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# Predictors Associated with Type 2 Diabetes Mellitus Complications over Time: A Literature Review

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**Abstract:** Early detection of type 2 diabetes mellitus (T2DM) complications is essential to prevent disability and death. Risk prediction models are tools to estimate the probability that an individual with specific risk factors will develop a future condition within a certain time period. A predictive model that incorporates time to quantify the risk of T2DM complications such as cardiovascular diseases (CVD) event is still lacking. Well-established and validated predictive models of T2DM complications are vital to stratify patients based on their risks; thus, individualization therapy could be optimized. New approaches (e.g., the parametric approach) are needed in developing predictive models of T2DM complications by incorporating new and time-varying predictors that may improve the existing models' predictive ability. This review aimed (1) to summarize the reported predictors for the five main complications of T2DM, which include cardiovascular diseases, ischemic stroke, diabetic nephropathy, diabetic neuropathy, and diabetic retinopathy, and (2) to highlight the persistent need for future risk score models as screening tools for the early prevention of T2DM complications.

**Keywords:** T2DM complications; predictive models; diabetic neuropathy; diabetic nephropathy; CVD



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## 1. Introduction

Type 2 diabetes mellitus (T2DM) is a chronic disease characterized by insulin resistance [1] and is considered to be the fourth-leading cause of death in high-income countries, with a 2-fold additional risk of mortality and 2- to 4-fold rise in the risk of cardiovascular disease [2]. According to the 2020 American Diabetes Association (ADA) guidelines, patients with T2DM are defined by the presence of a fasting plasma glucose (FPG) level equal to 126 mg/dL (7.0 mmol/L) or higher, or a 2 h plasma glucose level equal 200 mg/dL (11.1 mmol/L) or higher after a 75 g oral glucose tolerance test, and/or a random plasma glucose equal to 200 mg/dL (11.1 mmol/L) or higher in patients with classic hyperglycemia or hyperglycemic crisis symptoms, and/or a hemoglobin A1c (HbA1c) level equal 6.5% (48 mmol/mol) or higher [3].

Macrovascular complications of T2DM include coronary artery disease, peripheral arterial disease, and stroke, whereas T2DM microvascular complications include diabetic retinopathy and nephropathy [4], and these complications may be present at diagnosis in people with T2DM [4]. Therefore, early detection is essential to prevent disability and death [5]. Risk-prediction models are tools to estimate the probability that an individual with specific risk factors will develop a future condition, such as stroke, within a certain period of time. This review aimed to summarize the reported predictors for the five main complications of T2DM, which include cardiovascular diseases, ischemic stroke, diabetic nephropathy, diabetic neuropathy, and diabetic retinopathy (Table 1) [6–14], and to highlight the persistent need for future risk score or predictive models as screening tools for early prevention of T2DM complications.

**Table 1.** Reported predictors of T2DM complications.

| Cardiovascular Disease Predictors [6,7,9,10,15,16] | Ischemic Stroke Predictors [7,9,11,16] | Diabetic Kidney Disease Predictors [12,13] | Diabetic Neuropathy Predictors | Diabetic Retinopathy Predictors [14] |
|---|---|---|---|---|
| Nonmodifiable predictors | | | | |
| Age<br>Age at diagnosis of diabetes<br>Ethnicity<br>Gender | Age<br>Age at diagnosis of diabetes<br>Gender<br>Previous stroke | Age<br>Age at diagnosis of diabetes<br>Gender | No prediction models | Family history of diabetes |
| Modifiable predictors | | | | |
| HbA1c<br>Antidiabetic<br>Duration of diabetes<br>Fasting blood glucose variation<br>UACR<br>Smoking status<br>Presence of atrial fibrillation<br>Presence of microalbuminuria<br>SBP<br>White blood cell count<br>TC<br>LDL<br>HDL | HbA1c<br>UACR<br>Antidiabetic<br>History of arterial embolism history<br>History of atrial fibrillation<br>Fasting blood glucose variation<br>Cardiovascular medication<br>Duration of diabetes<br>History of coronary heart disease<br>TC-to-HDL ratio<br>Smoking status at diagnosis of diabetes.<br>SBP<br>Thrombosis history<br>White blood cell count | HbA1c<br>LDL<br>SBP<br>UACR<br>TC<br>Albuminuria<br>Antidiabetic<br>Antihyperlipidemic<br>Antihypertensive<br>Serum creatinine<br>Retinopathy<br>eGFR | | Waist-to-hip ratio<br>HbA1c<br>Duration of diabetes |

