

The Common Disease Trajectories: Are They Relevant to Guide Care as Older People with Diabetes Progress towards their End of Life?

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Abbreviations ACD-Advance Care Directive; BMI -Body Mass Index; EOL-End of Life;

GLM-Glucose Lowering Medicine; GSF-Gold Standards Framework; RRT-Rapid Response Team sometimes called Medical Emergency Team (MET); T2DM-Type 2 diabetes; T1DM-Type 1 diabetes; WHO-World Health Organization

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Abstract

The aim of the paper is to provide a brief overview of diabetes, its associated complications and related morbidity and mortality to highlight the importance of proactively discussing and planning for palliative and end of life care with older people. It suggests palliative and end of life care are essential components of quality diabetes management. Palliative care is no longer only associated with terminal cancer care in hospices: it is also recommended for other life limiting illnesses, including diabetes. Palliative and end of life care are defined, and the relationship among diabetes, the four health trajectories and end of life care is outlined. Strategies that can be used to help people maintain quality of life, dignity and autonomy are suggested for each trajectory. These strategies include health professionals having timely, meaningful conversations about palliative and end of life care with older people with diabetes and their families.

Introduction

Diabetes is a chronic, progressive disease that affects quality of life, life transitions and life expectancy. Unless normalizing the underlying metabolic derangements early in the course of the disease can prevent or limit and associated complications and other comorbidities. This in turn improves life expectancy e associated risk of death can be reduced by implementing quality diabetes care [1]. Diabetes has a predicted heritability between 30% and 70% [2]. Prediabetes, an intermediate state between normal and diabetic blood glucose level, can be present for long periods before diabetes becomes overt and may not produce symptoms [3].

Dysglycaemia is prevalent and often undetected in people with treated hypertension and/or dyslipidaemia [4]. Such people should be proactively assessed for diabetes because long-standing dysglycaemia and hyperglycemia (high HbA1c) contributes to the development of inflammation and, oxidative stress, which, reduced beta cell mass and function and lead to, glucose toxicity, which and impaired insulin release that contributes to tissue and organ damage [5,6]. High HbA1c is associated with increased risk of morbidity and mortality [6]. Significantly, progressive increase in hyperglycemia, even within the normal range, occurs relatively late in the evolution of diabetes and hyperglycemia is associated with altered protein and lipid metabolism [7]. Glucose variability as well as hyperglycemia contributes to oxidative damage and complications such as cardiovascular disease, which is a leading cause of diabetes-related death [6-8].

Significant progress has been made towards understanding the complex genetic basis for type 2 diabetes (T2DM) that will improve treatment and disease predictability in the future [2]. Type-1 diabetes (T1DM) is an autoimmune disease of increasing prevalence usually presents before age 40. People with T1DM survive to older age. CT1DM can be first diagnosed in older age but is rare [9]. Research suggests environmental triggers interact with specific genes, especially those on the HLA 11 region of 6p2, which contains genes involved in adaptive immune function [10].

Usual management of T1DM and T2DM consists of a healthy diet, low in saturated fat, salt and alcohol, regular physical activity, stress management, not smoking and adequate sleep. Self-care education, and regularly monitoring blood glucose, HbA1c, lipids and complication status provide self-report and physiological information about the effectiveness of management strategies. T1DM, including older people, require insulin from diagnosis. Some people with T2DM can be managed with weight loss, a balanced diet and exercise. Many usually require oral or injectable other Glucose Lowering Medicines (GLM) over time. Most eventually need insulin because T2DM is associated with progressive loss of beta cell function and reduced insulin production [3,6].

