HHS Public Access

Author manuscript

J Geriatr Med Gerontol. Author manuscript; available in PMC 2019 November 05.

Published in final edited form as:

J Geriatr Med Gerontol. 2016 ; 2(2): . doi:10.23937/2469-5858/1510014.

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

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Author Contributions

DB wrote the manuscript; **WH** reviewed/edited the manuscript.

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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 cardio metabolic 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]. Most importantly, further studies on the impact of ethnicity on diabetic treatment therapeutics and detailed pharmacogenetic studies are needed, as "one size" may not fit all in diabetes management.

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, [60] and increased use of medications that increase hyperglycemic propensity [61,62]. 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 [6], 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 macro vascular and micro vascular 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

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_h2) and regulatory T (T_{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_h2s, T_{regs}, and AAMacs. Accordingly, eosinophildeficiency 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, [135] 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 (TNFα) by innate immune cells, and directly increases CD4+ T_h1 polarization and inhibits T_{reg} proliferation. Both leptin and MHCII expression promote T_h1 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_h2 and T_{reg} cells [141].

Emerging evidence highlights the importance of T_{regs} in defining the immunologic milieu of lean and obese AT. In the lean state, the stability of T_{regs} 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_{reg} abundance

[139]. Surprisingly, T_{regs} 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 T_{regs} also regulate systemic insulin action and strongly inhibit pro-inflammatory responses of other T cell subtypes. Insulin-sensitizing PPARγ ligands increase adipose T_{reg} content, while T_{reg}-specific PPARγ deficiency impairs ligand-induced insulin sensitivity [144]. Adoptive transfer of T_{regs} to obese, insulin-resistant mice improves insulin action, underscoring the role of T_{regs} in insulin sensitivity [145]. In fact, we found remarkably high T_{reg} 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 T_{reg} abundance and function [140]. In humans we found not only that adipocyte MHCII up-regulation occurs in obesity [140], but expression of adipose tissue T_{reg} markers decrease, and expression of T_h1 markers and IFNγ increases [145–147]. Of relevance to the aging process, the VAT T_{reg} 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 T_{regs} are protected against age-associated insulin resistance [148]. If confirmed, the decrease in T_{regs} may be due to reduced IL-33 [149]. Recently, IL-33 was identified as an indispensable factor for the development and maintenance of VAT T_{regs}, since genetic ablation of IL-33 or its receptor severely reduces adipose T_{reg} abundance [150]. IL-33 thus has important actions on both T_{regs} 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 T_{regs} 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 nonpharmacological 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.

Acknowledgements

This study was supported by grants from the American Diabetes Association 1–16-ICTS-049 and the National Institutes of Health KL2 Scholar Award KL2TR001068.

Sources of Support

This study was supported by grants from the American Diabetes Association 1–16-ICTS-049 and the National Institutes of Health KL2 Scholar Award.

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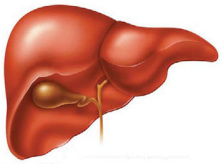
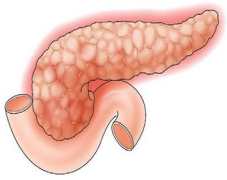


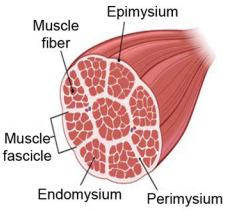
Changes to Liver

- Reduction in blood supply of ~1% per year [239]
- Decrease in number of liver cells and elasticity [239]
- Reduced capacity for metabolic function and detoxification [240]
- Possible decline in hepatic insulin sensitivity (ability to suppress glucose production) [72,89,91]

Changes to Pancreas

- Increase lipofuscin and adipose tissue [241]
- Duct hyperplasia [242]
- Disorderly insulin release, decrease in insulin pulse amplitudes and decreased response to glucose oscillations as well as alterations in insulin clearance [97]
- Reduction in β-cell mass and proliferation [94-96].
- Possible decline in β-cell function [97]





Changes to Skeletal Muscle

- Muscle fibers shrink [243]
- Decrease fast twitch fibers [244]
- Increase lipofuscin and adipose tissue [245]
- Progressive decline in muscle mass, quality, and strength [243,246]
- Possible decline in glucose uptake [73]

Changes to Adipose Tissue

- Increase in total body fat percentage [247]
- Increase in pro-inflammatory adipokine/cytokine expression [118,119,248]
- Increase in proinflammatory macrophages and crown-like structures [114,126,131]
- Possible decrease in T_H1/T_H2+Treg [249]
- Possible decline in Treg abundance [148,250]

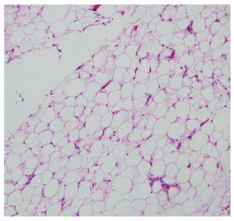


Figure 1:
Changes in hepatic, skeletal muscle, pancreas and adipose tissue during the aging process.

