Discoveries from the study of longstanding type 1 diabetes

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Abstract

Award programmes that acknowledge the remarkable accomplishments of long-term survivors with type 1 diabetes have naturally evolved into research programmes to determine the factors associated with survivorship and resistance to chronic complications. In this review, we present an overview of the methodological sources of selection bias inherent in survivorship research (selection of those with early-onset diabetes, incidence–prevalence bias and bias from losses to follow-up in cohort studies) and the breadth and depth of literature focusing on this special study population. We focus on the learnings from the study of longstanding type 1 diabetes on discoveries about the natural history of insulin production loss and microvascular complications, and mechanisms associated with them that may in future offer therapeutic targets. We detail descriptive findings about the prevalence of preserved insulin production and resistance to complications, and the putative mechanisms associated with such resistance. To date, findings imply that the following mechanisms exist: strategies to maintain or recover beta cells and their function; activation of specific glycolytic enzymes such as pyruvate kinase M2; modification of AGE production and processing; novel mechanisms for modification of renin–angiotensin–aldosterone system activation, in particular those that may normalise afferent rather than efferent renal arteriolar resistance; and activation and modification of processes such as retinol binding and DNA damage checkpoint proteins. Among the many clinical and public health insights, research into this special study population has identified putative mechanisms that may in future serve as therapeutic targets, knowledge that likely could not have been gained without studying long-term survivors.

Keywords Beta cell · Cardiovascular disease · Cognitive function · Diabetes · Long duration · Longevity · Nephropathy · Neuropathy · Retinopathy · Review · Type 1 diabetes

Abbreviations

ANG-II	Angiotensin-II
AT1	Angiotensin 1
DKD	Diabetic kidney disease
PKM2	Pyruvate kinase M2
RAAS	Renin–angiotensin–aldosterone system
RBP3	Retinol binding protein 3
RVR	Renal vascular resistance

SGLT	Sodium–glucose cotransporter
SOLID	Study Of Longevity In Diabetes

Introduction

Although the discovery of insulin in 1921 converted type 1 diabetes from a universally fatal to a chronic condition, in the middle of that century there was approximately 50% mortality risk, primarily from end-stage renal failure, in people with type 1 diabetes who had survived to their 40s [1]. It was in this context that the Joslin Diabetes Center in Boston acknowledged that surviving decades was a self-management accomplishment worthy of immense pride and accolade [2, 3]. Thus began in 1948 the Joslin Medalist Program awarding 25 year medals and, in later years, the 50 and 75 year medals to honour these duration milestones. Rather than assuming such success is purely behavioural, in 1997 Joslin Diabetes Center investigators began a formal research programme to create cross-sectional and cohort study analyses with the goal of better understanding

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the factors (genetic, physiological, environmental) associated with protection from complications. Such initiatives were not unique. Many international groups have acknowledged long-term survivors and contributed descriptive and causal inference research into complications susceptibility. Interestingly, mortality rates have appeared to decline in the past decades [4], and it is likely that life expectancy for many people with type 1 diabetes may approach or even exceed that of the age-, sex- and race-standardised general population [5]. Table 1 provides a non-exhaustive list of the investigational centres that have focused on long-term survivors, either through the direct recruitment of

participants into traditional cohort studies or through analyses nested within larger longitudinal cohorts and registry designs. Analyses most frequently align with the Joslin Medalist cohort's initial operating definition of long-duration diabetes exceeding 50 years, yet many of these have examined, for different purposes, cohorts and subgroups of perfectly valid shorter or longer extreme durations (shown in Table 1).

For this review, our main objective was to present the rationale for the study of such a specialised population, present the key methodological issues that inform analytical design, and highlight key research findings that may not have been

Table 1 Non-exhaustive list and characteristics of studies focused on descriptive, comparative or causal inference analyses in longstanding type 1 diabetes