Usual diabetes management is not the focus of this paper: some guidelines that describe usual diabetes management are listed in table 1. Care must be personalized to the individual and consider

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Table 1: Commonly used guidelines that describe usual diabetes care.

http://www.diabetes.org/newsroom/press-releases/2017/american-diabetes-association-2018-release-standards-of-medical-care-in-diabetes.html
Diabetes Australia.
Diabetes UK (2012) Diabetes and end of life care: clinical care recommendations.
International Diabetes Federation Global Guideline for Managing Older People with Diabetes.
Scottish Intercollegiate Guidelines Network.
American Geriatrics Society. Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. <i>J Am Geriatr Soc.</i> 2015; 63: 2227-2246.
Gallagher, O'Connor M, O'Mahony D. Prevention of potentially inappropriate prescribing for elderly patients: A randomised controlled trial using STOPP/START criteria. <i>Clin Pharmacol Ther.</i> 2011; 89: 854-854.
Dunning T, Savage S, Duggan N, Martin P. <i>Guidelines for Managing Diabetes at the End of Life.</i> Centre for Nursing and Allied Health Deakin University and Barwon Health. 2010.
Dunning, T., Savage, S. & Duggan, N. The McKellar Guidelines for Managing Older People with Diabetes in Residential and Other Care Settings. 2013.

the increasing complexity of assessing and managing diabetes that occurs over decades with increasing age and changes in function and health status [11].

It is important to keep blood glucose in or close to the normal range to prevent complications [12,13]. It is equally important to avoid hypoglycemia. Older people are at high risk of severe hypoglycemia [11,14,15]. Severe hypoglycemia increases the risk of cardiovascular disease in people with T2DM [15] and has a high one-year mortality risk~20% in people admitted to hospital with severe hypoglycemia. Hypoglycemia affects cognition in the short term and is associated with dementia in the longer term [16-18] and causes/contributes to falls and related injuries [19]. Hypoglycemia has adverse consequences for older people in all trajectories, but some people are more at risk than others. Table 2 outlines the key hypoglycemia risk factors [20,21].

Age-related changes also affect tissue; organ and hormone function and compound the effects of hyperglycemia. Older age is generally defined as 65 years and older [22]. However, chronological age is not a good basis for planning care and may not reflect the individual's social situation, physical or cognitive function, their self-care capacity or life expectancy. Social and psychological factors influence the way people respond to stressors and usual life transitions such as marriage, childbirth and growing older. Growing older often eventually involves stopping usual activities such as driving, which in turn affect autonomy; self-efficacy and can lead to isolation and depression [23,24].

Thus, modern diabetes management focuses primary prevention and early diabetes diagnosis, including diagnosing gestational diabetes (GDM). GDM is increasing in prevalence increases the risk of T2DM in the mother and child in later life [25]. It is important to determine whether the individual has T1DM or T2DM to ensure medicine management and other treatment is appropriate to keep metabolic parameters in a safe range for the individual to and reduce the risk of short and long term complications. Personalizing care, including metabolic target ranges, is an important safety issue in older people [11].

These are not new concepts. Ancient healers and philosophers espoused the importance of a healthy lifestyle (diet and activity), sleeping well, and learning something new every day to preserve mental function., and They also advocated planning for older age and end of life when young [26]. Modern research largely supports the need for a healthy lifestyle. More recently, the need to plan for old age and end of life (EOL) from a young age and to accept death as inevitable and sometimes desirable is emerging. That is, older age and death are normal, important aspects of a person's life journey. Indeed, the World Health Organization (WHO) [27] promotes dying as normal and suggests optimal EOL care affirms life.

Modern treatment means many people now live longer than they did in ancient Greece and Rome. Some, like many people with diabetes, often live for a long time with significant disease, and treatment, medicines (polypharmacy) and lifelong self-care, which can become burdensome to manage. People with diabetes tend

Table 2: Important hypoglycaemia risk factors in older people. The more risk factors the individual has the great the risk.

Treated with insulin or sulphonylureas.
Long duration of diabetes
Hypoglycaemic unawareness, which can be due to long duration of diabetes and reduced autonomic response to falling blood glucose, autonomic neuropathy, dementia, sedation and delirium.
Cognitive impairment or dementia
Consistently low HbA1c or blood glucose
Renal disease
Liver disease
Recent hypoglycemic episode
Fasting for procedures.
On sedative medicines
Gastrointestinal and/or swallowing problems that affect food absorption
Using reactive 'top up' insulin doses to manage hyperglycemic episodes in aged care facilities [20, 21].

to follow a similar chronic disease trajectory. However, they have varying individual journey within the disease trajectories and their life expectancy are highly individualized. Some of the combined and cumulative burden could be alleviated using a palliative approach with usual diabetes care.