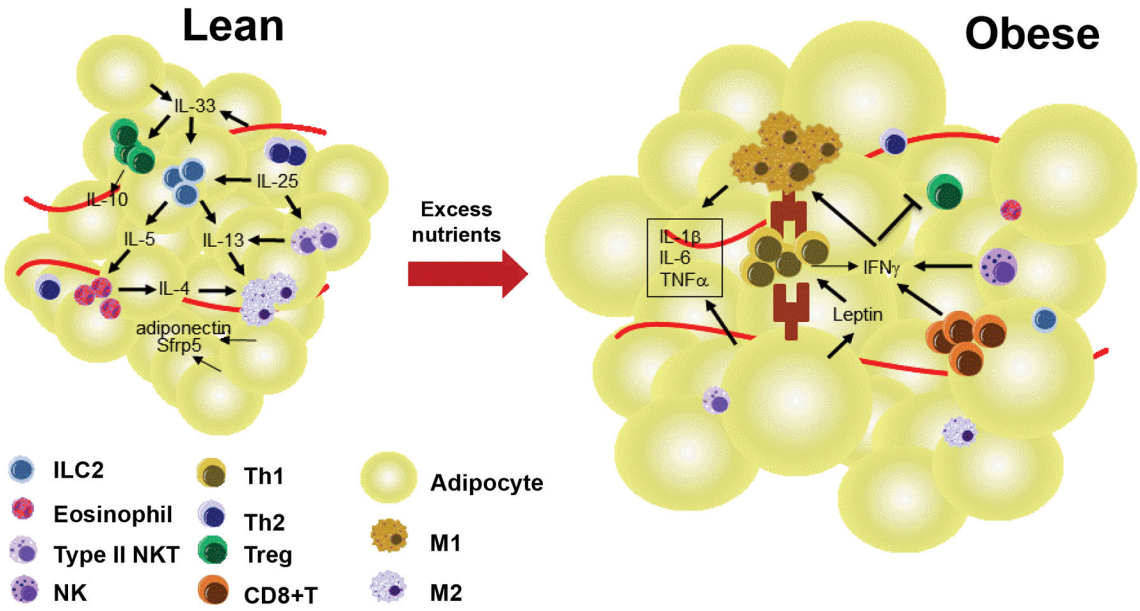


Figure 2:

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 (T_h2) 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 (T_h1) 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.

J Geriatr Med Gerontol. Author manuscript; available in PMC 2019 November 05.

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 • Low cost • Modest Weight Loss • Low Risk of Hypoglycemia	• Caution with Renal Disease, Heart Failure, Liver Disease Due to Risk of Lactic Acidosis
Sulfonylureas (glimepiride, glyburide, glipizide)	Insulin Secretagogue	• High efficacy • Low cost	• Hypoglycemic risk with Advancing Age • Caution in Liver Disease
Meglitinides (nateglinide, repaglinide)	Insulin Secretagogue	• Lower Risk of Hypoglycemia Compared to Sulfonylureas	• Hypoglycemic risk with advancing age • Frequent administration • Caution in Liver Disease
Glucagon-like peptide-1 Agonists (liraglutide, exenatide, exenatide XR, albiglutide, dulaglutide)	Insulin Secretagogue Increase Incretin Effect	• Low risk for Hypoglycemia • Weight loss	• Gastroparesis • Pancreatitis • Injectable therapy
Dipeptidyl-peptidase IV Inhibitors (sitagliptin, linagliptin, alogliptin, saxagliptin)	Insulin Secretagogue Increase Incretin Effect	• Low Risk for Hypoglycemia; Weight neutral	• Pancreatitis • Modest Reduction in HgBA1c • Expensive
Thiazolidinediones (pioglitazone, rosiglitazone)	Increase Insulin Sensitivity	• Low risk of hypoglycemia	Lower BMD and increase fracture risk[249] Caution in Renal and Liver disease, Heart Failure 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 • Gastrointestinal side effects common
Sodium-glucose co-transporter-2 Inhibitors (empagliflozm, canagliflozin, dapagliflozin)	Increase Urinary Glucose Excretion	• Possible Cardiovascular Benefit [238]. • Reduction in blood pressure	• Increased risk of UTI and yeast infection • Dehydration common side effect • Increased urinary frequency

Type of Medication (Generic names)	Primary Mechanism of Action	Benefits in the Elderly	Concerns in the Elderly
			• Limited efficacy with chronic kidney disease • Expensive
Amylin replacement (pramlintide)	Amylin Replacement	• Weight Loss	• Gastro paresis • Multiple daily injections • Modest HgBA1c reduction