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EDITORIAL

Explaining the increased mortality in type 1 diabetes

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Abstract

Despite large improvements in the management of glucose levels and in the treatment of cardiovascular risk factors, the mortality rate in individuals with type 1 diabetes (T1D) is still high. Recently, Lind *et al* found that T1D individuals with glycated hemoglobin levels of 6.9% or lower had a risk of death from any cause or from cardiovascular causes that is twice as high as the risk for matched controls. T1D is a chronic disease with an early onset (*e.g.*, pediatric age) and thus in order to establish a clear correlation between death rate and the glycometabolic control, the whole history of glycemic control should be considered; particularly in the early years of diabetes. The switch from a normo- to hyperglycemic milieu in an individual with T1D in the pediatric age, represents a stressful event that may impact outcomes and death rate many years later. In this paper we will discuss the aforementioned issues, and offer our view on these findings, paying a particular attention to the several alterations occurring in the earliest phases of T1D and to the many factors that may be associated with the chronic history of T1D. This may help us to better understand the recently published death rate data and to develop future innovative and effective preventive strategies.

Key words: Type 1 diabetes; Hyperglycemia; Death rates; Adolescence; Autonomic neuropathy; Children; Endothelial dysfunction; Exercise; Metabolic memory

Core tip: Despite large improvements in the management of glucose levels and in the treatment of cardiovascular risk factors, the mortality rate in individuals with type 1 diabetes (T1D) is still high. A better understanding of the several different alterations occurring in the earliest phases of T1D and of the many factors that may be associated with a chronic history of T1D may help us to develop future innovative and effective preventive strategies.

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INTRODUCTION

Whether mortality in type 1 diabetes mellitus (T1D) is improved by intensive glycemic therapy has not been clarified yet. A number of studies have recently been published claiming that mortality rate is still higher than in age-matched controls without diabetes, despite improvements in management of glucose levels and treatment of cardiovascular risk factors[1-3]. Lind *et al*[1] reported data on current life expectancy for adults with T1D in a population-based sample using Swedish national registries of adults with and without diabetes. The Authors found that individuals with T1D and glycated hemoglobin (HbA1c) level of 6.9% or lower had a risk of death from any cause or from cardiovascular causes that was twice as high as the risk for matched controls. The multivariable-adjusted hazard ratios for death from any cause according to the HbA1c level for individuals with T1D as compared with controls are reported in Table 1.

Livingstone *et al*[2] report data on current life expectancy for adults with T1D in a population-based sample using Scottish national registries of adults with and without diabetes. At the age of 20 years, women and men with T1D could expect to live 12.9 years (95%CI: 11.7-14.1) and 11.1 years (95%CI: 10.1-12.1), respectively, less than aged-matched adults without it. Finally, Orchard *et al*[3] report survival data on the selective cohort of North Americans with T1D who participated in the Diabetes Control and Complications Trial (DCCT)[4] and its observational follow-up study, Epidemiology of Diabetes Interventions and Complications (EDIC)[5]. They found that 27 years after entry into the trial, 6.5 years of initial intensive diabetes therapy was associated with a modestly lower all-cause mortality rate when compared with conventional therapy. Few editorials accompanied[6] or commented[7] these data, without suggesting any conclusive hypothesis about the reason why this happens. T1D is known to be associated with an increased risk of premature mortality among the affected individuals, as documented by a recent systematic review on this topic by Morgan *et al*[8]. Authors identified thirteen relevant publications with mortality data, describing 23 independent studies. Standardized mortality ratios varied markedly ($P < 0.0001$). The increased mortality in childhood/adolescent-diagnosed with T1D was apparent across countries worldwide. Excesses were less marked in more recent studies and in countries with lower infant mortality and higher health expenditure. Given that good metabolic control has been shown to be effective reducing micro-vascular and macrovascular complication rates, one should expect that also the mortality rate might be reduced, but this is not the case[4,5]. Therefore, we would like to propose our appraisal to these important findings.