Study group and selected citation	Primary area of focus	Observational study design	Year of first publication	T1D duration
Joslin Medalist [14, 15, 32, 63, 70, 92]	Complications, their mechanisms and associated factors	Cross-sectional and traditional cohort	2007	>50 years
UK Golden Years [93, 94]	Kidney function and disease	Cross-sectional and traditional cohort	2003	>50 years
FinnDianne [60, 95]	Microvascular complications	Cross-sectional and nested cohort	2003	>30 years
Dialong [57, 96]	Bone health	Cross-sectional and traditional cohort	2017	>45 years
Pittsburgh IDDM [97]	Cardiovascular complications	Cross-sectional and nested cohort	1981	>20+ years
DCCT/EDIC [16, 98]	Complications	Cohort study arising from an interventional trial	2003	>20–30 years
Swedish National Diabetes Register [28]	Micro/macrovacular complications	Registry-based cohort	2017	>50 years
Denmark [53, 55]	Complications in T1D patients	Cross-sectional and traditional cohort	2009	>20+ years
Lainz T1DM cohort [27]	Renal function	Cross-sectional and traditional cohort	2006	15 years
Japanese cohort [99]	Clinical values	Cross-sectional and traditional cohort	2019	>50 years
SDRNT1BIO (Scotland) [19]	Complications	Registry-based cohort	2017	>20 years
Exeter NIHR cohort [18]	β cell preservation	Cross-sectional and traditional cohort	2014	>30 years
T1D Exchange Clinic Network [17]	C-peptide	Cross-sectional and nested cohort	2015	>40 years
Paris cohort [7]	Lifestyle	Cross-sectional and traditional cohort	2009	>50 years
SOLID cohort (California) [74–76]	Cognition and neurological complications	Cross-sectional and traditional cohort	2020	>30 years
Kaiser Permanente (North California) [71]	Dementia	Registry-based cohort	2018	>50 years
Canadian study of longevity in type 1 diabetes [29, 52, 65, 67, 69, 82, 88, 100–102]	Renal and peripheral nerve complications	Cross-sectional and traditional cohort	2016	>50 years
University of Newcastle [26]	Renal function	Cross-sectional and traditional cohort	1996	>30 years
Johannesburg Centre for Diabetes and Epidemiology [103]	Cardiovascular	Cross-sectional and traditional cohort	2006	>18 years
EURODIAB [58]	Cardiovascular	Cross-sectional and traditional cohort	2002	>30 years
Helsinki University Central Hospital [104]	Cardiovascular	Cross-sectional and traditional cohort	2002	>20 years

DCCT, Diabetes Control and Complications Trial; EDIC, Epidemiology of Diabetes Interventions and Complications; IDDM, Insulin-Dependent Diabetes Mellitus; SDRNT1BIO, Scottish Diabetes Research Network Type 1 Bioresource; T1D, type 1 diabetes

possible through the study of only participants with diabetes of shorter duration.

Key methodological considerations in the study of longstanding diabetes: Incidence–prevalence bias

The core objective in the study of longstanding diabetes is to better understand an ‘extreme phenotype’ such as an individual who, despite more than 50 years, for example, of diabetes duration has survived without substantial burden of complications. This survival occurred, in part, through the era that included lack of physiological insulins, lack of capacity for self-monitoring of glucose, or even the knowledge of interventions such as intensive insulin therapy, access to measures of mean glucose exposure (e.g. HbA_{1c}), or limitations in the screening tests for early complications [2, 3]. It stands to reason, then, that such an individual is very likely to have a major protective behaviour or environment such as regular exercise or a supportive spouse or social network [6, 7], or perhaps biological resistance to a pathophysiological process, or existence of a protective gene profile. On the other hand, though complications can occur at any age and duration of diabetes beyond 5 years, after 50 years of diabetes there is greater certainty that an individual at risk of an outcome will have declared this risk or not [8]. The extreme phenotype of an individual with 50 years of diabetes without complications could be compared, for example, to an individual with short duration of diabetes who has developed extensive diabetes complications. A less-extreme comparison frequently used is with individuals in whom complications are present (rather than absent) after longstanding diabetes.

These research approaches, however, are susceptible to forms of selection bias. First, they favour selection of childhood-onset type 1 diabetes. Second, incidence–prevalence bias (frequently referred to as Neyman’s bias or survivor bias) occurs when the risk of a complication is estimated on the basis of data collected at a given time point in a series of survivors rather than data gathered during a certain time period in a study population of incident diabetes [9, 10]. Imagine a hypothetical population cohort of 2000 individuals followed from birth wherein eight individuals develop type 1 diabetes, four of whom have greater disease severity such that they die within a decade and the other four have more indolent disease such that their survivorship is similar to that of the general population. If at a point in time a group of investigators seek to recruit all individuals with type 1 diabetes from this implicit, but unknown, underlying cohort, they are most likely to select those with more indolent diabetes as they are more likely to be alive at the time of screening (see Fig. 1). Furthermore, if they seek individuals with diabetes of 50 years’ duration, those with greater disease severity have not survived

for the opportunity to be accrued. However, creating an incident type 1 diabetes cohort does not fully overcome this bias as selection bias may be induced by censorship, either through losses to follow-up or death from competing risks. In summary, selection bias occurs from the focus on childhood-onset type 1 diabetes, the existence of incidence–prevalence bias, and selection from losses to follow-up in cohort studies. Rather than focus on measures such as cumulative incidence, researchers have focused efforts on the less-biased objectives of determining factors associated with the extreme phenotypes, through inventive adaptations of case series and cross-sectional, case–control and cohort study designs.