HbA1c: glycated hemoglobin, eGFR: estimated glomerular filtration rate, LDL: low-density lipoprotein, HDL: high-density lipoprotein cholesterol, TC: total cholesterol, SBP: systolic blood pressure, UACR: urine albumin-to-creatinine ratio.

## 2. Cardiovascular Diseases

The most common and classic types of CVD associated with diabetes are coronary heart disease, cerebrovascular disease, peripheral artery disease, and congestive heart failure. Cardiovascular complications in T2DM are commonly associated with arteriosclerosis incidence, which is greater in people with diabetes than those without diabetes. Patients with diabetes have an increased risk of atherothrombotic events, attributed in part to platelet dysfunction [17]. The increased incidence of CVD events in patients with T2DM is associated with a high blood glucose level, insulin resistance, low-grade inflammation, and activation of the coagulation cascade [18,19], which is collectively considered the largest cause of both morbidity and mortality for people with diabetes [20]. CVD complications in T2DM are commonly manifested as specific events such as hospitalizations, procedures, and deaths from acute coronary syndromes, myocardial infarction, and ischemic and hemorrhagic stroke, as well as sudden death [21].

### *2.1. Nonmodifiable and Modifiable Predictors of CVD Events in T2DM*

Systematic reviews indicated that the relative risk of CVD events among diabetics is between 1.6 and 2.6, while the relative risk is surprisingly higher among diabetic women and those at a younger age [22,23]. Risks of cardiovascular diseases in patients with T2DM vary considerably among different ethnic groups [15,24] (Table 1).

Each standard deviation (SD) in fasting blood glucose, HbA1c, or 2-h glucose test results is associated with 6–20% increased risk of CVD events [25]. Many studies have

illustrated that the risk of cardiovascular events increases in patients with an increased HbA1C [26–29]. However, most of the previous studies used a cross-sectional value or baseline blood glucose value to determine the risk of CVD complication. Blood glucose is time-varying, and the progression rate over time could be affected by many covariates, including changes in weight, the dose of antidiabetic drugs, and the patient's compliance with lifestyle and diet [30]. The impact of the progression rate of blood glucose over time on the risk of CVD events may need to be investigated [31]. Moreover, patient care directed at controlling the covariates affecting the blood glucose progression rate and its role in reducing CVD events' risk over time should be investigated.

Longer duration of diabetes increases the risk of CVD complication in T2DM. This may suggest early prevention of diabetes itself may play an important role in reducing the risk [32]. According to the International Diabetes Federation (IDF), CVD risk in diabetics is also strongly affected by smoking and low physical activity levels [5]. These risk estimates were calculated based on the duration of diabetes, age at diagnosis of diabetes, current age, gender, ethnicity, smoking status, presence or absence of atrial fibrillation, and microalbuminuria or its severity. Moreover, factors such as HbA1c, systolic blood pressure (SBP), variations in fasting blood glucose, the use of anti-diabetic medication, urine albumin-to-creatinine ratio (UACR), white blood cell count, total cholesterol, low-density lipoprotein, and high-density lipoprotein cholesterol collectively were found to be associated with risk of CVD in T2DM [6,7,9,10,16]. An elevated concentration of natriuretic peptides [33–38] and high-sensitivity cardiac troponin [39] in patients with T2DM have been associated with increased cardiovascular risk, particularly heart failure. However, none of the previous predictive models incorporated these new biomarkers during the model building.

