REVIEW PAPER

JMS Journal of Medical Science

Factors determining the prognosis of people with type 1 diabetes – current perspective

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😳 doi: https://doi.org/10.20883/medical.e1122

Keywords: type 1 diabetes, life expectancy, mortality, complication risks, risk factors

Received 2024-08-21 Accepted 2024-12-28 Published 2024-12-31

How to Cite: Araszkiewicz A, Trzaska K, Soukharev A, Spławski J, Wolbach J, Marek P, et al. Factors determining the prognosis of people with type 1 diabetes – current perspective. Journal of Medical Science. 2025 March;94(1);e1122. doi:10.20883/medical.e1122



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ABSTRACT

A multitude of factors strongly influences the prognosis of subjects with type 1 diabetes. In the literature, it's notable that only a limited number of studies simultaneously address multiple factors. Our objective is to identify and compile current papers that thoroughly examine these factors, offering a comprehensive overview of the various elements that can influence both life expectancy and the prevalence of complications among individuals with type 1 diabetes. In the overview, we included modifiable and non-modifiable factors. The paper covers technology development, comorbidities as well as acute and chronic complications as predictors. Greater focus on the significance of sex and age as a risk of macrovascular diabetes-related complications, age at onset of diabetes, and episodes of acute complications, can lead to more targeted management of type 1 diabetes and therefore, higher life expectancy. The article also discusses such environmental

factors as lifestyle, education, and access to the healthcare system affecting better handling of type 1 diabetes. This overview emphasizes the plurality of factors that are considered in type 1 diabetes, which might be crucial to prolonging life expectancy and reducing the prevalence of complications.

Introduction

Diabetes type 1 (T1D) remains one of the most commonly occurring chronic diseases with its incidence steadily increasing in recent years [1]. Despite advancements in various aspects, including diagnosis, treatment, and management, leading to more positive outlooks and reduced overall mortality, individuals with type 1 diabetes still experience a notably lower life expectancy compared to the general population [2,3]. Various factors can influence the lifespan of subjects with type 1 diabetes, ranging from modifiable lifestyle choices to non-modifiable demographic characteristics [4]. In the literature, it's notable that only a limited number of studies simultaneously address multiple factors. Our objective is to identify and compile current papers that thoroughly examine these factors, offering a comprehensive overview of the various elements that can influence both life expectancy and the prevalence of complications among individuals with type 1 diabetes.

The Significance of Technology in Diabetes Management

There is no doubt, that the greatest progress in recent years in the treatment of patients with type 1 diabetes has occurred in the field of new technologies, those supporting the measurement of glycemia, and those facilitating precise insulin administration.

Self-Monitoring of Blood Glucose (SMBG) and Continuous Glucose Monitoring (CGM) Systems

In recent years, tremendous technological advances have significantly improved the prognosis for patients with type 1 diabetes (T1D), enhancing their daily functioning and simplifying the monitoring and management of their condition. Glucometers have been the most fundamental and widely used devices for daily blood glucose monitoring for many decades by the vast majority of diabetes patients [5,6]. One of the recent advancements in diabetes management includes the development of smartphone applications (apps) specifically designed for diabetes management. These apps offer various features to help individuals with diabetes monitor their blood glucose levels, track insulin dosages, record food intake, and log physical activity. Despite the glucometer's relatively high reliability in blood glucose measurements [7,8], it has drawbacks, notably the need for daily finger pricking, and above all, only current, glycemia measurement without insight into the past or future. Consequently, more technologically advanced methods of blood glucose measurement have been developed, namely the CGM systems.

CGM systems consist of sensors that continuously monitor interstitial glucose levels, and transmitters that send wirelessly data to a receiver or smartphone app, providing real-time glucose readings and trend information [9]. This significantly enhances the ability to manage glycemia fluctuations in response to meals or exercise. By providing alerts CGM systems increase the safety of treatment and reduce the risk of hypoglycemia, especially severe and nocturnal ones. In the DIAMOND trial, the mean glycated hemoglobin level (A1c) after twelve weeks of CGM use decreased by 1.1% in the type 1 diabetes group and only by 0.5% in the control group. Additionally, the mean time below range (TBR) <70 mg/dl in the two groups was 43 min/day and 80 min/ day respectively [10]. CGM systems are an excellent educational tool and can motivate patients to improve self-care. They have also demonstrated long-term positive effects on increased physical activity, weight loss, reduced calorie intake, and greater treatment satisfaction, indirectly improving the prognosis of patients with T1D [11].