Residual beta cell function in longstanding diabetes

The study of people with longstanding diabetes has drastically changed the traditionally accepted model of type 1 diabetes, which states that endogenous insulin production declines within 5 years of diabetes onset and that there is a complete loss of beta cells and insulin production [11]. While the study of long-term survivors might be expected to overestimate the proportion with endogenous insulin production if it is indeed associated with survival (owing to the issues of selection bias just discussed), we must accept that the finding of even a small proportion of long-term survivors would challenge the traditionally accepted model. Such preservation could protect against hypoglycaemia and extreme glycaemic exposure and therefore may be a key protective factor for the development of glucose-dependent long-term complications such as retinopathy [12–14]. Leading advances in this line of research, the Joslin Medalist investigators examined endogenous insulin production through multiple physiological stimuli including random and mixed-meal stimulated C-peptide production, and a hyperglycaemic i.v. clamp with arginine infusion for stimulation of insulin and thus C-peptide production [15]. C-peptide, proinsulin’s cleaved ‘connecting peptide’ between the α - and β -chains that make up the functioning insulin molecule, serves as a dependable measure of endogenous insulin production as it is not present in pharmaceutical insulin. These research methods indicated that a large proportion (one-third to one-half) of the individuals surviving for 50 years had some form of detectable C-peptide production and that levels of production fluctuated over a subsequent follow-up period of 4 years. Furthermore, examination of 68 post-mortem pancreases (from an innovative collaboration with the National Disease Research Interchange and its affiliated organ procurement networks) revealed detectable beta cells in all individuals, either atypically as single cells or within morphologically distinct islets. Although the forces of selection may have led to an overestimate of preserved function, studies of shorter-duration diabetes in which C-peptide expression is substantial suggest that selection cannot fully explain these

Fig. 1 Schematic representation of incidence–prevalence bias. In a hypothetical reference population of 2000 general population members, eight have new onset diabetes. Of these eight index cases, four have ‘mild disease’ such that they survive longer, while four have ‘severe disease’ (perhaps owing to adverse genetic, environmental, behavioural or physiological factors) such that survival is shorter. At the time of recruitment into a research study of type 1 diabetes (indicated by the dashed vertical line in the figure), available cases for recruitment are imbalanced in favour of those with greater survival. Rather than selection of all eight individuals, the four with ‘mild disease’ are available for recruitment but only one with ‘severe disease’ is available. In the process of selection of

prevalent type 1 diabetes cases, the probability of selecting individuals with longer survival is greater than if all new-onset cases had been included on their index (diagnosis date). This phenomenon is referred to as incidence–prevalence bias (Neyman’s bias or survivor bias). Incidence–prevalence bias, preferential selection for childhood-onset diabetes and selection based on losses to follow-up (from competing events such as death or outcomes like admission to long-term care facilities) make up the three fundamental sources of selection bias in the traditional cohort studies and registry-based cohort studies for longstanding type 1 diabetes. T1D, type 1 diabetes. Adapted from Tripepi et al. [9]. This figure is available as part of a [downloadable slideset](#)

findings, and detectable beta cells by post-mortem histological examination was ubiquitous [13, 16–18]. Large-scale registry data from the Scottish Diabetes Research Network Type 1 Bioresource (SDRNT1BIO) study has revealed that persistent C-peptide secretion may have a particular association with aspects of the type 1 diabetes phenotype, including variants in HLA gene regions that are different from the specific regions associated with early-onset type 1 diabetes [19]. A focus on determining the relevance of these HLA regions and how they impact maintenance of insulin secretion may in future help determine mechanisms of islet cell autoimmunity and may inform novel pathways that could be targeted to limit, or ideally reverse, the loss of insulin production in type 1 diabetes [19]. Taken together, these findings raise the possibility that hypoglycaemia-related outcomes, long-term glycaemic control, and even retinopathy risk may be better in those who maintain some insulin production [14, 20, 21], and that interventions that counteract autoimmunity or that have trophic effects on beta cells could have putative impact beyond the time surrounding the diagnosis of type 1 diabetes.