Life limiting illness, palliative and end of life care

The term Life limiting illness describes people at high risk of dying in the subsequent 12-months. Many people admitted to hospitals and ICUs have a life limiting illness. The Gold Standards Framework (GSF) Prognostic Indicator [28] outlines indicators of life limiting illnesses for cancer, chronic obstructive pulmonary disease, heart failure, renal disease, neurological diseases, frailty, dementia, and stroke. Diabetes is not specifically included in the GSF: it is an underlying cause of many of the diseases included in the GSF. It can be difficult to determine what the 'initial' disease was and when the underlying disease process commenced. Many of the diseases included in the GSF and diabetes may have a common underlying inflammatory process, especially those related to obesity.

Diabetes-related factors that affect life expectancy were identified in a structured literature review undertaken to inform the revision of the Guidelines for Managing Diabetes at the End of Life (2010) [29] and are listed in Table 3. These, and other such guidelines recommend people document their end of life preferences while they are able to make autonomous decisions. However, fewer than 50% of people with life limiting illnesses have documented goals of care and < 24% identified their care goals and values [30-39].

Palliative care focuses on improving Quality of Life (QOL) by relieving suffering and managing distressing symptoms [40]. Palliative care emphasizes the importance of good communication to support individuals to make informed decisions about and document their values and treatment preferences and goals including their end of life care preferences. Palliative care can be used at any time and in any trajectory [41] and can complement usual diabetes care. Most benefit occurs when palliative care is introduced early [41,42]. For example, Implementing palliative care early it improves comfort, function, reduces unnecessary burden of treatment and care and increases satisfaction with care. Many older people with diabetes could benefit from palliative care in addition to their usual diabetes care and from support to document Advance Care Directives (ACD) much earlier than occurs in current practice [43,44].

People admitted to hospital near their end of life are more likely to receive burdensome treatment such as resuscitation, dialysis and blood transfusions that may not be beneficial and may be futile [45,46] and is often distressing for them and their relatives. Clinicians

have an important role helping older people with diabetes to plan for predictable changes in health status and to initiate timely palliative and EOL care to prevent unnecessary admissions to hospital and/or invasive intensive care that have little benefit even when it prolongs life, especially when it does and may not accord with the individual's core values. It is difficult for clinicians and family to make care decisions when the individual's values and wishes are not known/ documented.

EOL generally refers to the last 12 months of life [28] and includes imminent death in a few hours or days and progressive incurable life threatening illnesses such as diabetes. EOL can be unpredictable. Sudden, unexpected deaths occur in ~ 25% of deaths [44].

Advance Care Directives (ACD)

It is important to encourage older people with diabetes to document the care they want to receive. It is equally important that they document their values and the care they do not want in an ACD. ACDs are an outcome of advance care planning and enable surrogate decision makers, family and health professionals to make 'in the moment decisions' [22,44]. However, ACDs are often first documented when the individual has a Rapid Response Team (RRT) call to assess whether sudden deterioration [45,46].

People who are older and have multiple comorbidities are more likely to die in hospital. Significantly, 20% - 30% of people who die in hospital receive a RRT review and 20% - 35% of RRT calls result in death [45]. A clearly documented ACD can help the RRT and other careers decide whether the episode of deterioration can be treated to restore stability, whether palliative could be implemented to reduce suffering or whether the person is dying and end of life care is required. Table 4 outlines some of the information that can be included in an ACD.

Diabetes-related deaths may not be due to a single cause, which makes it difficult to predict life expectancy. Prognostic indicators, the GSF, risk tools and regular comprehensive geriatric and palliative care assessments can inform care planning. Many 'life expectancy' calculators and are available and can be used with other indicators of life expectancy. A number of changes and well-defined patterns accompany functional decline. These patterns are described in a series of disease trajectories [44,47]. Trajectories, the GSF [28], diabetes-related factors associated with reduced life expectancy, and life expectancy calculators can be used together or independently to guide diabetes care planning for older people.

Trajectories and Prognostication

'Disease trajectories' describe well documented patterns of decline in the course of a disease from onset to death [47]. The GSF

Table 3: Diabetes-related factors that affect life expectancy.