Metabolomics is a growing field in personalized medicine. Although notable metabolic differences were revealed between high blood pressure and coronary heart disease in T2DM patients [40], prediction models for CVD complications in T2DM that include metabolomics-based markers are still lacking (Figure 1). This area opens new opportunities for prediction of T2DM that may go beyond the classical biochemistry assays [41].

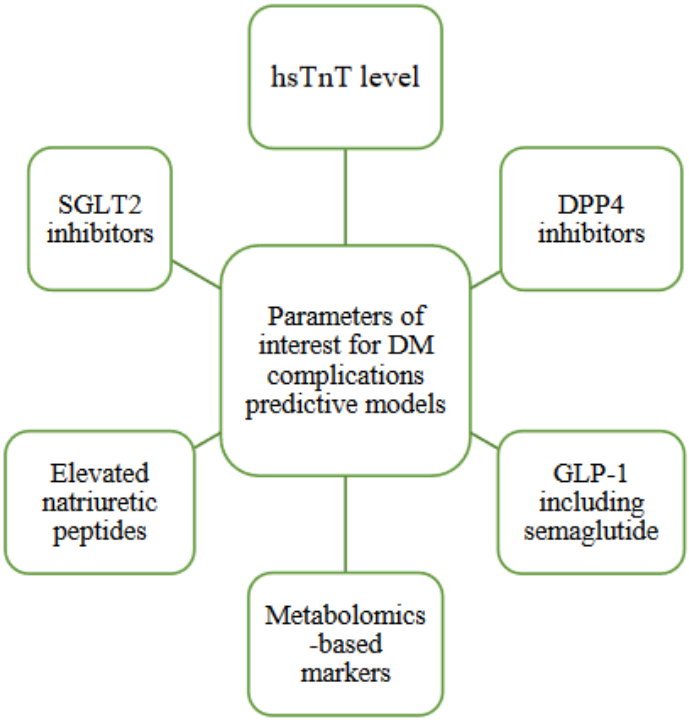


**Figure 1.** Parameters of interest for future DM complication prediction models. DPP4, dipeptidyl peptidase; DM, diabetes mellitus; GLP-1, glucagon like peptide-1; hsTnT, high-sensitivity troponin T; SGLT2, sodium-glucose cotransporter-2.

### 2.2. Diabetic Cardiomyopathy

Cardiomyopathy is one of the reported CVD complications of diabetes. In particular, the metabolic abnormalities of mitochondrial bioenergetics in diabetic hearts contribute to the development of impaired contractility observed in diabetic-associated cardiomyopathies [42–44]. A healthy heart obtains energy from the generation of adenosine triphosphate (ATP) in mitochondria and the oxidation process of substrates such as free fatty acids (FFA), glucose lactate, ketone bodies, and some other amino acids [45]. In fact, the myocardium has the capability to be highly flexible in selecting substrates that are suitable and available in order to ensure efficient pumping function [46]. Nevertheless, in T2DM, the reduction in insulin sensitivity leads to lipolysis, which increases the circulating FFA. The decrease in myocardium insulin-dependent glucose uptake results in ATP production that only relies on mitochondrial FFA oxidation [47]. This may impair the metabolic flexibility of the myocardium, which has been strongly linked to cardiac damage and dysfunction [48]. Previous animal studies showed the impaired ability of the myocardium to utilize glucose caused diminished glucose uptake and glucose oxidative capability, which eventually led to energetic efficiency [48,49]. Restoration of glucose uptake may lead to an excessive level of non-catabolized glucose levels within cardiomyocytes [48], and may result in glucotoxicity. The excessive cardiomyocyte non-catabolized glucose or glucotoxicity have been suggested to explain the cardiac dysfunction or cardiomyopathy in diabetes.