THE IMPORTANCE OF CHILDHOOD YEARS OF T1D

All studies reporting mortality rates in T1D refer to adult individuals, most of the time with a diabetes which occurred in childhood. For instance all individuals studied in the Lind paper were at least 18-year-old at the moment of enrollment, with a mean age at baseline of 35.8 years and mean diabetes duration of 20.4 years[1]. This implies that the average age for the onset of diabetes was 15.4 years, during their adolescence. The study does not provide any information at all with respect to HbA1c levels between diabetes onset and the time of data collection (on average 40 to 50 years after T1D diagnosis). From previous studies, (*e.g.*, DCCT and EDIC), we know how "metabolic memory" provides an important footprinting to future long-term complications[4,5,9]. We can thus argue that "metabolic memory" may partially be accounted for the higher death rate observed in individuals with T1D, whose onset was during childhood or adolescence. This aforementioned aspect reinforces the important of obtaining an optimal glycometabolic control in the first years of T1D. This is an important issue, since T1D incidence rate increases from birth, and peaks between the ages 10-14 years[10], with an even increased incidence especially marked in the youngest children (0-4 years)[11], making T1D the second most frequent chronic disease of childhood, after asthma. Further emphasis should be pointed to vascular complications, which start at the onset of the disease[12], although the consequences become clinically evident later in adulthood[13,14]. Once again, we may speculate that the reported excess mortality in adult individuals showing HbA1C < 6.9% in the study by Lind *et al*[1], may be the residual effect of previous cardiovascular insults started in infancy, childhood or adolescence. It is still unclear and partially unexplained why cardiovascular complications start so early in the disease history of T1D; indeed we can only speculate that a chronic state of mild hyperglycemia might be the culprit of cardiovascular morbidity, and thereby of excess death, as unaccounted in the Swedish observational trial[1].

Table 1 Adjusted hazard ratios for death from any cause and death from cardiovascular disease among individuals with type 1 diabetes *vs* control according to the glycated hemoglobin

	Hazard ratios	
Mean HbA1c	Death from any cause	Death from cardiovascular disease
≤ 6.9%	2.36 (95%CI: 1.97-2.83)	2.92 (95%CI: 2.07-4.13)
7.0%-7.8%	2.38 (95%CI: 2.02-2.80)	3.39 (95%CI: 2.49-4.61)
7.9%-8.7%	3.11 (95%CI: 2.66-3.62)	4.44 (95%CI: 3.32-5.96)
8.8%-9.6%	3.65 (95%CI: 3.11-4.30)	5.35 (95%CI: 3.94-7.26)
≥ 9.7%	8.51 (95%CI: 7.24-10.01)	10.46 (95%CI: 7.62-14.37)

Adapted from Lind *et al*[1]. HbA1c: Glycated hemoglobin.

Indeed, according the A1c-Derived Average Glucose study group, a HbA1c value of 6.9% indicate an average glucose level as high as 151 mg/dL (8.4 mmol/L)[15].

Additionally, the HbA1c measurement has some limitations itself. It has been shown to be unreliable in several different clinical scenarios, such as anemia or hemolysis, in presence of implanted mechanical heart valves, hypothyroidism, or during the use of medications such as erythropoietin[16]. Moreover, there is a recognized biological variability in the glycation process of the hemoglobin molecule in response to hyperglycemia. This is the result of a different glycation rate in "high glycating" *vs* "low glycating" subjects, where the same mean blood glucose was associated with an HbA1c level of 9.6% *vs* 7.6%, respectively[17]. To summarize, besides the issues related to the use of HbA1c, multiple factors contributed to the augmented risk of death in T1D individuals despite a good metabolic control. Indeed, several challenges are offered by the constantly evolving age-appropriate care needed by diabetic individuals transitioning from infancy to adulthood[18].

ENDOTHELIAL DYSFUNCTION AND EARLY ATHEROSCLEROSIS

Several different systems show altered homeostasis early along the course of diabetes[19-21]. Among them, the endothelium is definitely one of the most important and earlier targeted organs. Evidence suggests that impairment in nitric oxide-mediated smooth muscle vasodilation is an early pathophysiologic process and underlies the onset endothelial dysfunction, a key event for the development of atherosclerosis[22]. Among factors that may worsen endothelial function in individuals with T1D, we should mention: a long disease duration[23], a severely altered glycemic control[24], high low density lipoprotein cholesterol levels[25], high levels od advanced glycated end products[26], and altered mitochondrial dynamics[27]. Our group recently observed a high prevalence of endothelial dysfunction (76.7%) in adolescents with T1D for a mean duration of 9 years, particularly in those individuals with impaired glycometabolic control, subclinical signs of autonomic neuropathy and sedentary lifestyle. We did not observe any correlations between endothelial dysfunction and diabetes duration or individuals' age. A HbA1c below 7.5% (58 mmol/mol) and regular physical activity of at least 4 h per week, were indeed associated with better endothelial function. Atherosclerosis, the late event of endothelial dysfunction, is frequently linked to the likelihood of death from cardiovascular origin, especially in individuals with T1D. Compared to non-diabetic subjects, individuals with T1D show an increased risk up to 10-fold to develop atherosclerotic plaques, starting since childhood and adolescence[28]. Furthermore, intima media thickness measurement of the carotid artery is considered another valid surrogate marker for cardiovascular risk allowing assessment of atherosclerotic changes at a very early stage[29]. Finally, Paroni *et al*[30] showed that hyperhomocysteinemia in individuals with T1D may further increase the risk of endothelial dysfunction.

