrowska G (2014) Sarcopenia: monitoring, molecular mechanisms, and physical intervention. Physiol Res 63: 683–691. [PubMed: 25157651]

89. Lanza IR, Short DK, Short KR, Raghavakaimal S, Basu R et al. (2008) Endurance exercise as a countermeasure for aging. Diabetes 57: 2933–2942. [PubMed: 18716044]

90. Petersen KF, Befroy D, Dufour S, Dziura J, Ariyan C, et al. (2003) Mitochondrial dysfunction in the elderly: possible role in insulin resistance. Science 300: 1140–1142. [PubMed: 12750520]

91. Fink RI, Kolterman OG, Griffin J, Olefsky JM (1983) Mechanisms of insulin resistance in aging. J Clin Invest 71: 1523–1535. [PubMed: 6345584]

92. Smith GI, Yoshino J, Reeds DN, Bradley D, Burrows RE, et al. (2014) Testosterone and progesterone, but not estradiol, stimulates muscle protein synthesis in postmenopausal women. J Clin Endocrinol Metab 99: 256–265. [PubMed: 24203065]

93. Kreel L, Sandin B, Slavin G (1973) Pancreatic morphology--a combined radiological and pathological study. Clin Radiol 24: 154–161. [PubMed: 4733275]

94. Tavana O, Puebla-Osorio N, Sang M, Zhu C (2010) Absence of p53-dependent apoptosis combined with nonhomologous end-joining deficiency leads to a severe diabetic phenotype in mice. Diabetes 59: 135–142. [PubMed: 19833883]

95. Reers C, Erbel S, Esposito I, Schmied B, Büchler MW, et al. (2009) Impaired islet turnover in human donor pancreata with aging. Eur J Endocrinol 160: 185–191. [PubMed: 19004984]

96. Butler AE, Janson J, Bonner-Weir S, Ritzel R, Rizza RA, et al. (2003) Beta-cell deficit and increased beta-cell apoptosis in humans with type 2 diabetes. Diabetes 52: 102–110. [PubMed: 12502499]

97. Chang AM, Halter JB (2003) Aging and insulin secretion. Am J Physiol Endocrinol Metab 284, E7–12. [PubMed: 12485807]

98. Ohtsubo K, Takamatsu S, Minowa MT, Yoshida A, Takeuchi M, et al. (2005) Dietary and genetic control of glucose transporter 2 glycosylation promotes insulin secretion in suppressing diabetes. Cell 123: 1307–1321. [PubMed: 16377570]
99. Anello M, Lupi R, Spampinato D, Piro S, Masini M, et al. (2005) Functional and morphological alterations of mitochondria in pancreatic beta cells from type 2 diabetic patients. Diabetologia 48: 282–289. [PubMed: 15654602]

100. Harman D (1956) Aging: a theory based on free radical and radiation chemistry. J Gerontol 11: 298–300. [PubMed: 13332224]

101. Harman D (1972) The biologic clock: the mitochondria? J Am Geriatr Soc 20: 145–147. [PubMed: 5016631]

102. Furukawa S, Fujita T, Shimabukuro M, Iwaki Y, Yamada Y, et al. (2004) Increased oxidative stress in obesity and its impact on metabolic syndrome. J Clin Invest 114: 1752–1761. [PubMed: 15599400]

103. Grattagliano I, Vendemiale G, Boscia F, Micelli-Ferrari T, Cardia L, et al. (1998) Oxidative retinal products and ocular damages in diabetic patients. Free Radic Biol Med 25: 369–372. [PubMed: 9680184]

104. Grattagliano I, Vendemiale G, Caraceni P, Domenicali M, Nardo B, et al. (2000) Starvation impairs antioxidant defense in fatty livers of rats fed a choline-deficient diet. J Nutr 130: 2131–2136. [PubMed: 10958803]

105. Sies H (1997) Oxidative stress: oxidants and antioxidants. Exp Physiol 82: 291–295. [PubMed: 9129943]

106. Palmieri VO, Grattagliano I, Portincasa P, Palasciano G (2006) Systemic oxidative alterations are associated with visceral adiposity and liver steatosis in patients with metabolic syndrome. J Nutr 136: 3022–3026. [PubMed: 17116714]

107. Couillard C, Ruel G, Archer WR, Pomerleau S, Bergeron J, et al. (2005) Circulating levels of oxidative stress markers and endothelial adhesion molecules in men with abdominal obesity. J Clin Endocrinol Metab 90: 6454–6459. [PubMed: 16189262]

108. Stocker R, Keaney JF Jr (2004) Role of oxidative modifications in atherosclerosis. Physiol Rev 84: 1381–1478. [PubMed: 15383655]

109. Powell DJ, Hajduch E, Kular G, Hundal HS (2003) Ceramide disables 3-phosphoinositide binding to the pleckstrin homology domain of protein kinase B (PKB)/Akt by a PKCzeta-dependent mechanism. Mol Cell Biol 23: 7794–7808. [PubMed: 14560023]

110. Pitocco Dario, Zaccardi Francesco, Di Stasio Enrico, Romitelli Federica, Santini Stefano A., et al. (2010) Oxidative stress, nitric oxide, and diabetes. Rev Diabet Stud 7: 15–25. [PubMed: 20703435]

111. Collins AR, Lyons CJ, Xia X, Liu JZ, Tangirala RK, et al. (2009) Age-accelerated atherosclerosis correlates with failure to upregulate antioxidant genes. Circ Res 104: e42–54. [PubMed: 19265038]