It is necessary to acknowledge that these study populations may include individuals with a classification of diabetes other than type 1. For example, monogenic diabetes variants (especially the more common *HNF1 α* and *HNF4 α* [also known as *HNF1A* and *HNF4A*, respectively] may be confused with a diagnosis of type 1 diabetes [22, 23]. This was systematically studied in the Joslin Medalist cohort in which 7.9% of

participants were found to have likely pathogenic variants in genetic studies [15]. However, the relevance of these variants as the sole cause of the diabetes is quite unlikely. Specifically, such monogenic forms of diabetes would most likely be associated with levels of C-peptide much higher than the levels observed in these longevity studies [24]. For example, in a study of 77 individuals with fairly long-duration *HNF1 α* diabetes, the lowest C-peptide level was 0.36 nmol/l, which far exceeded the highest level observed in the Joslin Medalist cohort. Moreover, 0.2 nmol/l has recently been proposed as a threshold above which to prompt monogenic diabetes screening, again exceeding the highest levels in the Joslin Medalist cohort [22]. However, future work should focus on the determination of genetic factors, including the polygenic risk score for type 1 diabetes and targeted genetic screening.

Diabetic kidney disease and renin–angiotensin–aldosterone system activation

Even at the end of the last century it was evident that individuals with longstanding diabetes maintained risk for chronic kidney disease. Research from the Newcastle group demonstrated that albuminuria was present in approximately 27% of individuals with 30 or more years of type 1 diabetes [25] and that this was independently associated with greatly augmented 7 year

mortality risk [26, 27]. These prevalence estimates were consistent with Swedish National Registry data showing that chronic kidney disease, primarily defined by albuminuria, was present in nearly half of those with type 1 diabetes of 50 or more years' duration [28]. Cumulative incidence from these earlier reports stands in contrast to cohorts accrued more recently in which prevalence of albuminuria and chronic kidney dysfunction appears to be much lower, likely in view of secular trends in the use of intensive insulin and renoprotective therapies, as well as the successful strategies in those earlier reports of employing long-term cohort and registry data to reduce selection bias [29, 30]. Though undoubtedly underestimating lifetime diabetic kidney disease (DKD) risk, these studies can nevertheless serve the important purpose of identifying specific pathways and protective factors.

Through examination of post-mortem renal glomerular specimens from 50 year Medalists, the Joslin investigators were able to determine that those protected from clinical nephropathy displayed exaggerated glycolytic flux. This appears to be associated with decreasing accumulation of toxic glucose metabolites which in turn improves mitochondrial function, podocyte survival and other morphological markers of glomerular pathology. Extending this finding to rodent models, activation of the key glycolytic enzyme pyruvate kinase M2 (PKM2) resulted in normalisation of renal haemodynamic and mitochondrial dysfunction, and subsequent glomerular morphological changes [31–33]. While renal handling of dynamic glycolytic flux appeared to be salutary, there are also data to suggest that the renal handling of AGEs may play a role. Higher exposure of kidneys to circulating levels of AGEs would generally be predicted to be associated with chronic kidney disease, such as exposure to higher N_{ϵ} -(1-carboxyethyl)lysine (CEL) and pentosidine level. However, it was observed that lower levels of certain AGEs (N_{ϵ} -carboxymethyl-lysine [CML] and fructosyl lysine) were associated with nephropathy [30], perhaps through increased renal processing of these toxic metabolites leading to their increased clearance but resulting in greater renal tubule-interstitial exposure and damage [34]. Similar lower levels of other markers of protein glycation damage were observed for retinopathy and other complications in Joslin Medalists [30]. This concept that hyperglycaemia may initiate renal damage by altering both haemodynamics and metabolism to cause dysfunction of renal vascular, glomerular and tubulo-interstitial cells in parallel is plausible since therapeutics that only affect haemodynamics, such as traditional inhibition of the renin–angiotensin–aldosterone system (RAAS), have not appeared to substantially counteract the burden of kidney disease in diabetes populations [31, 35].