Insulin Administration

The most crucial aspect of insulin therapy is selecting the appropriate type of insulin and its

proper administration. The first commercially available insulin was of animal origin. Only in the 1980s did human insulin preparations obtained through genetic engineering appear. The next generation of preparations are insulin analogues. Compared to human insulin, insulin analogues have an action profile closer to physiology. Undoubtedly insulin analogues offer advantages in daily life, among others preventing nocturnal hypoglycemia and improving postprandial glycemia [12]. Thanks to advancements in genetic engineering, insulins are now being developed to reduce the frequency of daily injections or, in case of basal insulin, are planning to be administered weekly [13]. Regarding insulin delivery, there are various methods available. Insulin syringes were the first to appear on the market, now being replaced in many countries by pen injectors [14,15]. Additionally, so-called 'smart pens' are being further developed to transmit information on insulin administration times and doses via Bluetooth to a dedicated smartphone application, which also provides dose reminders and monitors insulin levels [16]. Moreover, unconventional methods of insulin administration, such as oral, or inhalable delivery, have gained interest among researchers and may potentially replace subcutaneous administration in the future [17].

Insulin Pumps. Closed-Loop Systems

Closed-loop insulin delivery systems, also known as artificial pancreas systems, represent the most advanced technology mimicking the function of the natural pancreas. These systems integrate CGM with an insulin pump and algorithm to automatically adjust insulin delivery based on real-time glucose readings. Initially introduced in Europe in 2015, they have rapidly evolved, with increasingly sophisticated solutions available today [18].

While most closed-loop systems primarily administer insulin, some incorporate glucagon or a combination of both hormones [19]. They demonstrate high efficiency in automatic glucose regulation, notably reducing the risk of hypoglycemia. Despite potential inaccuracies in carbohydrate estimations, adaptive algorithms effectively compensate meal estimation, enhancing overall system performance. This represents an amelioration in patients' quality of life and a reduction in associated stress, ultimately improving their prognosis [20].

Patients also have the option of choosing standalone insulin pumps, which provide them with simplified daily routines and enhanced treatment satisfaction. However, their effectiveness outside the closed-loop setting is notably diminished. Research suggests that two years after training in flexible insulin therapy, the reduction in A1c levels was considerably better on a pump compared to MDI, with pumps resulting in a decrease of 0.85% compared to 0.42% for MDI [21].

The Role of Immuno-based Therapy and Transplantations

Currently, the sole known cure for T1D is pancreas transplantation, with over 900 procedures performed annually in the United States alone. These surgeries offer the opportunity to maintain euglycemia permanently, prevent hypoglycemia, and sometimes mitigate or eliminate the effects of the disease [22,23]. Due to co-existing renal-related complications, patients often undergo kidney transplantation simultaneously. Despite potential complications, the majority of patients achieve therapeutic success, with estimated survival rates of 87% at five years post-surgery and 70% at ten years for simultaneous pancreas-kidney (SPK) transplantation [24]. Patients experience increased empowerment leading to improvements in health, mental well-being and social interactions. Systemic changes are observed in glomerular structure and cardiovascular function [23].

An alternative to whole pancreas transplantation is islet cell transplantation, which is a simpler and lower-risk procedure. Although it does not guarantee total insulin independence, achieved by 52% of patients, it reduces the frequency and severity of hypoglycemic episodes. A1c level is reduced to <7.0% in most patients, reaching the median value of 5.6% at 1-year post-transplant [25]. However, graft survival is influenced by continued immunosuppression, which poses challenges for recipients. As a result, ongoing research aims to investigate alternative cell sources capable of producing functional pancreatic beta cells or to develop transplantation techniques that minimize immune system activation. Promising studies focus on macro-encapsulated human islets and pluripotent stem cells (iPSCs) obtained from patient tissues and reprogrammed in culture into stem cell-derived islets (SC-islets). These can be used not only for autologous transplantation but also for studying the pathogenesis of T1D [26,27].

Recently, immune-based therapies have gained significant interest in treating T1D due to their potential to modify the underlying autoimmune response responsible for destroying insulin-producing beta cells in the pancreas. These therapies aim to halt or slow down the progression of the disease, preserving beta cell function and improving glycemic control. Teplizumab, a humanized monoclonal antibody targeting CD3, has emerged as the first FDA (Food and Drug Administration) approved therapy for modifying the course of preclinical stage 2 diabetes [28].

