ORIGINAL ARTICLE International Diabetes Nursing, Vol. 14, 2017, 20–25

Mortality in older people with diabetes: A review of current research

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Older people with diabetes have reduced life expectancy compared to those without diabetes. They also have increased mortality risk. This paper looks at some of the factors that may explain the increased mortality risk in older people. Consideration is given to: comorbidities; polypharmacy and diabetes therapies; glycaemic control and targets; and frailty. The paper considers how we might be able to reduce the mortality hazard for older people, considering the heterogeneous nature of the population.

Keywords: Mortality, Diabetes, Older people, Glycaemic control

Introduction

Diabetes mellitus is associated with increased mortality levels,[1–3] and while it has been shown that people with diabetes are generally living longer, their mortality risk remains much greater than someone without diabetes.[4,5] A disparity that is equally evident in the older population of people with diabetes, where the risk and hazards associated with diabetes can be more complex.[6,7] Therefore, given that older people represent the largest segment of the diabetes population, it is important that we understand more about the factors that drive those risks, so we can develop more informed approaches to their care. In this paper, consideration is given to some of the factors that may help inform risk minimisation in managing diabetes in older people by considering what we currently know about mortality risks in older people. The paper is divided into two parts: an overview of mortality in older people with diabetes; and an exploration of some of the factors that may contribute to excess mortality in older people with diabetes.

Mortality risk in older people

As with the general diabetes population, increased longevity has been observed in older people with diabetes. A longitudinal study of people diagnosed with diabetes at an average age of 70 years ($n = 6504$) from 1940s to 2000s, found that survival increased significantly: from 6.4 (±5.7) years in the period 1943–1965; to 8.3(±4.9) years in the period 1989–2009.[8] However, while this seems encouraging, these data simply reflect overall improvements in longevity in the general population. When consideration is given to relative mortality hazard, older people with diabetes still have a significant excess risk compared to those without diabetes. Studies of mortality in older people with diabetes that include a non-diabetes reference group consistently report excess mortality. Barnett *et al.*[6] conducted a meta-analysis of 11 studies and showed an average excess mortality risk of about 70%, although there was significant study variation with reported hazard ratios ranging from 0.6 to 3.0. Furthermore, many of these studies were relatively small with heterogeneity in the length of follow-up, types of included patients and study designs. Subsequent to this review, we now have some data from larger cohort studies. Bethel *et al.*,[9] reported a longitudinal analysis (1994–2004) of Medicare data considering 11-year mortality risk in patients with ($n = 33, 772$) and without ($n = 25, 563$) diabetes, and the mean age was 75 years. They reported an overall excess mortality of around 9%. More recently, a UK population-based 10-year (2003–2013) retrospective cohort study comparing the mortality profiles of people aged ≥70 years with diabetes (DM) ($n = 35\,717$) and without diabetes (NoDM) ($n = 307\,918$), showed that 5- and 10-year survival rates were 8 and 11% lower in the diabetes cohort.[10] In terms of mortality hazard, the study showed an overall hazard ratio for morality in older people with diabetes of 1.29 (95% CI = 1.26–1.31), with people without diabetes as the reference population. This hazard was even higher in the female subjects at 1.36 (95% CI = 1.33–1.40). Therefore, despite the general improvement observed in mortality over time, there remains a significant gap of around 10% in survival between older people with diabetes compared to those without, together with an increased risk of mortality of around 30%.

Studies of mortality in older people with diabetes have also highlighted some important differences in the mortality risk within the older population, emphasising the heterogeneous nature of the older population. Two important population characteristics that are observed in these data are the differences in mortality risk in relation to gender and the duration of diabetes.