112. Romeo Giulio R., Lee Jongsoon, Shoelson Steven E. (2012) Metabolic syndrome, insulin resistance, and roles of inflammation–mechanisms and therapeutic targets. Arterioscler Thromb Vasc Biol 32: 1771–1776. [PubMed: 22815343]

113. Heilbron LK, Campbell LV (2008) Adipose tissue macrophages, low grade inflammation and insulin resistance in human obesity. Curr Pharm Des 14: 1225–1230. [PubMed: 18473870]

114. Olefsky JM, Glass CK (2010) Macrophages, inflammation, and insulin resistance. Annu Rev Physiol 72: 219–246. [PubMed: 20148674]

115. Osborn O, Olefsky JM (2012) The cellular and signaling networks linking the immune system and metabolism in disease. Nat Med 18: 363–374. [PubMed: 22395709]

116. Franceschi C, Capri M, Monti D, Giunta S, Olivieri F, et al. (2007) Inflammaging and anti-inflammaging: a systemic perspective on aging and longevity emerged from studies in humans. Mech Ageing Dev 128: 92–105. [PubMed: 17116321]

117. Franceschi C, Campisi J (2014) Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. J Gerontol A Biol Sci Med Sci 69: S4–9. [PubMed: 24833586]

118. Pedersen M, Bruunsgaard H, Weis N, Hendel HW, Andreassen BU, et al. (2003) Circulating levels of TNF-alpha and IL-6-relation to truncal fat mass and muscle mass in healthy elderly individuals and in patients with type-2 diabetes. Mech Ageing Dev 124: 495–502. [PubMed: 12714258]
119. Ferrucci L, Corsi A, Lauretani F, Bandinelli S, Bartali B, et al. (2005) The origins of age-related proinflammatory state. Blood 105: 2294–2299. [PubMed: 15572589]

120. Weisberg Stuart P., McCann Daniel, Desai Manisha, Rosenbaum Michael, Leibel Rudolph L., et al. (2003) Obesity is associated with macrophage accumulation in adipose tissue. J Clin Invest 112: 1796–1808. [PubMed: 14679176]

121. Cai Dongsheng, Yuan Minsheng, Frantz Daniel F, Melendez Peter A, Hansen Lone, et al. (2005) Local and systemic insulin resistance resulting from hepatic activation of IKK-beta and NF-kappaB. Nat Med 11: 183–190. [PubMed: 15685173]

122. Aguilar-Valles A, Inoue W, Rummel C, Luahesi GN (2015) Obesity, adipokines and neuroinflammation. Neuropharmacology 96: 124–134. [PubMed: 25582291]

123. Wada J, Makino H (2016) Innate immunity in diabetes and diabetic nephropathy. Nat Rev Nephrol 12: 13–26. [PubMed: 26568190]

124. McPhee JB, Schertzer JD (2015) Immunometabolism of obesity and diabetes: microbiota link compartmentalized immunity in the gut to metabolic tissue inflammation. Clin Sci (Lond) 129: 1083–1096. [PubMed: 26464517]

125. Cieslak M, Wojtczak A, Cieslak M (2015) Role of pro-inflammatory cytokines of pancreatic islets and prospects of elaboration of new methods for the diabetes treatment. Acta Biochim Pol 62: 15–21. [PubMed: 25781159]

126. Lumeng Carey N., Bodzin Jennifer L., Saltiel Alan R. (2007) Obesity induces a phenotypic switch in adipose tissue macrophage polarization. J Clin Invest 117: 175–184. [PubMed: 17200717]

127. Chawla A (2010) Control of macrophage activation and function by PPARs. Circ Res 106: 1559–1569. [PubMed: 20508200]

128. Arkan MC, Hevener AL, Greten FR, Maeda S, Li ZW, et al. (2005) IKK-beta links inflammation to obesity-induced insulin resistance. Nat Med 11: 191–198. [PubMed: 15685170]

129. MacDougald OA, Burant CF (2007) The rapidly expanding family of adipokines. Cell Metab 6: 159–161. [PubMed: 1776903]

130. Yun Sok Lee Pingping Li, Jin Young Huh In Jae Hwang, Lu Min, et al. (2011) Inflammation is necessary for long-term but not short-term high-fat diet-induced insulin resistance. Diabetes 60: 2474–2483. [PubMed: 21911747]

131. Martinez-Santibanez G, Cho KW, Lumeng CN (2014) Imaging white adipose tissue with confocal microscopy. Methods Enzymol 537: 17–30. [PubMed: 24480339]

132. Brestoff JR, Artis D (2015) Immune regulation of metabolic homeostasis in health and disease. Cell 161: 146–160. [PubMed: 25815992]

133. Wu Davina, Molofsky Ari B, Liang Hong-Erh, Ricard-Gonzalez Roberto R, Jouihan Hani A, et al. (2011) Eosinophils sustain adipose alternatively activated macrophages associated with glucose homeostasis. Science 332: 243–247. [PubMed: 21436399]

134. Zeyda M, Wernly B, Deymanets S, Kaun C, Hammerle M, et al. (2013) Severe obesity increases adipose tissue expression of interleukin-33 and its receptor ST2, both predominantly detectable in endothelial cells of human adipose tissue. Int J Obes (Lond) 37: 658–665. [PubMed: 22828942]

135. Molofsky Ari B., Jesse C Nussbaum, Liang Hong-Erh, Van Dyken Steven J, Cheng Laurence E, et al. (2013) Innate lymphoid type 2 cells sustain visceral adipose tissue eosinophils and alternatively activated macrophages. J Exp Med 210: 535–549. [PubMed: 23420878]