In our own work in the Canadian Study for Longevity in Type 1 Diabetes, we committed to a primary outcome of

determining the significance of RAAS activation on DKD. If indeed RAAS activation is the fundamental process of renal injury in type 1 diabetes, certainly this should be evident among individuals with a lifetime of diabetes in that they will have declared with certainty their risk of chronic kidney disease onset. By way of background, it has been established that a subset of individuals (even those with short-duration type 1 diabetes) exhibit hyperglycaemia-induced RAAS activation, in turn leading to increased renal vascular resistance (RVR) and consequent increased glomerular pressure and renal hyperfiltration as compared with during euglycaemia [36]. In those of intermediate age and diabetes duration, evidence of this activation appears to be amplified such that RVR is further increased compared with age- and sex-matched control individuals, and it is associated with the development of indicators of clinical chronic kidney disease [37, 38]. To probe the level of endogenous intrarenal RAAS activity, we applied an infusion of angiotensin-II (ANG-II) to people with 50 years or more of diabetes and a second group of generally age- and sex-matched non-diabetes control individuals to induce angiotensin 1 (AT1) receptors. AT1 receptors are primarily located on the efferent arteriole and their stimulation causes constriction of the efferent arteriole and raises intraglomerular pressure. The physiological role of this mechanism is to maintain glomerular filtration on renal blood flow in the setting of hypovolaemia or hypotension. Abnormal neurohormonal activation induced by hyperglycaemia in diabetes, rather than serving the purpose to maintain glomerular filtration, raises intraglomerular pressure to levels that can induce renal injury. Study of renal haemodynamics has established the degree of change in RVR as the reference measure of endogenous intrarenal RAAS activation. In simple terms, an individual who responds less to exogenous stimulation of the RAAS using ANG-II infusion has developed resistance to its effect because of chronic, maximal stimulation by endogenous ANG-II. An exaggerated RVR response to ANG-II is indicative of lower, nearer normal, endogenous RAAS activation [39–43]. We found that even nephropathy resisters (long-term survivors of type 1 diabetes without evidence of chronic kidney disease) did indeed have evidence of a substantial degree of endogenous RAAS activation compared with non-diabetic control individuals. This effect was most pronounced on the traditional target of this neurohormonal activation, the efferent arteriole (Fig. 2). Individuals with nephropathy had an even greater degree of RAAS activation; however, rather than the predominant effect being constriction of the efferent arteriole, there was greater dilatation of the afferent arteriole, with an amplified effect of increasing intraglomerular pressure (Fig. 2).

This was an important finding from a pathophysiological perspective, simply because RAAS inhibitors, the mainstay of

Fig. 2 RAAS activation in longstanding type 1 diabetes. In individuals with longstanding type 1 diabetes, when compared with age- and sex-matched control individuals, abnormal afferent arteriolar dilatation, rather than classical efferent constriction, is associated with DKD. AT1 receptors are predominantly expressed at the renal efferent arteriole with less relative expression at the afferent arteriole. In non-diabetic control individuals (a), upon exogenous RAAS stimulation with i.v. infusion of ANG-II, ANG-II freely interacts with available AT1 receptors at the afferent and efferent arterioles, initiating vasoconstrictive responses. In individuals with type 1 diabetes without DKD (DKD resistors) (b), locally within the kidney there is more endogenous intrarenal ANG-II at baseline occupying AT1 receptors (relative to non-diabetes controls), predominantly at the efferent arterioles compared with the afferent arterioles. In contrast, in individuals with DKD (c), there is exaggerated expression of

endogenous ANG-II both at the afferent and efferent arterioles at baseline, such that upon exogenous RAAS stimulation, there are fewer AT1 receptors available for ANG-II binding and therefore fewer vasoconstrictive changes relative to DKD resistors and controls predominantly at the afferent arteriole. This finding indicates that abnormal dilatation of the afferent arteriole is a key feature of individuals with DKD after longstanding type 1 diabetes, a process not amenable to pharmacological inhibition from angiotensin converting enzyme inhibitors or aldosterone receptor blockers. R_A, renal afferent arteriole; R_E, renal efferent arteriole; T1D, type 1 diabetes. Republished with permission of the American Society for Clinical Investigation from Lovshin et al. [29]; permission conveyed through Copyright Clearance Center, Inc. This figure is available as part of a [downloadable slideset](#)