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DOI 10.1080/20573316.2017.1352144

In terms of gender, there are distinctions between the absolute and relative mortality risks reported. In relation to absolute mortality risk, survival is lower in males with diabetes compared to females.[10] These absolute differences reflect the general difference in mortality between genders. However, when we consider the relative risks, these seem to be more emphasised in females with diabetes. Tan *et al.*[11] in an observational study comparing mortality risk in older people with ($n = 3914$) and without diabetes ($n = 7188$) reported that females had a 25% increased risk, whereas males had a 9% increased risk. In Forbes *et al.*'s[10] study, the overall difference in mortality hazard was similar, being 15% higher in females, with the risks being 21 and 36% in men and women, respectively. They observed an even greater difference in the age range 70–79 range in which the relative hazard for women was 20% greater than in males. However, it is important to note that the relative risks, when compared between older men and women with diabetes, were 21% higher in males.

In relation to diabetes duration, we can distinguish between those who were diagnosed with diabetes in older age and those who bring diabetes into older age following a mid-life diagnosis. Around 50% of older adults living with Type 2 diabetes develop it after the age of 65.[12] Type 2 diabetes developed in older age often follows a different pathophysiological model to that developed in the mid-life. In addition, those who develop diabetes in older age will have less glucose exposure and potentially fewer diabetes complications. This difference is evident in the mortality data for older people. In their systematic review, Barnett *et al.*[6] conducted a meta-analysis of five studies that considered diabetes duration and found that relative risk for mortality in men diagnosed between the ages of 60 and 70 was 38% greater than in those without diabetes, compared to 13% for those diagnosed aged 70 years or older. A similar pattern was found for the same diagnostic age groups for women, with relative risks of 40 and 19% compared to women without diabetes, respectively. In Forbes *et al.*'s study, duration of diabetes was also identified as the conferring significant risk, with those who had diabetes for more than 10 years having a 37% higher risk of mortality compared to those with a duration of less than 3 years in adults aged over 70 years. This risk was even higher, at 43%, in those ages between 70 and 75 years (see Figure 1).

Overall, we can see that there is an elevated mortality risk in older people with diabetes. Therefore, it is important that we try to identify the factors that may contribute to this risk, so we can develop care approaches that will extend both the quantity and quality of life in older people with diabetes. The mortality data also highlight the inherent heterogeneity in the older diabetes population, with these variations indicating that there are different types of risks within the population. This would suggest the need for more sensitive care models that can help clinicians identify and respond more appropriately to the needs of the older person.

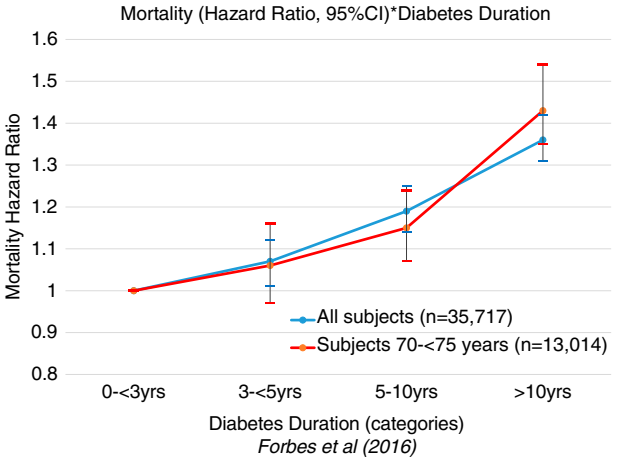

Figure 1 Mortality hazard by duration of diabetes in older (>70 years) adults.

Factors associated with excess mortality in older people with diabetes

In this second part of the review, consideration is given to some of the factors that may contribute to the excess mortality observed in older people with diabetes. The intention is to expose some potentially modifiable areas that may help reduce the risk of premature mortality in older people.