136. Hams E, Locksley RM, McKenzie AN, Fallon PG (2013) Cutting edge: IL-25 elicits innate lymphoid type 2 and type II NKT cells that regulate obesity in mice. J Immunol 191: 5349–5353. [PubMed: 24166975]

137. Huang Q, Niu Z, Tan J, Yang J, Liu Y, et al. (2015) IL-25 Elicits Innate Lymphoid Cells and Multipotent Progenitor Type 2 Cells That Reduce Renal Ischemic/Reperfusion Injury. J Am Soc Nephrol 26: 2199–2211. [PubMed: 25556172]

138. Lynch L, Nowak M, Varghese B, Clark J, Hogan AE, et al. (2012) Adipose tissue invariant NKT cells protect against diet-induced obesity and metabolic disorder through regulatory cytokine production. Immunity 37: 574–587. [PubMed: 22981538]
139. Carbone F, La Rocca C, Matarese G (2012) Immunological functions of leptin and adiponectin. Biochimie 94: 2082–2088. [PubMed: 22750129]

140. Deng Tuo, Lyon Christopher J, Minze Laurie J, Lin Jianxin, Zou Jia, et al. (2013) Class II major histocompatibility complex plays an essential role in obesity-induced adipose inflammation. Cell Metab 17: 411–422. [PubMed: 23473035]

141. Biswas SK, Mantovani A (2010) Macrophage plasticity and interaction with lymphocyte subsets: cancer as a paradigm. Nat Immunol 11: 889–896. [PubMed: 20856220]

142. Fujisaka Shiho, Usui Isao, Bukhari Agussalim, Ikutani Masashi, Oya Takeshi, et al. (2009) Regulatory mechanisms for adipose tissue M1 and M2 macrophages in diet-induced obese mice. Diabetes 58: 2574–2582. [PubMed: 19690061]

143. Feuerer Markus, Herrero Laura, Cipolletta Daniela, Naa Afia, Wong Jamie, et al. (2009) Lean, but not obese, fat is enriched for a unique population of regulatory T cells that affect metabolic parameters. Nat Med 15: 930–939. [PubMed: 19633656]

144. Liberato MV, Nascimento AS, Ayers SD, Lin JZ, Cvoro A, et al. (2012) Medium chain fatty acids are selective peroxisome proliferator activated receptor (PPAR) gamma activators and pan-PPAR partial agonists. PLoS One 7: e36297. [PubMed: 22649490]

145. van der Weerd K, Dik WA, Schrijver B, Schweitzer DH, Langerak AW, et al. (2012) Morbidly obese human subjects have increased peripheral blood CD4+ T cells with skewing toward a Treg and Th2-dominated phenotype. Diabetes 61: 401–408. [PubMed: 22228716]

146. Ilan Y, Maron R, Tukpah AM, Maioli TU, Murugaiyan G, et al. (2010) Induction of regulatory T cells decreases adipose inflammation and alleviates insulin resistance in ob/ob mice. Proc Natl Acad Sci U S A 107: 9765–9770. [PubMed: 20445103]

147. Deuliulis J, Shah Z, Shah N, Needleman B, Mikami D, et al. (2011) Visceral adipose inflammation in obesity is associated with critical alterations in regulatory cell numbers. PLoS One 6: e16376. [PubMed: 21298111]

148. Bapat SP, Myoung Suh J, Fang S, Liu S, Zhang Y, et al. (2015) Depletion of fat-resident Treg cells prevents age-associated insulin resistance. Nature 528: 137–141. [PubMed: 26580014]

149. Kolodin D, van Panhuys N, Li C, Magnuson AM, Cipolletta D, et al. (2015) Antigen- and cytokine-driven accumulation of regulatory T cells in visceral adipose tissue of lean mice. Cell Metab 21: 543–557. [PubMed: 25863247]

150. Vasanthakumar A, Moro K, Xin A, Liao Y, Gloury R, et al. (2015) The transcriptional regulators IRF4, BATF and IL-33 orchestrate development and maintenance of adipose tissue-resident regulatory T cells. Nature immunology 16: 276–285. [PubMed: 25599561]

151. Emerging Risk Factors Collaboration, Sarwar N, Gao P, Seshasai SR, Gobin R, et al. (2010) Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet 375: 2215–2222. [PubMed: 20609967]

152. Beckman JA, Creager MA, Libby P (2002) Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. JAMA 287: 2570–2581. [PubMed: 12020339]

153. Park M, Reynolds CF 3rd (2015) Depression among older adults with diabetes mellitus. Clin Geriatr Med 31: 117–137, ix. [PubMed: 25453305]

154. Schottker B, Brenner H, Koenig W, Muller H & Rothenbacher D (2013) Prognostic association of HbA1c and fasting plasma glucose with reduced kidney function in subjects with and without diabetes mellitus. Results from a population-based cohort study from Germany. Prev Med 57: 596–600. [PubMed: 23948106]

155. Kowall B, Rathmann W, Heier M, Giani G, Peters A, et al. (2011) Categories of glucose tolerance and continuous glycemic measures and mortality. Eur J Epidemiol 26: 637–645. [PubMed: 21785986]

156. Qato DM, Wilder J, Schum LP, Gillet V, Alexander GC (2016) Changes in Prescription and Over-the-Counter Medication and Dietary Supplement Use Among Older Adults in the United States, 2005 vs 2011. JAMA Intern Med 176: 473–482. [PubMed: 26998708]