management of DKD, are expected to exert protective effect through inhibition of efferent arteriolar AT1 receptors, leading to relative dilatation and reduction in renovascular resistance. However, given that the dominant finding was abnormal afferent arteriolar dilatation leading to greater intraglomerular pressure in individuals with DKD, this could explain the incomplete renoprotection observed with RAAS inhibitors [35]. In our study of renal haemodynamic abnormalities, we found that higher-than-normal uric acid was associated with afferent arteriolar dysfunction [44, 45]. Nevertheless,

a recent definitive clinical trial of uric-acid-lowering therapy in people with type 1 diabetes did not protect against renal function loss over 3 years [46]. The second putative strategy would be the normalisation of afferent arteriolar tone induced by sodium–glucose cotransporter (SGLT) inhibition, which has a proven dramatic cardio-renal protective effect in those with type 2 diabetes [47, 48], and substantial supportive physiological evidence in type 1 diabetes [49, 50]. The findings from the study of longstanding diabetes, in addition to key findings related

to endogenous mechanisms of protection from cardiovascular [6, 28, 51–62] and renal disease, such as maintenance of circulating progenitor cells [63], strongly support further research into the potential major effect of pharmacotherapies such as SGLT inhibition on cardio-renal protection in those with type 1 diabetes, especially on the progression of DKD and heart failure.

Peripheral and central nervous system disease

Though people with diabetes are susceptible to a number of types of peripheral nerve damage, by far the most common is the symmetrical, length-dependent clinical presentation of diabetic distal symmetric polyneuropathy [64]. When compared with other complications, such neuropathy has received less focus in previous studies of longevity cohorts, likely owing to the complexities in objective tests for its identification and quantification of severity. Using self-reported outcome scales or physical examination scales, it has been determined that 40–60% of individuals with longstanding diabetes may be resistant to the development of clinical neuropathy [30, 65–67]. However, in our Canadian Study for Longevity in Type 1 Diabetes research programme, we focused on objective measures of neuropathy examining peripheral nerve function. When subjected to objective testing, we found that the presence of at least one neuropathic symptom or sign corroborated by abnormal peripheral nerve function by the gold standard nerve conduction study testing in those with 50 or more years of diabetes was nearly ubiquitous (approximately 90% of participants studied) [68]. Neuropathy was associated with accentuated diabetes-related distress and depressive symptoms (even independent of the presence of neuropathic pain symptoms), greater than the level of distress associated with any other diabetes complication [69]. Furthermore, we found sex differences such that women appeared to have a greater burden of neuropathic pain than men even with lower severity of objective peripheral nerve dysfunction [68]. These findings have implications for treatment of people with neuropathy, in which strategies to reduce emotional distress and sex-specific strategies for the management of neuropathic pain should be considered.

Several research groups have examined aspects of cognitive function and dementia as central nervous system complications of diabetes [70]. The University of California at San Francisco group have contributed systematically through use of administrative databases (in which at least approximately 5% of those with 50 or more years of type 1 diabetes carry a diagnosis of dementia) and cross-sectional (and future cohort) methods through the Study Of Longevity In Diabetes

(SOLID). In SOLID, though the researchers did not define the proportion of participants with dementia, they found a number of factors to be associated with cognition: one's self-determination for diabetes management ('locus of control'); glycaemic exposure; history of severe hypoglycaemia; history of diabetic ketoacidosis; history of traumatic brain injury; and sleep quality [71–76]. Of great historical concern was the potential causal association between hypoglycaemia and subsequent cognitive impairment. This association was not observed in shorter duration of diabetes [77]. However, in SOLID, focusing on long-duration diabetes, recent severe hypoglycaemia was associated with an OR of 3.22 (95% CI 1.30, 7.90) for impaired global cognition and 3.15 (95% CI 1.19, 8.29) for cognitive impairment on the language domain, each defined by standardised *z* scores of less than 1.5 SD below the population mean from cognitive assessment tests. The Joslin Medalist Study similarly evaluated factors associated with cognitive functioning and found influence of concomitant CVD and retinopathy [70]. There is currently a major research effort examining cognitive function and neuro-imaging in the study population from the Diabetes Control and Complications Trial and Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC), now followed for over 30 years, as it includes a greater proportion of older adults reaching 50 years duration [78]. Additionally, compared with the studies discussed above, this analysis will permit evaluation of causality between hypoglycaemia and diabetic ketoacidosis with the risk of long-term cognitive impairment. The burden of cognitive dysfunction and dementia in those with longstanding diabetes and the identification of interventions for prevention of decline represent an urgent research need.