Comorbidities

Many older people with diabetes live with multiple health problems,[13] with the risk of some comorbidities such as dementia, depression and cardiovascular disease (CVD) being much higher in the diabetes population.[14-16] These comorbidities increase the stress on an individual's health and confer additional risks that may be important in explaining variations in mortality in older people with diabetes. In a study of 750 older people with diabetes (mean age 69 ± 7), Laiteerapong *et al.*[13] examined the impact of comorbid load on mortality. They clustered the patients into three groups expressing comorbid load as: low (63%, $n = 470$), medium (29%, $n = 215$), or high (9%, $n = 65$). Five-year mortality was significantly inflated in the 'high' group at 33%, compared to 17 and 9% in the medium and low groups, respectively. However, in the previously mentioned study of Forbes *et al.*[10] a comparison of the relationship between comorbidity and mortality was made between older people with and without diabetes. While the study showed increasing mortality hazard for older people with higher comorbidity index scores (0–≥4), the mortality risk was higher in people without diabetes. In older people with diabetes with a comorbidity index score ≥4, the mortality hazard ratio was 1.9 (95%CI = 1.7–2.1) compared to 2.0 (95%CI = 1.9–2.1) in those without diabetes. Hence, while morbidities confer mortality risk to older people with diabetes, this may not be any more so than for older people without diabetes.

In terms of individual comorbid conditions, most previous studies suggest that CVD conveys the greatest risk to people with diabetes.[4,16,17] However, in older people this relationship may be more complex. Forbes *et al.*[10] reported that while the prevalence of CVD was significantly greater in the older people with diabetes and was associated with elevated mortality risk, it did not explain the excess mortality observed. Although they did observe that in the younger group (those aged 70–75 years of age), the risk was much greater compared to those without diabetes. This concurs with the findings of a recent study showing lower overall excess mortality in those aged ≥75 years (10% more than controls) compared to those aged 65–74 years (30% more than controls), with the excess cardiovascular mortality being 9 and 40% for the same groups, respectively.[18] Therefore, cardiovascular prevention strategies may be a greater priority in the management of older people with diabetes in the younger old age groups. Another important comorbidity highlighted in the Forbes *et al.* study was heart failure. The incidence of heart failure was double that observed in the non-diabetes group; it was also the comorbidity that contributed most to mortality risk in older people with diabetes. Therefore, preventing, improving the detection and enhancing the management of heart failure may provide a dividend in reducing mortality in older people with diabetes. A recent meta-analysis of factors contributing to heart failure in diabetes suggests that strategies need to include more stringent glycaemic control and better prevention of cardiovascular disease.[19] It may also be an important consideration in determining metabolic targets and therapy selection for older people. Some newer oral hypoglycaemic agents have suggested improved mortality in respect of patients with heart failure and other cardiovascular morbidity, although trials in older people specifically would be needed to test that potential.[20,21] It is also known that some therapies such as thiazolidinediones are associated with increased risk of heart failure,[22] so perhaps these should be avoided in older people at risk of or with heart failure. In terms of specific diabetes complications, both end-stage-renal failure and advanced foot complications stand out as important areas of risk in older people with diabetes with high morbidity and mortality. The message with both these complications is on prevention through better diabetes care; however, in older people where these complications are present, careful consideration needs to be given as to how best to promote their quality of life.

Polypharmacy and diabetes therapies

Closely associated with comorbidity is polypharmacy, as people age and acquire more health problems, then the number of agents they are prescribed also increases, and studies have shown a link between polypharmacy and mortality in older people.[23,24] To achieve diabetes metabolic targets (glycaemic control, hypertension and lipids) often necessitates the use of multiple pharmacological agents[25] and some diabetes treatments such as insulin and sulphonylureas (SUs) have been linked with increased adverse outcomes in older people[26,27] and mortality.[28–31] Currie *et al.*[29] reported mortality hazards of 10 and 34% for SUs and insulin in combination with metformin and even higher levels when they considered them as monotherapies, although this is not a common practice in older people and their sample was younger with a mean age of 62(±13) years.

Returning to the study of Forbes *et al.*,[10] they considered the mortality hazard in respective of older people taking 0–2, 3–4, 4–6 and >7 drugs, and found that older people with diabetes were taking significantly more medications (see Chart 1). However, the hazard for mortality associated with polypharmacy was greater in the non-diabetes group with risks of 14, 23 and 45% in the 3–4, 4–6 and >7 medicine categories, respectively, compared to risks of 7, 15 and 32% for older people with diabetes in respect of the same groups. While this means that polypharmacy may not explain the difference between mortality risk in people with and without diabetes, it does not mean that we should be ambivalent about polypharmacy in older people with diabetes, as it still conveys an important hazard. Forbes *et al.*[10] speculated that the lower risk associated with polypharmacy in diabetes may be related to the nature of the therapies associated with diabetes, many of which aim to reduce complications, in contrast to other diseases such as Parkinson's disease where therapies alleviate symptoms rather than regress the cause of the disease.