The significance of late diabetic complications and selected comorbidities in diabetes prognosis

Chronic kidney disease (CKD), Diabetic peripheral neuropathy (DPN) and Cardiac autonomic neuropathy (CAN)

Stages of CKD were found to be one of the most significant factors predicting all-cause mortality in type 1 diabetes. Advanced eGFR stages G4-G5 were found to have some of the highest mortality rates per 100 person-years, at 9.11 and 11.42 respectively [29,30]. Patients with end-stage renal disease have more than three times increased risk of all-cause death compared to patients without such ailments [29,31]. Individuals on renal replacement therapy have a median survival time of 3.84 years since the beginning of the mentioned procedure [32]. Diabetic retinopathy is a highly specific neurovascular complication with prevalence strongly related to both the duration of diabetes and the level of glycemic management. Diabetic retinopathy is the most frequent cause of new cases of blindness among adults aged 20-74 years in developed countries

[33]. Distal symmetrical polyneuropathy is the cause of severe discomfort, significantly deteriorates the quality of life of patients, and is a recognized risk factor for the development of diabetic foot syndrome in the form of ulcers and Charcot's neuroarthropathy. Neuropathy increases the risk of amputations, fractures, and falls, as well as the costs of treatment, and is a predictor of increased mortality risk. Cardiovascular autonomic neuropathy is an independent risk factor for increased mortality in diabetes [34].

Cardiovascular disease (CVD)

Patients with T1D with a history of cardiovascular disease were found to have almost twice the risk of all-cause death than individuals without it. History of heart failure worsens the prognoses even more [29]. The co-existence of CVD and CKD further increases the risk of death [29]. In the past years, deaths and hospitalizations from CVD declined substantially in people with type 1 diabetes. In Sweden from 1998 through 2014 patients with type 1 diabetes had roughly even 40% greater reduction in cardiovascular outcomes than controls. Unfortunately, the risk of CVD events still remains clearly higher in the population with T1D [30,35].

Overweight and obesity

Normal body mass index (BMI) isn't indicative of the longest lifespan in individuals with T1D. Research across various BMI groups reveals that those with a BMI of 20 kg/m² tend to have the shortest predicted lifespans, while those with a BMI of 25 kg/m² demonstrate the best outcomes [4]. This seems consistent with the findings of other studies which suggest the lowest adjusted mortality rates within the 25-29.9 kg/ m2 BMI range [29]. However, the prognosis worsens with further increases in BMI. Nonetheless, differences in predicted lifespans between class I obesity and class II obesity are inconsistent. Some cases suggest that more obese patients might have slightly longer life expectancy than less obese ones, even though the exact opposite is often true [4]. This contrasts with the general population, where increasing BMI typically correlates with an increased risk of death [36]. The association between BMI and mortality in subjects with T1D may be influenced by confounders such as differences in age, duration of diabetes, glycemic control, and the presence of comorbidities like cardiovascular disease or nephropathy. Lower BMI in T1D individuals might be indicative of poor glycemic control, catabolic states, or the presence of diabetes-related complications that adversely impact longevity.

COVID-19

Patients with diabetes diagnosed with COVID-19 had a 2.26 times increased risk of experiencing diabetic ketoacidosis (DKA) incidents than those without infection [37]. People hospitalized with a COVID-19 infection and type 1 diabetes have a 2.86 times increased risk of death than those without diabetes [38]. This trend was more visible in the younger population with 6.39 times odds of death increase [38].

Depression

Depressive scores are higher in people with T1D overall and increased 7-fold in men as compared to the general population. Higher levels of depressive symptoms are associated with both lower engagement in self-management behaviors and physical activity [39]. Depressed patients with type 1 diabetes have more than 3 times increased risk of DKA event and more than 2 times increased risk of severe hypoglycemia [40]. A positive connection between a patient's history of depression diagnosis and the progression of diabetic nephropathy has been found. A study shows a 1.5 increased chance of renal damage progression in affected patients [41]. These data demonstrate that there is an urgent need to screen adults with T1D for depressive symptoms as part of routine medical care and to test interventions to minimize their impact on physical health outcomes.