Retinopathy and macular oedema

Although still susceptible to secular trends and the same forces of selection bias described previously (childhood-onset diabetes, incidence–prevalence bias, death and competing risks), cohort studies have suggested that the cumulative incidence of diabetic retinopathy likely exceeds 90% in people with type 1 diabetes, and that of macular oedema is likely substantially lower [79–81]. However, selected cohorts with longstanding type 1 diabetes demonstrate larger proportions of individuals free of retinopathy and macular oedema even after 50 or more years of diabetes duration (e.g. 35% of the Joslin Medalists and 16% of participants in the Canadian Study of Longevity in Type 1 Diabetes) [30, 82]. The role of long-term excess glycaemic exposure (and the formation of AGEs) has been clear from multiple experimental sources [83], including the Joslin Medalist Study that found higher levels of plasma carboxyethyl lysine and pentosidine but not traditional markers of glycaemic exposure (discussed above in the

context of renal injury) also associated with the presence of retinopathy [30]. In that same study, individuals free of retinopathy appeared to be at minimal risk of progression [30]; the forces of selection may explain this so it is important that clinicians consider the appropriate risk factor modification for prevention of incidence and progression of complications at any age or duration. However, a number of mechanisms have been identified to potentially explain resistance to retinopathy and other complications. Higher concentrations of retinol binding protein 3 (RBP3), a transport protein secreted mainly by the retinal photoreceptors, were observed in those resistant to the development of retinopathy [84, 85]. This fundamental discovery was of great importance as RBP3 overexpression in resistors could affect multiple known pathological pathways including inhibition of the tyrosine phosphorylation of vascular endothelial growth factor receptors, decreasing glucose uptake via GLUT1 into retinal endothelial cells and Müller cells, thus acting as a countermeasure to the downstream hyperglycaemia-induced injurious pathways including local cytokine production [86]. Additionally, impaired growth, reprogramming and differentiation of circulating inducible pluripotent stem cells were observed in those with any complication (but prevalence and severity of retinopathy was the greatest), and genomic and proteomic analysis revealed association with DNA damage checkpoint proteins, specifically the miT-200 microRNA transcriptional regulator [87]. Differential exaggerated responses to RAAS activation in the peripheral vasculature of those with proliferative retinopathy were observed in Canadian participants such that even in the absence of kidney disease, neurohormonal abnormalities are a fundamental pathway in those with retinopathy and longstanding type 1 diabetes duration as they have been demonstrated to have particular effect on novel aspects of renal vascular (afferent arteriole) and peripheral vascular dysfunction [52].

Taken together as an extensive literature, the study of retinopathy in longstanding diabetes has identified that greater glycaemic exposure and its downstream injurious mechanisms can putatively be modified by overexpression of a retinol binding protein pathway and that modification of the DNA damage checkpoint pathways in circulating stem cells and novel pharmacological mechanisms for modifying RAAS activation may serve as potential therapeutic targets for diabetic complications.

Concluding considerations

In this review, we have focused on the learnings from the study of longstanding type 1 diabetes on discoveries about the natural history of insulin production loss and microvascular complications and the mechanisms associated with them that may in future offer therapeutic targets. Such fundamental

findings likely could not have occurred without studying the extraordinary people who have survived longstanding diabetes. To date, prominent among these potentially beneficial approaches are strategies to maintain or recover existing beta cells and their function, activation of specific glycolytic enzymes (e.g. PKM2), modification of AGE production and processing, novel mechanisms for modification of RAAS activation (in particular, those that may normalise afferent rather than efferent renal arteriolar resistances), and activation and modification of processes such as retinol binding and DNA damage checkpoint proteins. Highlighting these particular discoveries in no way is meant to overshadow the wealth of descriptive data from longevity studies, implications on process of care and public health policies [66], or the need to better implement and emphasise standard clinical practices in the management of this unique patient group [51]. Additionally, we must further the knowledge on specific findings such as poorer bone health despite maintenance of adequate levels of bone density [88–90], the dramatically high risk of troublesome cheiroarthropathy [91], a better understanding of heart failure and atherosclerotic CVD, and the wealth of research around mental health, diabetes-specific emotional distress, and the factors associated with the resilience shown by so many outstanding people with a lifetime of type 1 diabetes.

Supplementary Information The online version contains a slideset of the figures for download available at <https://doi.org/10.1007/s00125-021-05403-9>.

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