157. Panza F, Frisardi V, Capurso C, Imbimbo BP, Vendemiale G, et al. (2010) Metabolic syndrome and cognitive impairment: current epidemiology and possible underlying mechanisms. J Alzheimers Dis 21: 691–724. [PubMed: 20571214]
158. Yaffe K, Blackwell T, Kanaya AM, Davidowitz N, Barrett-Connor E, et al. (2004) Diabetes, impaired fasting glucose, and development of cognitive impairment in older women. Neurology 63: 658–663. [PubMed: 15326238]

159. Benedict C, Brooks SJ, Kullberg J, Burgos J, Kempton MJ, et al. (2012) Impaired insulin sensitivity as indexed by the HOMA score is associated with deficits in verbal fluency and temporal lobe gray matter volume in the elderly. Diabetes Care 35: 488–494. [PubMed: 22301128]

160. Craft S, Asthana S, Cook DG, Baker LD, Cherrier M, et al. (2003) Insulin dose-response effects on memory and plasma amyloid precursor protein in Alzheimer’s disease: interactions with apolipoprotein E genotype. Psychoneuroendocrinology 28: 809–822. [PubMed: 12818666]

161. Rayasam GV, Tulasi VK, Sodhi R, Davis JA, Ray A (2009) Glycogen synthase kinase 3: more than a namesake. Br J Pharmacol 156: 885–898. [PubMed: 19366350]

162. Siervo M, Arnold R, Wells JC, Tagliabue A, Colantuoni A, et al. (2011) Intentional weight loss in overweight and obese individuals and cognitive function: a systematic review and meta-analysis. Obes Rev 12: 968–983. [PubMed: 21762426]

163. Gunstad J, Strain G, Devlin MJ, Wing R, Cohen RA, et al. (2011) Improved memory function 12 weeks after bariatric surgery. Surg Obes Relat Dis 7: 465–472. [PubMed: 21145295]

164. Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, Byington RP, Goff DC Jr, et al. (2008) Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 358: 2545–2559. [PubMed: 18539917]

165. Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, et al. (2009) Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 360: 129–139. [PubMed: 19092145]

166. Advance Collaborative Group, Patel A, MacMahon S, Chalmers J, Neal B, et al. (2008) Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 358: 2560–2572. [PubMed: 18539916]

167. American Diabetes Association (2008) Standards of medical care in diabetes—2008. Diabetes Care 31 Suppl 1: S12–54. [PubMed: 18165335]

168. Kirkman MS, Briscoe VI, Clark N, Florez H, Haas LB, et al. (2012) Diabetes in older adults: a consensus report. J Am Geriatr Soc 60: 2342–2356. [PubMed: 23106132]

169. Kirkman MS, Briscoe VI, Clark N, Florez H, Haas LB, et al. (2012) Diabetes in older adults. Diabetes Care 35: 2650–2664. [PubMed: 23100048]

170. Yehuda AB, Zinger A, Durso S (2014) The older patient with diabetes: a practical approach. Diabetes Metab Res Rev 30: 88–95. [PubMed: 24123811]

171. Selvin E, Coresh J, Brancati FL (2006) The burden and treatment of diabetes in elderly individuals in the u.s. Diabetes Care 29: 2415–2419. [PubMed: 17065677]

172. Wang Y, Qin MZ, Liu Q, Liu Q & Chang ZW (2010) Clinical analysis of elderly patients with elderly-onset type 2 diabetes mellitus in China: assessment of appropriate therapy. J Int Med Res 38: 1134–1141. [PubMed: 20819452]

173. Twito O, Ahron E, Jaffe A, Afek S, Cohen E, et al. (2013) New-onset diabetes in elderly subjects: association between HbA1c levels, mortality, and coronary revascularization. Diabetes Care 36: 3425–3429. [PubMed: 23877985]

174. Adler GK, Bonyhay I, Failing H, Waring E, Dotson S, et al. (2009) Antecedent hypoglycemia impairs autonomic cardiovascular function: implications for rigorous glycemic control. Diabetes 58: 360–366. [PubMed: 19056608]

175. Whitmer RA, Karter AJ, Yaffe K, Quesenberry CP Jr, Selhy JV (2009) Hypoglycemic episodes and risk of dementia in older patients with type 2 diabetes mellitus. JAMA 301: 1565–1572. [PubMed: 19366776]

176. Ismail-Beigi F, Moghissi E, Tiktin M, Hirsch IB, Inzucchi SE, et al. (2011) Individualizing glycemic targets in type 2 diabetes mellitus: implications of recent clinical trials. Ann Intern Med 154: 554–559. [PubMed: 21502652]

177. (1995) United Kingdom Prospective Diabetes Study (UKPDS). 13: Relative efficacy of randomly allocated diet, sulphonylurea, insulin, or metformin in patients with newly diagnosed non-insulin dependent diabetes followed for three years. BMJ 310: 83–88. [PubMed: 7833731]
178. Norris SL, Zhang X, Avenell A, Gregg E, Bowman B, et al. (2004) Long-term effectiveness of lifestyle and behavioral weight loss interventions in adults with type 2 diabetes: a meta-analysis. Am J Med 117: 762–774. [PubMed: 15541326]

179. Look AHEAD Research Group, Wing RR (2010) Long-term effects of a lifestyle intervention on weight and cardiovascular risk factors in individuals with type 2 diabetes mellitus: four-year results of the Look AHEAD trial. Arch Intern Med 170: 1566–1575. [PubMed: 20876408]

180. Diabetes Prevention Program Research Group, Knowler WC, Fowler SE, Hamman RF, Christophi CA, et al. (2009) 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. Lancet 374: 1677–1686. [PubMed: 19878986]

181. Diabetes Prevention Program (DPP) Research Group (2002) The Diabetes Prevention Program (DPP): description of lifestyle intervention. Diabetes Care 25: 2165–2171. [PubMed: 12453955]