Impact of age at diagnosis of type 1 diabetes on mortality, life expectancy and acute complications

Type 1 diabetes ranks as the second most prevalent chronic disease affecting children. Notably, the severity of its complications varies significantly based on the age at diagnosis. Individuals with type 1 diabetes face a considerable reduction in life expectancy, evident in the two- to eightfold increase in mortality rates. According to Rawshani et al. in the Swedish National Diabetes Register the onset of type 1 diabetes before the age of 10 is associated with a loss of 16 life-years, estimated at 17.7 life-years lost in females and 14.2 life-years lost in males. Conversely, diagnosis after the age of 20 results in a loss of 10 life-years. This highlights an inverse relationship between age at diagnosis and the risk of mortality, with cardiovascular complications being the primary cause. Moreover, in a Finnish population-based cohort of T1D subjects, the mortality risk from ischemic heart disease is exceptionally high in women with early-onset T1D compared with women in the background population. These observations underscore the importance of identifying risk factors early in women and delivering more aggressive treatment after diagnosis. [42,43] Cardiovascular-related deaths constitute a significant proportion, accounting for 70% and 61% of all major contributors to mortality in individuals diagnosed before the age of 10 and between 26-30 years of age, respectively. Interestingly, the data of Vuralli D et al in Turkey girls were 1.9 times more likely than boys to have two or more risk factors for CVD. Factors associated with risk for CVD in multiple logistic regression analyses were being a girl, followed by higher daily insulin dose, higher hemoglobin A1c, and longer duration of diabetes [44].

Diabetic ketoacidosis and severe hypoglycemia as acute complications of T1D

Diabetic ketoacidosis (DKA) and severe hypoglycemia (SH) are still life-threatening acute complications of type 1 diabetes. Poor glycemic control, considered as higher levels of A1c, remains one of the major factors contributing to the increased risk of DKA, SH, microvascular and macrovascular complications of T1D [45]. The highest frequency of DKA events concerns the suboptimal glycemic control with a rate of A1c >9.5% in patients aged 13 to <18 years [46,47]. The incidence of SH by its highest rate relates to 2–6 years old patients in the T1D Exchange Clinic Registry [47]. The frequency of this acute complication is widely influenced by the lev-

el of A1c. Patients with lower A1c (<6%) as well as with higher A1c (>13%) have a greater risk of SH (respectively 6.9% and 13.5%) than those patients with A1c >6.5% to 7% (3.3% of risk) [45]. Priorly highlighted the importance of firm glycemic control is crucial to preventing significant fluctuations of glycemia and further occurrences of hypoglycemia [45,47] However, glycemic control and therefore prevalence of DKA and SH closely correlate with other relevant factors such as BMI. Patients with BMI <30kg/m² (normal weight and overweight) have better glycemic control than obese patients and reduced risk of T1D-related complications [45]. It is remarkable that female sex and ethnic minority status correlate with a 23% and 27% increase in the likelihood of experiencing DKA, respectively [46,47]. Coexistent lower household income and lack of private health insurance are associated with elevated incidence of DKA and SH [45,47]. Younger patients are substantially exposed to a higher risk of DKA and SH resulting in morbidity and mortality. Having regard to age and reasonable management of T1D, including monitoring glucose levels and performing blood or urine tests to detect possible considerably increased ketone bodies, could distinctly reduce the occurrence of acute complications in type 1 diabetes patients [45,45]. Moreover, the wide use of closed-loop systems might significantly minimize the risk of severe hypoglycemia. Fortunately, data from multiple countries, T1D Exchange Quality Improvement Collaborative, and the SWEET initiative gathered between the years 2013-2022 show a decrease in the incidence of DKA from 3.1 events per 100 person-years to 2.2 events per 100 person-years in 2022. This progress is associated with a simultaneous increase in the frequency of insulin pump and CGM systems' usage [48].

Gender as a risk factor for CVD in patients with T1D

Certainly, when examining sex as a risk factor for cardiovascular disease, noticeable differences exist between the general population and individuals with T1D. Statistics report conducted by the European Society of Cardiology shows that males have both higher incidence and prevalence of CVD per 100.000 people compared to females after age standardization [49].

However, in a population of patients with T1D, an alarming statistic emerges. A study combining registries from multiple countries showed, that in patients with T1D, after age standardization females have a greater incidence of CVD such as stroke (1.37 female: male ratio) and have more than twice greater incidence for coronary heart disease (2.54 female: male ratio) with a mortality from CVD being almost twice as much in females than in males (1.86 female: male ratio) [50]. That statistic confirms previous studies in which a relation was found between females with T1D and more rapid arterial endothelial dysfunction such as artery calcification than in males [51,52]. However, more recent studies need to be made to find the underlying causes for the previously shown statistics.