CARDIOVASCULAR AUTONOMIC NEUROPATHY

Cardiac autonomic neuropathy is an often overlooked and common complication of diabetes mellitus and by itself it is associated with increased cardiovascular morbidity and mortality[31], together with cardiac abnormalities typical of individuals with diabetes[32,33]. Data demonstrate the dual (vagal and sympathetic) control of heart rate and the dominant role of respiration in the genesis of heart rate and blood pressure fluctuations, suggesting that reduced vagal control of the sinoatrial node and impaired vascular regulation are the two main pathophysiological alterations[34]. Few years ago, our group investigated the autonomic performance of 93 children and adolescents with uncomplicated well-controlled T1D compared to age-matched controls. We found a significant increase in arterial blood pressure, a blunted baroreceptor reflex, and an increase of the low-frequency component of systolic arterial pressure variability. These findings entail the simultaneous impairment of the capability of the vagal system to influence the heart function, together with an increased sympathetic vasomotor regulation[21]. A follow-up study conducted 1-year later showed further impairment of the neuro vegetative performance, thereby suggesting early progression of the autonomic disturbance[21]. Interestingly, a small weekly increase in exercise in these same individuals can greatly help to improve cardiac autonomic neuropathy.

INFLAMMATION AND OXIDATIVE STRESS

In the last fifteen years several groups worked in the direction of uncovering the association between the increased cardiovascular risk in individuals with T1D and inflammation. Schaumberg *et al*[35] measured levels of inflammatory biomarkers at baseline and after a 3-year follow-up in a random sample of 385 participants of the DCCT cohort. Results were controversial and emphasized the extremely complex interaction between

inflammation, T1D and insulin therapy. Some of the inflammation indexes were high in both intensive and conventional insulin treatment groups; others were higher in the intensive insulin therapy group, others in the conventional one. What seemed to be linked to increased inflammation status in individuals using intensive insulin therapy was the weight gain they showed[35], underlining the need for a more effective weight control in individuals with T1D. Indeed, a recent study by Valerio *et al*[36] found that T1D adolescents, particularly females, showed a considerable occurrence of abdominal adiposity and metabolic syndrome. That is why pediatric diabetologists need to make every effort to achieve normal weight and better health outcomes in their young T1D patients. Davì *et al*[37] found that newly T1D diagnosed individuals showed significantly augmented lipid peroxidation and platelet activation, paralleled by a higher degree of systemic inflammation. This data strongly support the idea of a significantly noxious effect of even the earliest form of damage triggered by the disease. The biochemical picture depicted is suggestive of a true acute inflammatory response accompanying the disease in its very earliest, hence pediatric, phase[37]. The SEARCH Case-Control Study showed that young individuals with T1D, when compared to healthy controls, were characterized by excess inflammation despite good glycemic control[38]. Interestingly, Folli *et al*[39] demonstrated that persistent cellular changes of anti-oxidative machinery and of aerobic/anaerobic glycolysis are present in individuals with T1D (with or without end-stage renal disease), and these abnormalities may play a key role in the pathogenesis of hyperglycemia-related vascular complications. Restoration of euglycemia and removal of uremia with kidney pancreas transplant can correct these abnormalities. Some of these identified pathways may become potential therapeutic targets for a new generation of drugs[39].

HYPOGLYCEMIC EVENTS

Another possible explanation for the increased death rate in individuals with T1D despite good glycemic control may be hypoglycemia. The T1D Exchange Registry seems to confirm this hypothesis[40]. Elderly individuals and children younger than 5 years seem to be the two populations at greater risk[41,42]. A value of HbA1c in the low range ("good" metabolic control) may not only be associated with well controlled glucose control but with recurrent episodes of hyper/hypoglycemic oscillations. We may speculate that, in the study by Lind *et al*[1], one of the factors potentially explaining the persistence of a sizeable mortality hazard ratio in individuals with low HbA1c could be a high rate of hypoglycemic events in those individuals.