182. Miller CK, Edwards L, Kissling G, Sanville L (2002) Nutrition education improves metabolic outcomes among older adults with diabetes mellitus: results from a randomized controlled trial. Prev med 34: 252–259. [PubMed: 11817922]

183. de Souza RJ, Swain JF, Appel LJ, Sacks FM (2008) Alternatives for macronutrient intake and chronic disease: a comparison of the OmniHeart diets with popular diets and with dietary recommendations. Am J Clin Nutr 88: 1–11. [PubMed: 18614716]

184. Larsen RN, Mann NJ, Maclean E, Shaw JE (2011) The effect of high-protein, low-carbohydrate diets in the treatment of type 2 diabetes: a 12 month randomised controlled trial. Diabetologia 54: 731–740. [PubMed: 21246185]

185. Gannon MC, Nuttall FQ, Saeed A, Jordan K, Hoover H (2003) An increase in dietary protein improves the blood glucose response in persons with type 2 diabetes. Am J Clin Nutr 78: 734–741. [PubMed: 14522731]

186. Samaha FF, Iqbal N, Seshadri P, Chicano KL, Daily DA, et al. (2003) A low-carbohydrate diet compared with a low-fat diet in severe obesity. N Engl J Med 348: 2074–2081. [PubMed: 12761364]

187. Parker B, Noakes M, Luscombe N, Clifton P (2002) Effect of a high-protein, high-monounsaturated fat weight loss diet on glycemic control and lipid levels in type 2 diabetes. Diabetes Care 25: 425–430. [PubMed: 11874925]

188. Djoussé L, Kamineni A, Nelson TL, Carnethon M, Mozaffarian D, et al. (2010) Egg consumption and risk of type 2 diabetes in older adults. Am J Clin Nutr 92: 422–427. [PubMed: 20534749]

189. Boden G, Sargrad K, Homko C, Mozzoli M, Stein TP (2005) Effect of a low-carbohydrate diet on appetite, blood glucose levels, and insulin resistance in obese patients with type 2 diabetes. Ann Intern Med 142: 403–411. [PubMed: 15767618]

190. Nielsen JV, Joensson EA (2008) Low-carbohydrate diet in type 2 diabetes: stable improvement of bodyweight and glycemic control during 44 months follow-up. Nutr metab (Lond) 5: 14. [PubMed: 18495047]

191. Evans Ellen M, Mojtahedi Mina C, Thorpe Matthew P, Valentine Rudy J, Kris-Etherton Penny M, et al. (2012) Effects of protein intake and gender on body composition changes: a randomized clinical weight loss trial. Nutrition & metabolism 9: 55. [PubMed: 22691622]

192. Layman DK, Boileau RA, Erickson DJ, Painter JE, Shiue H, et al. (2003) A reduced ratio of dietary carbohydrate to protein improves body composition and blood lipid profiles during weight loss in adult women. J Nutr 133: 411–417. [PubMed: 12566476]

193. Layman DK, Evans EM, Erickson D, Seyler J, Weber J, et al. (2009) A moderate-protein diet produces sustained weight loss and long-term changes in body composition and blood lipids in obese adults. J Nutr 139: 514–521. [PubMed: 19158228]

194. Lasker DA, Evans EM, Layman DK (2008) Moderate carbohydrate, moderate protein weight loss diet reduces cardiovascular disease risk compared to high carbohydrate, low protein diet in obese adults: A randomized clinical trial. Nutr metab (Lond) 5: 30. [PubMed: 18990242]

195. Layman DK, Shiue H, Sather C, Erickson DJ, Baum J (2003) Increased dietary protein modifies glucose and insulin homeostasis in adult women during weight loss. J Nutr 133: 405–410. [PubMed: 12566475]

196. Kitabchi AE, McDaniel KA, Wan JY, Tylavsky FA, Jacovino CA, et al. (2013) Effects of High-Protein Versus High-Carbohydrate Diets on Markers of beta-Cell Function, Oxidative Stress,
Lipid Peroxidation, Proinflammatory Cytokines, and Adipokines in Obese, Premenopausal Women Without Diabetes: A randomized controlled trial. Diabetes Care 36: 1919–1925. [PubMed: 23404297]

197. van Loon LJ, Kruijff M, Menheere PP, Wagenmakers AJ, Saris WH, et al. (2003) Amino acid ingestion strongly enhances insulin secretion in patients with long-term type 2 diabetes. Diabetes Care 26: 625–630. [PubMed: 12610012]

198. Westman EC, Yancy WS Jr, Mavropoulos JC, Marquart M, McDuffie JR (2008) The effect of a low-carbohydrate, ketogenic diet versus a lowglycemic index diet on glycemic control in type 2 diabetes mellitus. Nutr metab (Lond) 5: 36. [PubMed: 19099589]

199. Pedersen AN, Kondrup J, Borsheim E (2013) Health effects of protein intake in healthy adults: a systematic literature review. Food Nutr Res 57.