Age as a factor for CVD in patients with T1D

Cardiovascular diseases (CVD) are the leading causes of death in modern society. In the overall American population, in 2020 about 25% of all deaths were contributed to CVD [53]. Moreover, the percentage of CVD and associated deaths are directly proportional to advancing age. In the age group of 25–44 years old, CVD were responsible for 10.6% of all deaths and in the age group of 65 and older, amount of deaths associated with CVD increased to 27.7% [53].

Among patients with T1D age is still considered the strongest risk factor for CVD (including stroke and acute/silent myocardial infarction), followed by mean A1c levels [54]. Subsequently, atherosclerosis as a consequence of endothelial dysfunction plays a crucial role in the pathogenesis of CVD [55]. Studies show, that patients with T1D (mean age of ~46 years) had decreased reactive hyperemia index (RHI, a measure of endothelial function) when compared to healthy control group [56]. The difference in RHI was however not visible in younger patients with T1D (mean age of ~21 years) when compared to the healthy control group of similar age [57]. These results reveal that age as a risk factor for CVD in patients with T1D is significantly more important as a risk factor when compared to a healthy population.

The significance of health care access and education

Complications of T1D can be reduced or delayed by efficient control of A1c, blood pressure, and cholesterol levels (ABCs of diabetes). The strict relation between access to health care and managing disease among people is visible. The importance of access to healthcare in managing the disease is evident, with current health insurance coverage and frequency of medical visits serving as key indicators of access. Individuals with chronic illnesses, such as T1D, require regular communication with medical professionals for effective glycemic control [58,59]. Those without insurance tend to visit medical doctors less frequently compared to their insured counterparts (12.2% vs 2.1%; at least one visit during the last 12 months respectively), leading to poorer diabetes management outcomes [58]. Therefore, people with poor access to medical care (state insurance instead of private or lack thereof) showed a higher probability of having an A1c level > 9% and blood pressure > 140/90mmHg [58,59]. Moreover, the frequency of medical visits correlates with better diabetes control, with individuals reporting over four visits in the previous year demonstrating significantly improved A1c levels compared to those who did not disclose any medical visits (mean A1c 9.1 vs. 7.4% respectively) [58]. There is a strong and clinically relevant correlation between inadequate glycemic control, lack or poor level of insurance, and frequency of visits to the physician [59]. Enhancing the availability of healthcare services for individuals with T1D is crucial, as it plays a vital role in controlling risk factors and decreasing diabetes-related complications [58].

Adolescents diagnosed with T1D encounter difficulties adjusting to a way of life that necessitates self-management of food habits, exercise routines, and insulin dosage adjustments. The purpose of diabetes education is to assist patients in gaining the skills, information, self-care routines, coping mechanisms, and attitudes necessary for efficient diabetic self-control [60,61]. Patients who had obtained diabetes education (59%) were more inclined to conduct self-management than their counterparts who had not. It is associated with A1c level: 42% of educated patients had a level of A1c >8% vs 52% in a group of non-educated. These findings unequivocally demonstrate the advantageous effects of diabetes self-management on glycemic target achievement and the favorable correlation between diabetes education and self-management [62]. There are a dozen of established diabetes education programs. For individuals with T1D, PRIMAS is one of self-management-oriented education programme. Research proves that PRI-MAS is effective in lowering A1c, as evidenced by a 0.4 percentage point decrease in A1c compared to the control group [61]. Presented data shows that to improve the effectiveness of patient treatment and avoid acute complications all diabetic centers should incorporate health education throughout their diabetes care programs [60]. Adolescents with T1D may benefit from education intervention as a preventative measure against potential declines in their quality of life. Moreover, it has been proven that deterioration of glycemic control can be prevented through educational intervention, which translates into more effective treatment and better patient outcomes [60,62]. In conclusion, diabetes education fosters a favorable attitude toward patients' active involvement in the control and treatment of their condition in addition to imparting the knowledge and skills necessary to maximize self-management [62].

Lifestyle features are important for people with type 1 diabetes

Self-Management

It is known that self-management programs can significantly improve the quality of life for people with T1D. These programs encourage independence and empower individuals to take control of their health, potentially leading to improved emotional well-being. However, the situation is not without its challenges. Depression is a possible comorbidity in T1D and can significantly hinder a teenager's ability to stay motivated and adhere to the demanding regimen. Furthermore, research indicates that while self-management programs may improve the quality of life, their impact on metabolic control, as measured by A1c, might be less pronounced. This highlights the need for a multi-directional approach that addresses not just the physical aspects of diabetes manage-

31

ment but also the emotional well-being of the adolescent [34].