So, the central message would seem to be that both comorbidity and polypharmacy are important in relation to mortality hazard in older people with diabetes. Therefore, attempts should be made to try and minimise the development of diabetes=related comorbidities in older people. Given the high level of prescribing observed in older people with diabetes, it may also be important to review medicines regularly to maximise benefit and patient safety. Finally, selecting therapies that may be more suited in the presence of specific comorbidities

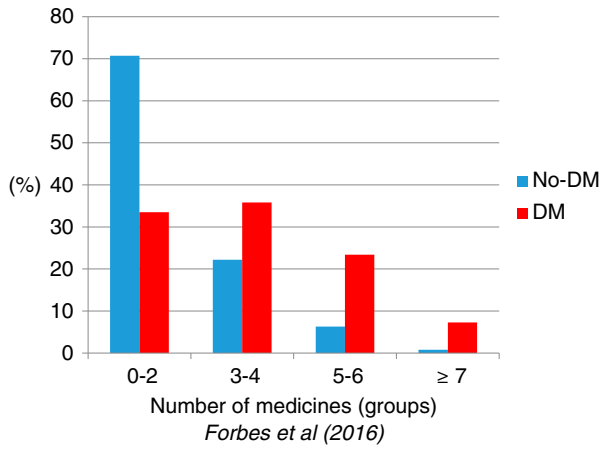

Chart 1 Number of medicines in older people with (n = 35 717) and without diabetes (n = 307 918).

such as heart or renal failure may help to reduce hazard. As many clinical trials exclude people aged over 65 years, it is also clearly an important priority to generate more clinical evidence on the effects of therapies in the older population.

Frailty

Frailty is a multifactorial condition associated with metabolic dysfunction, inflammatory processes and reduced physical capacity, it effects around a third of older people with diabetes.[32] Frailty increases risk for older people with diabetes[33] and it has been associated with elevated mortality.[34] Castro-Rodríguez *et al.*[35] reported findings of a prospective cohort study of people aged ≥65 years comparing mortality and frailty in those with ($n = 363$) and without diabetes ($n = 1462$) with a 5-year follow-up. They found higher mortality, lower functional status and higher levels of frailty in those with diabetes, and that frailty was the strongest predictor of mortality with an increasing hazard ratio of 1.83 (95% CI = 1.49–2.26) for each 10-point increase in the Frailty Index score. Therefore, frailty is another important factor in this population that confers added complexity and risk for older people with diabetes, with effects on metabolic function, nutritional deficits and vulnerability to treatment hazards such as hypoglycaemia.[33] Frailty is generally associated with a lower BMI and this may explain why a marginally elevated BMI in older people with DM has been shown to be protective.[36] Forbes *et al.*[10] confirmed this association showing a U-shaped distribution of mortality hazard with a low BMI ($<20\ kg/m^2$) being the most hazardous, whereas being overweight (BMI 25–30) was protective (see Figure 2).

Therefore, frailty is more common in older people with diabetes and is an important factor in mortality risk in this population. Clinically, it is important to consider frailty when assessing older people with diabetes. Frailty should be considered a marker for end of life, in such circumstances the emphasis on patient management should be on promoting quality of life and reducing treatment hazards as recommended in end-of-life guidelines.[37,38] It is also important to consider how frailty can be delayed in older people with diabetes with potential interventions being enhanced physical exercise regimens targeting those at risk and nutritional interventions.[39]

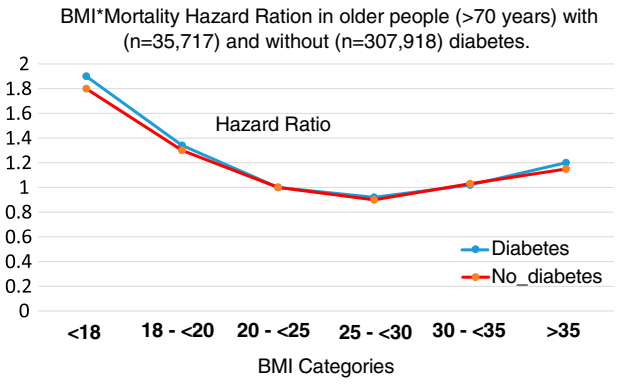

Figure 2 Mortality hazard by BMI in older (>70 years) adults.