The use of certain antidiabetic drugs that enhance the restoration of glucose in cardiomyocytes has been hypothesized to lead to CVD complications in T2DM [45]. Nevertheless, the use of newer antidiabetics such as SGLT2 inhibitors have been shown to have a safe effect on CV [50]. Incorporating pharmacokinetic and pharmacodynamic parameters of this antidiabetic on the risk of diabetic cardiomyopathy development may suggest an optimal dose response relationship and its optimal dosing to reduce the risk. The role of biomarkers such as FFA or ketone bodies as a predictor of T2DM CVD complications may need to be investigated further in the clinical setting to confirm the findings of the animal studies. The future predictive model of T2DM complication development may also need to incorporate medications such as calcium channel blockers and statins to confirm their possible roles in bioenergetic modifications in predicting the risk of diabetic cardiomyopathy [45].

## 3. Ischemic Stroke

Stroke is considered as one of the cerebrovascular accidents and is the third-leading cause of disability and accounted for over 6 million deaths worldwide in 2015 [51]. Diabetes is associated with an increased risk of subsequent strokes [52,53], greater functional disability, longer hospital stays, and increased mortality [54–56]. A higher risk of developing stroke-related dementia has also been reported in the diabetic population [57].

### *Nonmodifiable and Modifiable Predictors of Stroke in T2DM*

T2DM patients possess about a four times higher risk for stroke, and this population usually has additional risk factors for stroke such as obesity, hypertension, and dyslipidemia, which multiply the vascular risk [58]. Four-stroke prediction models were developed for patients with T2DM [7,9,11,16], and 18 variables were proved to be associated with ischemic stroke in patients with T2DM. The UK Prospective Diabetes Study Risk 60 (UKPDS60) [7] model concluded that there were seven ischemic stroke predictors in diabetic patients: duration of diabetes, female gender, age at diagnosis of diabetes, atrial fibrillation, SBP, total cholesterol (TC) to high-density lipoprotein (HDL) ratio, and smoking status at diagnosis of diabetes. In the extended UKPDS60 model; the UK Prospective Diabetes Study Risk 66 (UKPDS66) [16] model included five risk factors of stroke fatality that included gender, SBP, HbA1c, previous stroke, and white blood cell count. Another stroke-predictive model was developed among the Hong Kong population with diabetes [9], and reported four significant predictors of an initial stroke attack: age, history of coronary heart disease (CHD), HbA1c, and albumin-to-creatinine ratio. A predictive model of stroke in Taiwanese T2DM patients [11] reported 14 predictors similar to those

aforementioned found in the previous stroke predictive models in T2DM patients, and additional significant risk factors also were reported. These factors were: variations in fasting blood glucose readings, arterial embolism and thrombosis, the use of antidiabetic medication, and the use of cardiovascular medication.

Nevertheless, all of these predictive models were published in the 2000s, and the database used to develop the models, especially for antidiabetic medications, was published before 2003. Thus, antidiabetic medications such as sodium-glucose cotransporter-2 (SGLT2) inhibitors, dipeptidyl peptidase-4 (DPP4) inhibitors, and glucagon-like peptide-1 (GLP1) (including most recently approved drug, semaglutide), which were introduced to the market later, may not be included into models as possible covariates to explain the risk of stroke in the T2DM population (Figure 1).

## 4. Diabetic Kidney Disease

The development and progression of diabetic nephropathy occur through four stages: microalbuminuria, macroalbuminuria, persistently elevated serum creatinine or renal replacement therapy (RRT), and death. Adler et al. [59] concluded that the rate of microalbuminuria progression from the diagnosis of diabetes occurred at 2.0% per year. In comparison, the progression rate from microalbuminuria to macroalbuminuria was reported at 2.8% per year. The progression rate from macroalbuminuria to elevated serum creatinine ($\geq$175 micromole/L) or RRT was 2.3% per year. Furthermore, the prevalence of microalbuminuria, macroalbuminuria, and elevated serum creatinine or RRT within 10 years after the T2DM diagnosis were 24.9%, 5.3%, and 0.8%, respectively.