200. Knight EL, Stampfer MJ, Hankinson SE, Spiegelman D, Curhan GC (2003) The impact of protein intake on renal function decline in women with normal renal function or mild renal insufficiency. Ann Intern Med 138: 460–467. [PubMed: 12639078]

201. Toeller M, Buyken A, Heitkamp G, Brämswig S, Mann J, et al. (1997) Protein intake and urinary albumin excretion rates in the EURODIAB IDDM Complications Study. Diabetologia 40: 1219–1226. [PubMed: 9349605]

202. Jesudason DR, Pedersen E, Clifton PM (2013) Weight-loss diets in people with type 2 diabetes and renal disease: a randomized controlled trial of the effect of different dietary protein amounts. Am J Clin Nutr 98: 494–501. [PubMed: 23719550]

203. Wycherley TP, Noakes M, Clifton PM, Cleaugh X, Keogh JB, et al. (2010) A high-protein diet with resistance exercise training improves weight loss and body composition in obese patients with type 2 diabetes. Diabetes Care 33: 969–976. [PubMed: 20150293]

204. Sargrad KR, Homko C, Mozzoli M, Boden G (2005) Effect of high protein vs high carbohydrate intake on insulin sensitivity, body weight, hemoglobin A1c, and blood pressure in patients with type 2 diabetes mellitus. J Am Diet Assoc 105: 573–580. [PubMed: 15800559]

205. Byberg L, Hakan Melhus, Rolf Gedebo, Johan Sundström, Anders Ahlbom, et al. (2009) Total mortality after changes in leisure time physical activity in 50 year old men: 35 year follow-up of population based cohort. BMJ 338.

206. Sun Q, Townsend MK, Okereke OI, Franco OH, Hu FB, et al. (2010) Physical activity at midlife in relation to successful survival in women at age 70 years or older. Arch Intern Med 170: 194–201. [PubMed: 20101015]

207. Sofi F, Valecchi D, Bacci D, Abbate R, Gensini GF, et al. (2011) Physical activity and risk of cognitive decline: a meta-analysis of prospective studies. J Intern Med 269: 107–117. [PubMed: 20831630]

208. Paterson DH, Warburton DE (2010) Physical activity and functional limitations in older adults: a systematic review related to Canada’s Physical Activity Guidelines. The international journal of behavioral nutrition and physical activity 7: 38. [PubMed: 20459782]

209. Smith PJ, Blumenthal JA, Hoffman BM, Cooper H, Strauman TA, et al. (2010) Aerobic exercise and neurocognitive performance: a meta-analytic review of randomized controlled trials. Psychosomatic medicine 72: 239–252. [PubMed: 20223924]

210. Yaguez L, Shaw KN, Morris R, Matthews D (2011) The effects on cognitive functions of a movement-based intervention in patients with Alzheimer’s type dementia: a pilot study. Int J Geriatr Psychiatry 26: 173–181. [PubMed: 20876665]

211. Kemoun G, Thibaud N, Roumagne N, Carette P, Albinet C, et al. (2010) Effects of a physical training programme on cognitive function and walking efficiency in elderly persons with dementia. Dementia and geriatric cognitive disorders 29: 109–114. [PubMed: 20150731]

212. Pasinetti GM, Wang J, Porter S, Ho L (2011) Caloric intake, dietary lifestyles, macronutrient composition, and alzheimer’s disease dementia. International journal of Alzheimer’s disease 2011.

213. (2015) Centers for Disease Control, C.

214. (2015) American Diabetes Association, A.

215. Neumiller JJ, Setter SM (2009) Pharmacologic management of the older patient with type 2 diabetes mellitus. Am J Geriatr Pharmacother 7: 324–342. [PubMed: 20129254]
216. Abdelhafiz AH, Rodriguez-Manas L, Morley JE, Sinclair AJ (2015) Hypoglycemia in older people - a less well recognized risk factor for frailty. Aging Dis 6: 156–167. [PubMed: 25821643]

217. Bruce DG, Davis WA, Casey GP, Starkstein SE, Clarnette RM, et al. (2008) Predictors of cognitive impairment and dementia in older people with diabetes. Diabetologia 51: 241–248. [PubMed: 18060658]

218. Goto A, Arah OA, Goto M, Terauchi Y, Noda M (2013) Severe hypoglycaemia and cardiovascular disease: systematic review and meta-analysis with bias analysis. BMJ 347.

219. (2015) Standards of medical care in diabetes-2015: summary of revisions. Diabetes Care 38.

220. Vijoen Adie, Claire L Meek Roger Gadsby, Viljoen Sumarie, Langerman Haya, et al. (2013) The tolerability and safety of DPP-4 inhibitors for the treatment of older people with type 2 diabetes mellitus: an observational study. The British Journal of Diabetes and Vascular Disease 13: 187–191.

221. Schwartz SL (2010) Treatment of elderly patients with type 2 diabetes mellitus: a systematic review of the benefits and risks of dipeptidyl peptidase-4 inhibitors. Am J Geriatr Pharmacother 8: 405–418. [PubMed: 21335294]

222. Herman WH, Ilag LL, Johnson SL, Martin CL, Sinding J, et al. (2005) A clinical trial of continuous subcutaneous insulin infusion versus multiple daily injections in older adults with type 2 diabetes. Diabetes Care 28: 1568–1573. [PubMed: 15983302]

223. Lee P, Chang A, Blaum C, Vlajnic A, Gao L, et al. (2012) Comparison of safety and efficacy of insulin glargine and neutral protamine hagedorn insulin in older adults with type 2 diabetes mellitus: results from a pooled analysis. J Am Geriatr Soc 60: 51–59. [PubMed: 22239291]

224. Buchwald H, Estok R, Fahrbach K, Banel D, Jensen MD, et al. (2009) Weight and type 2 diabetes after bariatric surgery: systematic review and meta-analysis. Am J Med 122: 248–256 e245. [PubMed: 19272486]

225. Dixon JB, Straznicky NE, Lambert EA, Schlaich MP, Lambert GW (2011) Surgical approaches to the treatment of obesity. Nat Rev Gastroenterol Hepatol 8: 429–437. [PubMed: 21727936]