Glycaemic control and mortality

An area that has become increasingly controversial in recent years is the determination of safe glycaemic targets, particularly for people with Type 2 diabetes. This controversy has, in part, been driven by the findings of recent trials of intensive glucose lowering.[40–42] The ACCORD trial found increased mortality in the intensified arm of their study as they sort a rapid reduction in HbA1c, achieving an average HbA1c of 6.4% in 4 months. It has been suggested that this rapid intensification, which involved using higher levels of insulin and thiazolidinediones compared to the control arm, may have raised cardiovascular risks by increasing weight gain and hypoglycaemia. In relation to older people where such risks may be even higher, in response to these studies it has been suggested that there is a need for less stringent targets and a more subtle approach to glucose intensification.[7] Although it should also be noted that the long-term follow-up data from the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study were the intensive groups showed average HbA1cs of 7.2 and 7% respectively, continue to show reduced mortality in the intensively treated population over time.[43,44] However, the extent to which we can extrapolate these observations to the management of older people is limited, given that the mean age of the participants in the intensive therapy trials for people with Type 2 diabetes was between 60 and 66 years, with exclusions for both comorbidities and older age.

They have been some recent observational studies that have looked more specifically at glycaemic control and mortality in older people[45,17]; these studies have consistently shown a J-shaped distribution of mortality hazard, with higher levels of mortality being observed in respect of both elevated and lower (HbA1c ≤7.0%) HbA1c values. However, a more recent population study by Palta *et al.*,[46] of 1279 adults with diabetes aged >65years reported that the level of hazard associated with a lower HbA1c is less than has been previously been estimated. Their data showed that all-cause mortality incrementally rose with increased HbA1c levels (with HbA1c <6.5% as a reference) by: 20% with HbA1c values from 6.5 to 7.9%; 60% with HbA1c 8–8.9%; and 80% in those with a HbA1c>9%. Hence, the overall picture on what might be an optimal target range for glycaemic control in respect of mortality risk in older people is somewhat unclear at present.

Despite the limitations of these studies, many current guidelines have revised their glycaemic targets upwards, with an emphasis on developing more individualised targets with less stringent targets being set for those deemed to be of higher risk. Many of the risk factors

identified for less stringent control have high relevance to older people, as they include life expectancy, comorbidity and frailty.[47] Therefore, there is something of a dilemma in setting glycaemic targets for older people: with the need to be cautious on the one hand; and the need to reduce the risk of diabetes complications and glucotoxicity on the other. However, perhaps the more important considerations are how the target is set and achieved for an individual older person, rather than trying to generate generic targets that may be naïve to the variations we see in the older diabetes population. Unfortunately, the fact that older people have been excluded from most of the clinical trials evaluating glucose-lowering models means that our evidence base for this is shallow.

Conclusion

This review has highlighted the excess mortality burden that endures in the older population of people with diabetes. The review has identified some important factors that may be contributing to this increased mortality hazard. While we may have to accept that diabetes has a significantly detrimental effect on the health of older people, this review has shown that there are some areas where we may be able to reduce mortality risks in the older population. A key factor in achieving this is to recognise that older people with diabetes constitute a heterogeneous population, emphasising the need for an individualised approach. However, at present we have not yet developed optimal models to help support this; therefore, we need better processes for assessing older people with diabetes to ensure adequate overall risk reduction for the individual. Given that the older population contributes a significant part of the older population this needs to be a much higher priority than it has been thus far. We urgently need research to consider optimal assessment strategies, therapies and care models for diabetes in older people in respect of the divergent needs of this important population.

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