HOW TO IMPROVE OUTCOMES

T1D is a complex disease whose management may be extremely awkward and demanding[43]. Diet and exercise, in combination with a correct insulin therapy, play a pivotal role in obtaining and maintaining the best glycemic control possible. In the evaluation of a subgroup of individuals from the treatment group of the DCCT cohort, Delahanty *et al*[44] established the relation between diet and glycemic control beyond the sole intensive insulin therapy. A higher content of total and saturated fat, associated with a lower carbohydrate intake are linked to worse glycemic control, thereby further increasing the cardiovascular risk[44]. Adequate fibers intake, usually lower than suggested, is also recommended. Indeed, fibers offer a beneficial dietary profile: (1) by reducing or at least delaying the overall glucose absorption; (2) by blunting post-prandial glycemic peaks, and finally (3) by impacting low-density lipoproteins by enhancing biliary acid secretion. For the aforementioned reasons, a proper nutritional education is a crucial part of diabetes management and needs to be promoted in all pediatric individuals with T1D and their families[45]. Interestingly, recent study reported that children with T1D show less healthy food habits than same age healthy subjects[46].

Routine physical exercise is known to have beneficial effects on the cardiovascular system in the general population, and even more in individuals with T1D[47]. For this reason, we should strongly encourage individuals with T1D to participate in regular physical activity since childhood. One hour of moderate, aerobic exercise every day is currently recommended. Lucini *et al*[48] recently found the favorable effects of moderate increase (10%) in spontaneous exercise load in adolescents with T1D. Similarly, in children with T1D (mean age 11 years old), 60 min per day of exercise improves endothelial dysfunction, a well-known risk factor for cardiovascular diseases[49]. Moreover, in the recent years, technology has helped to reduce the impact of T1D especially in children[50]. Continuous glucose monitoring has emerged as one of the most significant innovation in the management of children with T1D. The combination of continuous glucose monitoring and insulin pumps, provides better glycemic control with less hypoglycemic episodes[51,52]. The ultimate technological advance of such automated insulin administration systems, currently under development, is the completely automated glycemic management, the closed-loop system also known as "external artificial pancreas"[53].

Finally, we would like to highlight recent stem cell-based trials, for which expectations in the scientific community and among individuals with T1D are high[54]. One of the most promising is cord blood stem cells that have been demonstrated to became a powerful tool not only for regenerative medicine but for autoimmune (*e.g.*, T1D) and inflammatory diseases as well[55,56]. Recently, a novel hematopoietic stem cell-based strategy has been tested in individuals with new-onset T1D, suggesting that remission of the disease is possible by combining hematopoietic stem cell transplantation and immunosuppression; however safer hematopoietic stem cell-based therapeutic options are required[57].

MORTALITY IN INDIVIDUALS WITH TYPE 2 DIABETES

As the prevalence of type 2 diabetes (T2D) continues to increase worldwide, diabetes-related morbidity and mortality increase as well. There is scarce evidence on the effect of HbA1c reduction on mortality rate in T2D individuals. Recently a study by Skriver *et al*[58] in a large cohort (n = 11205) of Danish individuals with T2D, showed that HbA1c variability was associated with mortality irrespective of the magnitude of absolute change in HbA1c. An increased mortality was observed even in those individuals with a HbA1c $\leqslant$ 8% if presenting a higher HbA1c variability[58]. However, in T2D individuals many factors other than glycometabolic control may contribute to increase the mortality rate (*e.g.*, hypertension, obesity, dyslipidemia, elevated uric acid and insulin resistance). Therefore, an early diagnosis and a prompt management of T2D comorbidities is required[59-62].

CONCLUSION

In conclusion, the recent findings describing an increased mortality in individuals with T1D as compared to age-matched population, even in the presence of on-target HbA1c, are important. Whenever the outcomes of a chronic disease like T1D are being studied, it is important to acquire data from the onset. Indeed, any events in the early phase may affect its future course and especially its final outcome (*i.e.*, death rates). A better understanding of the several alterations occurring in the earliest phases of T1D and of the factors that may be associated with the chronic history of T1D may help us to develop future innovative and effective preventive strategies.

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