226. (1991) NIH conference. Gastrointestinal surgery for severe obesity. Consensus Development Conference Panel. Ann Intern Med 115: 956–961. [PubMed: 1952493]

227. Fried M, Hainer V, Basdevant A, Buchwald H, Deitel M, et al. (2007) Interdisciplinary European guidelines for surgery for severe (morbid) obesity. Obes Surg 17: 260–270. [PubMed: 17476884]

228. Sugerman Harvey J, DeMaria Eric J, Kellum John M, Sugerman Elizabeth L, Meador Jill G, et al. (2004) Effects of bariatric surgery in older patients. Ann Surg 240: 243–247. [PubMed: 15273547]

229. Sosa JL, Pombo H, Pallavicini H, Ruiz-Rodriguez M (2004) Laparoscopic gastric bypass beyond age 60. Obes Surg 14: 1398–1401. [PubMed: 15603658]

230. St Peter SD, Craft RO, Tiede JL, Swain JM (2005) Impact of advanced age on weight loss and health benefits after laparoscopic gastric bypass. Arch Surg 140: 165–168. [PubMed: 15723998]

231. Varela JE, Wilson SE, Nguyen NT (2006) Outcomes of bariatric surgery in the elderly. Am Surg 72: 865–869. [PubMed: 17058723]

232. van Rutte PW, Smulders JF, de Zoete JP, Nienhuijs SW (2013) Sleeve gastrectomy in older obese patients. Surg Endosc 27: 2014–2019. [PubMed: 23344504]

233. Soto FC, Gari V, de la Garza, Szomstein S, Rosenthal RJ (2013) Sleeve gastrectomy in the elderly: a safe and effective procedure with minimal morbidity and mortality. Obes Surg 23: 1445–1449. [PubMed: 23733390]

234. Huang CK, Shabirir A, Lo CH, Tai CM, Chen YS, et al. (2011) Laparoscopic Roux-en-Y gastric bypass for the treatment of type II diabetes mellitus in Chinese patients with body mass index of 25–35. Obes Surg 21: 1344–1349. [PubMed: 21479764]

235. Chow A, Switzer NJ, Gill RS, Dang J, Ko YM, et al. (2016) Roux-en-Y Gastric Bypass in the Elderly: a Systematic Review. Obes Surg 26: 626–630. [PubMed: 26667164]

236. Schwartz AV, Sellmeyer DE, Vittinghoff E, Palermo L, Lecka-Czernik B, et al. (2006) Thiazolidinedione use and bone loss in older diabetic adults. J Clin Endocrinol Metab 91: 3349–3354. [PubMed: 16608888]
237. Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, et al. (2003) Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial. JAMA 290: 486–494. [PubMed: 12876091]

238. Zinman Bernard, Wanner Christoph, John M Lachin David Fitchett, Bluhmki Erich, et al. (2015) Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med 373: 2117–2128. [PubMed: 26378978]

239. Zehe J, Platt D (2002) The aging liver: structural and functional changes and their consequences for drug treatment in old age. Gerontology 48: 121–127. [PubMed: 11961363]

240. Zehe J (2001) The aging liver: consequences for drug treatment in old age. Archives of gerontology and geriatrics 32: 255–263. [PubMed: 11395171]

241. Cnop M, Igoillo-Esteve M, Hughes SJ, Walker JN, Cnop I, et al. (2011) Longevity of human islet alpha- and beta-cells. Diabetes Obes Metab 13: 39–46. [PubMed: 21824255]

242. Detlefsen S, Sipos B, Feyerabend B, Klöppel G (2005) Pancreatic fibrosis associated with age and ductal papillary hyperplasia. Virchows Arch 447: 800–805. [PubMed: 16021508]

243. Phillips CM, Perry IJ (2013) Does inflammation determine metabolic health status in obese and nonobese adults? J Clin Endocrinol Metab 98: E1610–1619. [PubMed: 23979951]

244. Chen YS, Torroni A, Excoffier L, Santachiara-Benerecetti AS, Wallace DC (1995) Analysis of mtDNA variation in African populations reveals the most ancient of all human continent-specific haplogroups. Am J Hum Genet 57: 133–149. [PubMed: 7611282]

245. Dai FF, Bhattacharjee A, Liu Y, Batchuluun B, Zhang M, et al. (2015) A novel GLP-1 receptor interacting protein ATP6ap2 regulates insulin secretion in pancreatic beta cells. J Biol Chem 290: 25045–25061. [PubMed: 26272612]

246. Cheng CY, Reich D, Haiman CA, Tandon A, Patterson N, et al. (2012) African ancestry and its correlation to type 2 diabetes in African Americans: a genetic admixture analysis in three U.S. population cohorts. PLoS One 7: e32840. [PubMed: 22438844]

247. Brady AO, Straight CR, Evans EM (2014) Body composition, muscle capacity, and physical function in older adults: an integrated conceptual model. J Aging Phys Act 22: 441–452. [PubMed: 23945551]

248. Van Gammeren D, Damrauer JS, Jackman RW, Kandarian SC (2009) The IkappaB kinases IKKalpha and IKKbeta are necessary and sufficient for skeletal muscle atrophy. FASEB journal : official publication of the Federation of American Societies for Experimental Biology 23: 362–370. [PubMed: 18827022]

249. Gren Peter J (1995) Reversible jump Markov Chain Monte Carlo computation and Bayesian model determination. Biometrika 1: 711–732.