### *Modifiable and Nonmodifiable Predictors of Diabetic Kidney Disease*

The significant reported predictors of chronic kidney disease (CKD) in T2DM patients include age, gender, age at diabetes onset, the use of antihypertensive medication, level of serum creatinine, HbA1c, systolic blood pressure, diabetic retinopathy, eGFR, urinary albumin-to-creatinine ratio (UACR), albuminuria, the use of antidiabetic medications, LDL, total cholesterol level, and the use of antihyperlipidemic medication [12,13,60]. According to the IDF recommendations [5], maintaining blood glucose and blood pressure at near-normal levels can greatly reduce the risk of CKD. Increased concentrations of urinary albumin indicate the presence of CKD [8,61]. In people without CKD, UACR is typically 10 mg/g. However, even smaller increases in urinary albumin between 10 mg/g and 30 mg/g have been associated with the progression of renal disease and increased mortality [62,63]. For CKD detection, the ADA recommends [64] screening at least once a year by measuring urinary albumin, e.g., spot UACR and eGFR in all patients with T2DM, and in all patients with comorbid hypertension.

Elevated serum lipids and smoking also play roles as risk factors for CKD in T2DM patients. Treating dyslipidemia (LDL cholesterol < 100 mg/dL) is not only an effective strategy in preventing the development of microalbuminuria, but also in delaying the progression to more advanced stages of nephropathy in these patients [65].

It was found that 13 urinary metabolites were significantly reduced in chronic kidney disease complications in T2DM patients [66]; nevertheless, as mentioned for CVD complications, prediction models for CKD complications in T2DM that include metabolomics-based markers are still lacking. Moreover, elevated natriuretic peptides and high-sensitivity troponin T (hsTnT) levels have been associated with an increase in the risk of T2DM microvascular complication, particularly nephropathy [67]. Incorporating these biomarkers into a future predictive model of diabetic nephropathy is needed to improve T2DM complication prediction (Figure 1).

## 5. Diabetic Neuropathy

The most common form of diabetes-related neuropathy is diabetic peripheral neuropathy (DPN). DPN mostly affects the distal nerves of the feet. Lower-limb amputation in

people with diabetes is 10 to 20 times higher than those without diabetes [68], and more common among people with T2DM than those with type 1 diabetes [69].

Intensive blood glucose management can lead to a 35% reduction of amputation risk compared to less intensive glycemic management [70]. Diabetic neuropathy was significantly associated with duration of diabetes, dyslipidemia, the occurrence of diabetic retinopathy, and cardiovascular disease. Other risk factors include being unemployed, old age, poor glycemic control, and hypertension [71,72]. Furthermore, a large-scale study that examined the major determinants associated with the risk of DPN in adult patients with T2DM demonstrated that the presence of moderate and severe elevation of albuminuria and FPG-CV were important predictors of DPN [73]. In another study, DPN in T2DM patients was highly associated with age, duration of diabetes, body weight, gender, history of foot ulcers, and patient's education [74].

Nevertheless, most of the developed DPN prediction models focused on predicting DPN severity degree among T2DM patients who were already prediagnosed with DPN [75–77]. Less than one-third of physicians can detect diabetes-related peripheral neuropathy manifestations, even when they are symptomatic [78]. Therefore, establishment of prediction models for DPN in these patients is highly recommended.

## 6. Eye Disease (Diabetic Retinopathy)

Diabetic retinopathy is a highly specific vascular complication of diabetes with a prevalence strongly associated with the level of glycemic control and the duration of diabetes [79]. Factors that increase the risk of retinopathy include a long duration of diabetes [80], high HbA1C level, fasting blood glucose [81,82], nephropathy [83], high blood pressure level [80,84], and dyslipidemia [80,85]. However, only one study established a model for retinopathy prediction based on four related parameters (duration of diabetes, waist-to-hip ratio, HbA1c, and family history of diabetes) [14]. Future perspectives on T2DM complication predictive models are needed.