Duration of diabetes > 10-15 years [29] and long standing hyperglycemia (HbA1c > 7%).
Glycaemia: higher mortality rates are reported with both high and low HbA1c levels [30,31] and with rapid reductions in HbA1c [32,33,34].
Comorbid load. Cardiovascular disease, renal disease, dementia and depression all affect life expectancy [35].
Severe hypoglycemia, which is associated with sulphonylurea and insulin use [35].
Lower limb and foot disease [36].
Frailty in older people with diabetes [37]. Frailty is associated with adverse events such as falls and fall-related injuries and hypoglycemia. Polypharmacy [38].
Comorbid depression [30]. Diabetes and older age increase the risk of diabetes-related distress and depression.

Table 4: Key issues to discuss with older people with diabetes to help them decide what to document in their Advance Care Plan

Values and preferences that underpin their individual's desired goals of care. These are particularly useful in aged care facilities to help staff decide whether to treat reversible illnesses and comfort/dignity care or to refer for acute care.
Resuscitation Cardio Pulmonary Resuscitation (CPR).
Airway support (intubation).
Non-oral feeding (intravenous fluids, enteral/parenteral feeds).
Rapid Response Team (RRT) calls when they are in hospital. The RRT can provide palliative care or enact the ACD.
Pain management.
Admission to Intensive Care.
Continue b Blood glucose monitoring.
Continue G glucose lowering medicines including insulin use, especially people with T1DM.
Use medicines such as antibiotics to manage intercurrent infections.
Commence dialysis.
Preferred place of death and who they would like present at their death.

Other important advance planning issues include cultural and religious customs, living wills, funeral arrangements nominating proxy decision makers (medical power of attorney) or other types of powers of attorney.

These issues will be influenced by the laws and regulations in the relevant country.

[28] encompasses the 'surprise question': 'would I be surprised if this person died soon?' The answer, yes or no, can be a useful to guide to when to implement palliative care and initiate conversations about EOL and ACDs with the individual and relevant others.

Comprehensive predictors of mortality include functional status and quality of life. They may not overtly encompass the individual's personal quality of life issues, which often include reading to and playing with grandchildren and pets. Social, cultural, religious and spiritual needs must be considered when personalizing diabetes care with the individual and often family careers [22,48]. Diabetes and other comorbidity-related indicators are only part of the individual's story in any trajectory. The trajectories are inter-related, rather than discrete. Older people with diabetes may move among trajectories as comorbidities accumulate and function changes; but the end point off or all trajectories is end of life.

The following discussion outlines issues to consider and assess in each trajectory. Most trajectories are inter-related in some way. Four trajectories are discussed:

Trajectory 1: Health

Health is not usually included as a discrete trajectory. However, as ancient health philosophies and modern epigenetic research indicate, health in older people begins before birth. Most people are born relatively healthy with a genetic makeup and related epigenetic factors that can predispose them to diabetes in early or later life and affect life expectancy. The aim from birth is to maintain health, preserve function, prevent diabetes and its complications and maintain quality of life.

People need to be informed about likely health outcomes and understand the importance of early diagnosis and lifelong management if they are at risk of prediabetes/diabetes and their responsibility for keeping blood glucose, lipids, BMI, and other metabolic parameters as close to normal as possible to mitigate risk. Significantly, achieving normoglycaemia early in the course of diabetes has lasting effects in later life [7,49], often referred to as 'metabolic memory.'

Early diagnosis and appropriate diabetes management is important, because high blood glucose occurs relatively late in the evolution of T2DM [3-5]. Diabetes and or its complications can be present > 7 years before diagnosis [3,49]. Likewise obesity at age 17 is associated with increased mortality risk [50] and the offspring of women with GDM are at increased risk T2DM, hypertension and Coronary Heart Disease [51].

Thus, many people with T2DM present with few symptoms or a complication after long duration of hyperglycemia. The annual progression rate to diabetes in older people with known risk factors: insulin resistance, reduced insulin secretion and obesity, is 5-10% [3] but diagnosis is influenced by health professional and public awareness, ethnicity and a number of other factors.