250. Beiroa D, Imbernon M, Gallego R, Senra A, Herranz D, et al. (2014) GLP-1 agonism stimulates brown adipose tissue thermogenesis and browning through hypothalamic AMPK. Diabetes 63: 3346–3358. [PubMed: 24917578]

251. Deng T, Lyon CJ, Bergin S, Caligiuri MA, Hsueh WA (2016) Obesity, Inflammation, and Cancer. Annu Rev Pathol 11: 421–449. [PubMed: 27193454]
Figure 1:
Changes in hepatic, skeletal muscle, pancreas and adipose tissue during the aging process.
Figure 2:
Inflammatory regulation in lean and obese adipose tissue. Recent animal studies highlight the importance of several immune cells in maintaining lean adipose tissue. Lean adipose tissue in rodents is populated predominantly by alternatively-activated macrophages (AAMacs), eosinophils, type 2 innate lymphoid cells (ILC2s), invariant natural killer T (iNKT) cells, and CD4+ helper Type 2 (Th2) and regulatory T (T_{reg}) cells that contribute to a Type 2 anti-inflammatory axis. In obesity, the immunologic environment of adipose tissue shifts from a cytokine-associated Type 2 anti-inflammatory to a Type 1 pro-inflammatory environment populated predominantly by M1 macrophages, CD4+ helper Type 1 (Th1) cells, and CD8+ cells. In this context, the normal architecture, energy storage, and endocrine activities of adipocytes are changed. Abbreviations: Sfrp5: Secreted frizzled-related protein 5.

Figure reproduced with permission from Annual Reviews of Pathology [251].
Table 1:

Consensus framework for considering treatment goals for glycemia in older adults with diabetes. Adapted with permission from American Diabetes Association Older Adults. Section 10. In Standards of Medical Care in Diabetes - 2016. Diabetes Care 2016; 39 (Suppl. 1): S81–S85.

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

* Coexisting chronic illnesses are conditions serious enough to require medications or lifestyle management and may include arthritis, cancer, congestive heart failure, depression, emphysema, falls, hypertension, incontinence, stage 3 or worse chronic kidney disease, myocardial infarction, and stroke. By “multiple,” the authors mean at least three, but many patients may have five or more.

** The presence of a single end-stage chronic illness, such as stage 3–4 congestive heart failure or oxygen-dependent lung disease, chronic kidney disease requiring dialysis, or uncontrolled metastatic cancer, may cause significant symptoms or impairment of functional status and significantly reduce life expectancy. Abbreviations: LTC: Long-term care; ADL: Activities of Daily Living.
Table 2:
Non-Insulin pharmacotherapy options for Type 2 Diabetes Mellitus in the elderly. Listed medications are limited to those commercially available in the U.S. at time of manuscript submission.

| Type of Medication (Generic names) | Primary Mechanism of Action | Benefits in the Elderly | Concerns in the Elderly |
|------------------------------------|-----------------------------|-------------------------|-------------------------|
| Biguanide (metformin)              | Reduce Hepatic Glucose Production | • High Efficacy<br>• Low cost<br>• Modest Weight Loss<br>• Low Risk of Hypoglycemia | • Caution with Renal Disease, Heart Failure, Liver Disease Due to Risk of Lactic Acidosis |
| Sulfonylureas (glicipiride, glyburide, glipizide) | Insulin Secretagogue | • High efficacy<br>• Low cost | • Hypoglycemic risk with Advancing Age<br>• Caution in Liver Disease |
| Meglitinides (nateglinide, repaglinide) | Insulin Secretagogue | • Lower Risk of Hypoglycemia Compared to Sulfonylureas | • Hypoglycemic risk with advancing age<br>• Frequent administration<br>• Caution in Liver Disease |
| Glucagon-like peptide-1 Agonists (liraglutide, exenatide, exenatide XR, albiglutide, dulaglutide) | Insulin Secretagogue Increase Incretin Effect | • Low risk for Hypoglycemia<br>• Weight loss | • Gastroparesis<br>• Pancreatitis<br>• Injectable therapy |
| Dipeptidyl-peptidase IV Inhibitors (sitagliptin, linagliptin, alogliptin, saxagliptin) | Insulin Secretagogue Increase Incretin Effect | • Low Risk for Hypoglycemia; Weight neutral | • Pancreatitis<br>• Modest Reduction in HgBA1c<br>• Expensive |
| Thiazolidinediones (pioglitazone, rosiglitazone) | Increase Insulin Sensitivity | • Low risk of hypoglycemia | Lower BMD and increase fracture risk<sup>249</sup><br>Caution in Renal and Liver disease, Heart Failure<br>Weight gain and Fluid retention |
| Alpha-glucosidase inhibitors (acarbose, miglitol) | Reduce Carbohydrate Absorption | • Possible reduction in Cardiovascular events [237]. | • Caution in Renal, Liver Disease and Malabsorptive Syndromes<br>• Gastrointestinal side effects common |
| Sodium-glucose co-transporter-2 Inhibitors (empagliflozin, canagliflozin, dapagliflozin) | Increase Urinary Glucose Excretion | • Possible Cardiovascular Benefit [238].<br>• Reduction in blood pressure | • Increased risk of UTI and yeast infection<br>• Dehydration common side effect<br>• Increased urinary frequency |
| Type of Medication (Generic names) | Primary Mechanism of Action | Benefits in the Elderly | Concerns in the Elderly |
|-----------------------------------|-----------------------------|------------------------|------------------------|
| Amylin replacement (pramlintide)  | Amylin Replacement           | • Weight Loss          | • Limited efficacy with chronic kidney disease  
|                                   |                             |                        | • Expensive             
|                                   |                             |                        | • Gastro paresis         
|                                   |                             |                        | • Multiple daily injections 
|                                   |                             |                        | • Modest HgBA1c reduction |