Several predictive models or risk-assessment tools have been developed for predicting the risk of T2DM complications that serve as a means of their early detection. A predictive model is a tool made up of many predictors or risk factors that are likely to influence future outcomes. Thus, several risk factors have been detected as significant predictors of experiencing T2DM complications in most of the developed predictive models, as discussed in the section above. Nevertheless, the published models' outcomes varied due to the different definitions of T2DM complications and patients included. Predictive models can be developed by using several methods. Most of the predictive models were developed using analysis methods such as logistic regression and Cox regression survival analysis. The use of poorly developed methods could jeopardize model development, including univariate prescreening of variables, categorization of continuous risk predictors, and poor handling of missing data. Besides, the use of poorly developed methods affects the prediction model's reliability and ultimately compromises the accuracy of the probability estimates of experiencing T2DM complications.

A predictive model that incorporates factor of time to quantify the risk of T2DM complications such as CVD events may need to be used, and to our knowledge, such a model is still lacking. For instance, variations in fasting blood glucose throughout the time until a follow-up visit have been reported to be significantly associated with an increased risk of CVD events [86], Achieving normal and consistent glycemic levels is vital to improve clinical outcomes [86]. Determining the impact of variability in fasting blood glucose over time may capture the pathological process, which may lead to the complication process [86]. Therefore, approaches to minimize the variability need to be determined. Variability in blood glucose progression over time could be influenced by various factors, including the severity of diabetes status, antidiabetic drugs, the patient's compliance with medication, and management of diet and exercise [30]. These factors may explain the variability in blood glucose within the individual patient.

Moreover, not all diabetic patients may have a similar magnitude of blood glucose variability, which requires quantification of factors to determine the variability in blood glucose between patients to reduce the bias in predicting the risk of CVD events. In addition to the two variabilities mentioned, a confounded residual, such as in the blood glucose measurement method, may also contribute to the variability in blood glucose progression [86].

Quantifying the effect of all factors affecting the blood glucose progression or covariates may improve precision in predicting the CVD events as complications of T2DM. Nevertheless, blood glucose progression is time-varying, and thus the impact of the progression rate on the risk of CVD events may provide better knowledge in minimizing the risk. Covariates that may slow, accelerate, modify, or retard the progression rate could be the focus of precision medicine in optimizing T2DM therapy and minimizing T2DM complications.

A new approach to developing the model must be applied. A population approach using a nonlinear mixed effect model is one of the analysis methods that may overcome poorly developed methods in the previous developed predictive model, including univariate prescreening of variables, categorization of continuous risk predictors, and poor handling of missing data. The parametric approach allows missing data or dropout data to be quantified, and this may reduce the biases of the model prediction. Moreover, time-varying and time-invariant risk factors can be included in the model without categorizing the continuous data. As an element of time can be included, the predictive model developed using this parametric approach permits the prediction of experiencing T2DM complications beyond the studied time through a simulation method.

To prove the prediction models' usefulness, they must demonstrate how their uses generate better patient outcomes. Although extensive efforts have been put into building these predictive models, there is a remarkable scarcity of impact studies [87]. Very few developed predictive models were externally validated, and knowledge of their clinical impact is lacking. The tool should also be able to provide a computer-generated visual presentation [88]. Thus, a predictive model that able to stratify the risk of having T2DM complications and provide appropriate interventions to delay the progression needs to be developed.

## 7. Conclusions

Increasingly promising predictive models of T2DM complications can and will be developed in the future. Development of well-established and validated predictive models of T2DM complications is vital to stratify patients with T2DM based on their risks. Thus, individualization therapy could be optimized. However, the use of new approaches (e.g., the parametric approach) is needed to develop predictive models of T2DM complications and incorporate new and time-varying predictors that may improve the existing models' predictive ability and generalizability via further external validation in a diverse population.

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