Eating a healthy diet, being active and managing stress is important to reduce the negative genetic impact. Sleeping well promotes neuroplasticity and memory [52]. Likewise, regular activity helps maintain muscle mass and flexibility and reduces the risk of sarcopenia and frailty, which can begin in middle age [11]. Frailty is a major contributor to death and disability in older people with diabetes and begins in middle age [37]. Medicines are often needed to manage lipids, blood pressure and reduce the risk of diabetes and other life limiting complications. Regular comprehensive assessments, diabetes risk screening and medicine reviews are important care strategies and can indicate when the person could enter another trajectory.

General health care is important in all trajectories from an early age and includes relevant risk screening and immunization programs, many of which need to continue in older age. Older people need regular dental care, cancer screening programs such as breast, bowel and prostate cancers and have relevant immunizations such as influenza, pneumonia and Zoster Vax. If the individual is diagnosed with cancer they may enter trajectory 2. If they are diagnosed with diabetes they may follow trajectory 3 or 4.

Trajectory 2: Steady progression to a usually clear terminal stage

Trajectory 2 is sometimes known as the cancer trajectory. The aim of care in trajectory 2 is to diagnose cancer early through population based-screening and awareness programs, manage the

cancer effectively to preserve function and quality of life and to plan for palliative and end of life care when relevant.

There is an association between some forms of cancer and diabetes [53,54]. In fact chronic disease may be an overlooked risk factor for cancer [54]. Huakang et al., found chronic disease contributed to the risk of incident cancer in a dose-response way and to life years lost and cancer death [54]. Most cancer occurs after age 65 in many countries; therefore it is important to monitor for cancer in people with diabetes and for diabetes in people diagnosed with cancer, especially people with cancer treated with glucocorticoid medicines [55].

Recent research suggests women with stage 3 breast cancer and diabetes > 5years duration are at higher risk of all-cause and cancer-specific mortality and are less likely to receive chemotherapy and radiotherapy than women with breast cancer who do not have diabetes [56]. Some cancers such as pancreatic cancers may be the underlying cause of new diagnosis of diabetes. Pancreatic cancer is beginning to be referred to as type 3 diabetes [57].

Older people with diabetes receiving palliative care regard blood glucose monitoring useful to identify underlying hypo- or hyperglycemia that can contribute to distressing and uncomfortable symptoms, but indicate it can be ceased in the last days of life [58]. Health professionals often regard blood glucose monitoring at the end of life as invasive and painful [58]. Keeping the blood glucose a safe range for the individual helps manage some of symptoms that cause discomfort and reduce dignity and quality of life. Insulin should be continued in people with T1DM until the final stages of life but the insulin regimen can be modified so insulin used to prevent short term consequences of hyperglycemia such as ketoacidosis. Both are largely preventable and cause dehydration incontinence and delirium. That is, think about using insulin for palliation to reduce suffering.

Insulin can also be used to manage hyperglycemic symptoms in T2DM when other GLMs are contraindicated or cannot be taken orally: for example, a single daily dose of a long acting basal insulin and a dose of rapid acting insulin when the person eats. Insulin is also being required to manage hyperglycemia induced by diabetogenic medicines such as glucocorticoids [59].

As the disease progresses and prognosis changes preventing diabetes long term complications become less important than managing them to reduce discomfort and maintain function..People on the cancer trajectory are more likely to have end of life discussions with their GP [60] despite evidence that people with other life limiting illnesses have similar trajectories of reducing function and survival [61,62].

Many people with cancer survive (cancer survivors) and have specific care needs, some of which are similar to the needs of people with chronic disease. Prognosis, including the likelihood of surviving, need to be discussed with the individual and their family when the cancer is first diagnosed. If they develop an ACD and survive it may need to be reviewed to ensure it still reflects the person's values, goals and preferences at a later time in their life.

Trajectory 3: The chronic disease trajectory

Periods of deterioration and recovery are a common feature of the chronic disease trajectory [47]. The aim of trajectory 3 is to appropriately manage diabetes to prevent complications to maintain

function and quality of life. It is also important to proactively assess for the development of complications and manage early to limit the associated functional and sensory deficits and their consequences, see guidelines listed in table 1. General health care should continue when a person is diagnosed with diabetes. Timely discussions about changing life expectancy and advance care planning are important considerations as function declines.