Physical Activity

A sedentary lifestyle often correlates with a diminished quality of life for individuals with T1D. Physical inactivity can lead to fatigue, reduced motivation, and a decline in overall well-being. However, there is promising evidence: incorporating regular physical activity into one's daily routine can bring about transformative changes. Studies demonstrate that exercise improves sleep quality, enhances overall enjoyment of life, and increases motivation for further physical activity. Systematic physical exercise increases insulin sensitivity and allows people with type 1 diabetes to optimize glycemia with lower insulin demand [34]. This positive cycle not only improves quality of life but also offers significant health benefits.

One major concern for people with T1D is the risk of hypoglycemia during exercise. However, this fear can be addressed by implementing a well-designed training plan. High-Intensity Interval Training (HIIT) has emerged as a promising approach. By incorporating short bursts of intense activity followed by recovery periods, HIIT allows for effective exercise while minimizing the risk of hypoglycemia. Additionally, regular exercise offers a plethora of benefits beyond blood sugar control. It improves fasting glucose levels and reduces cardiovascular risk, potentially leading to a longer and healthier life. However, research suggests that achieving a significant reduction in A1c levels through exercise is more likely when adhering to a structured training plan like HIIT. This underscores the importance of tailoring exercise regimens to individual needs and preferences to maximize their effectiveness [64-66].

Diet

Diet plays a crucial role in managing blood sugar levels in T1D. Studies suggest that there is a need for a personalized approach to dietary planning, taking into account factors such as age, gender, and physical activity level. The standards of care of Diabetes Poland state that individuals with type 1 diabetes should avoid easily digestible carbohydrates and follow the general principles of a properly balanced diet. There is insufficient scientific evidence to determine one optimal

amount of carbohydrates for individuals with diabetes, so carbohydrates should make up about 45% of total energy [34]. There is a growing body of research on dietary management strategies for individuals with type 1 diabetes. Turton et al. conducted a single-arm non-randomized clinical trial to investigate the effects of a low-carbohydrate diet in adults with type 1 diabetes management. The preliminary findings suggest that a professionally supported low-carbohydrate diet may lead to improvements in markers of blood glucose control and quality of life with reduced exogenous insulin requirements and no evidence of increased hypoglycemia or ketoacidosis risk in adults with T1D. Muntis et al. indicate a possible link between high protein intake and improved glycemic control after exercise. This suggests that incorporating lean proteins into the diet can further optimize blood sugar management during physical activity. Gluten-free diets, however, have not been shown to improve quality of life or glycemic control in individuals with T1D who are not diagnosed with celiac disease. Interestingly, research on adolescent dietary habits reveals a concerning trend. A study suggests that the average diet of teenagers with T1D is often lacking in essential nutrients. Addressing these challenges through education and personalized dietary counseling can significantly improve the quality of life for adolescents with T1D [67-70].

Conclusions

Prognosis and management of people with type 1 diabetes involve many crucial determinants. These factors are strongly connected with morbidity, mortality, and life expectancy of patients. This review highlights two main groups of features influencing the prognosis of patients with T1D. The first group includes key-role factors such as sex, age at onset of T1D, presence of comorbidities, and cardiovascular and acute complications of T1D. The data emphasize the importance of considering these factors, especially in patients with early onset T1D, and implementing more targeted guidelines, particularly in cardiovascular prevention, which could significantly lower the mortality of people diagnosed with type 1 diabetes at a young age. Greater focus on these characteristics during early diagnosis and treatment is crucial for mitigating the risk of lower life expectancy and achieving better control of the disease in individuals with T1D. The second group comprises environmental aspects, including consistent self-management, access to diabetes educational programs, enhanced healthcare system access, and recent technological advancements. These factors are closely associated with improved prognosis in patients with T1D. Strengthening these areas could significantly simplify T1D management, and improve quality of life and daily functioning while reducing the occurrence of severe diabetes-related complications. The review discusses the current perspective on the prognosis of patients with T1D, which is markedly dependent on a wide range of factors. Incorporating their relevance into guidelines could significantly prolong life expectancy, reduce morbidity, and enhance daily well-being for individuals living with T1D.

Acknowledgements

Large language models (Gemini 1.0, ChatGPT-3.5, Grammarly) were used to provide the language correctness of this text.

Conflict of interest statement

The authors declare no conflict of interest.

Funding sources

There are no sources of funding to declare.

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