The blood glucose range and HbA1c must be personalized to balance the risk of hyperglycemia and its consequences against those of hypoglycemia [11,63]. Thus, optimal glycaemic control (HbA1c <7%) when diabetes is first diagnosed is an important outcome determinant [5,12,14], but may be unsafe for older people with diabetes where HbA1c 8% might confer a lower hypoglycemia risk [11,63].

Pharmacovigilance, using non-medicine options when possible and safe and stopping medicines before prescribing new medicines is essential [63]. Polypharmacy is common in older people with diabetes and may be warranted. However, it is associated with adverse events, admissions to hospital and affects life expectancy [38,63]. It is essential to ask about complementary medicine (CAM) use because people with diabetes and those with cancer frequently use CAM complementary medicines [63,64]. Some CAM such as music, cognitive behavior therapy and massage can be useful non-medicine options; others, especially CAM medicines, can cause adverse events, interact with conventional medicines and contribute to polypharmacy.

People in the chronic disease trajectory, including people with diabetes, usually experience episodes of deterioration and recovery, many times before they progress to their end of life [47]. This is often referred to as stable and unstable diabetes. Unstable diabetes is often due to intercurrent illness, 'acopia' and psychological stressors. Having a documented plan for transitions among care services can reduce negative outcomes, readmissions and further deterioration. If the person has an ACD it should be communicated to all relevant care providers, including emergency services.

Each deterioration and progression of complications increases the risk of adverse events such as falls, severe hypoglycemia and cognitive changes such as dementia. Each deterioration and every clinical encounter represents opportunities to refer the person for palliative care and/or comprehensive geriatric assessment. It is also and opportunity and/or to discuss the person's values, goals and preferences and document their ACD and other relevant documents such as Medical P

Power of Attorney (also known as a medical treatment or surrogate decision maker), funeral plan and a will, depending on the laws and regulations of the relevant country.

Trajectory 4: Prolonged decline/dwindling: the frailty trajectory

People who do not have cancer or chronic diseases that cause organ damage/failure are likely to die at an older age from dementia or generalized frailty that involves multiple body systems. Frailty is a geriatric syndrome characterized by sarcopenia and declining capacity to manage internal and external stressors, which leads to prolonged recovery and often compromises autonomy and life expectancy [11,65].

Interestingly, older people do not apply the term 'frail' to themselves because they associate frailty with dependency, cancer and end of life (negative) [66]. They recognize frailty in other people and describe them as 'frail' [66]. Recognizing the impact of language and labels on older people's outcomes and behaviors and adopting a positive autogenic approach that focuses on enhancing an individual's capabilities through rehabilitation/restorative care can help maintain dignity, quality of life and hope [67].

A range of tools is used to assess the number and type of deficits present and can help monitor functional decline and changing life expectancy [11]. Factors assessed include gait speed, handgrip strength, physical activity, exhaustion and weight loss. There is an incremental relationship between the number of deficits the person has and their risk of death [11,68,69]. Frailty is often the reason older people are admitted to an aged care home or supportive care at home [70].

Family cares

Family cares play a key role in all trajectories. They may be old and have comorbidities that affect their capacity to provide care. Caregiver age and health status strongly predict care recipient admission to a care home, especially when the cares is a spouse [70]. Family cares often assume a significant unpaid burden of care and are at risk of inter-current illness and dying in the 12 months following the death of the person they care for [71]. Thus, they may also require care and counseling after a bereavement and in some cases help to document their own ACD.

Concluding summary

Death is a normal part of life but the time of death is unpredictable. This paper outlined the common disease trajectories: health, cancer, chronic disease and frailty. It highlighted the value of proactively planning for palliative and end of life care, especially for older people and those with chronic life limiting illnesses such as diabetes. Prognostication and risk assessment is likely to improve as blood tests and genetic testing becomes more precise and affordable, which will make discussions about care options and life limiting illnesses easier.

As a final note, many health professionals are old and some have diabetes and other life limiting illnesses. These health professionals could also consider their personal values, preferences and goals and the wisdom of documenting an ACD.

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