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Time to develop chronic kidney disease in an Ecuadorian Type 2 Diabetes Mellitus cohort: Survival analysis in primary care

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ABSTRACT

Chronic Kidney Disease (CKD) represents a high burden to health systems. However, the survival time for CKD in a Type 2 Diabetes Mellitus (T2DM) population is unknown.

Aims: Determine the risk factors, survival time and the incidence rate of CKD in T2DM.

Methods: Retrospective clinical cohort study (follow up 10 years). 513 patients with T2DM were included. Numerical variables were compared using the mean difference. Chi squared and odds ratios were calculated for categorical variables. Survival analysis was done through life tables and Kaplan-Meier.

Results: The mean difference between the group that developed CKD and those who did not, was significant in: age, age at diagnosis of T2DM and years with T2DM. Risk factors for developing CKD were: the presence of hypertension, albuminuria, retinopathy, high triglycerides and high HbA1c. The incidence rate was 32.07 per 1000 person-years of follow-up and 207 (40.4%) of patients developed CKD during the study. The median for developing CKD was 20.52 years of disease with an increasing risk with time.

Conclusions: Half of the patients with T2DM will develop CKD by the second decade of disease. Time, arterial hypertension, retinopathy, albuminuria and triglycerides are factors associated with CKD in patients with T2DM.

Chronic Kidney Diseases (CKD) have been defined as alterations in kidney structure or function for more than three months.[1] CKD has a great economic impact on health systems, has been recognized as a public health problem and went from position 27 to 18 in the global death rank in two decades.[2] In newly diagnosed patients with Type 2 Diabetes Mellitus (T2DM) more than 5% will already present CKD. Those patients who do not have CKD at the moment of T2DM diagnosis would likely develop CKD within ten years. Furthermore, CKD increases the risk of progression to End-Stage Renal Disease (ESRD) and patients with both conditions have a poorer quality of life than those having a single one.[3,4] Among patient with T2DM the prevalence of CKD has been reported 38.3% in a 5-year gap. The presence of this complication in patients with T2DM has been associated with older age, longer time of disease, higher Haemoglobin A1c (HbA1c), retinopathy, higher systolic blood pressure and arterial hypertension (HTN).[5–7]

Low-income countries have a higher burden of undiagnosed Diabetes Mellitus (DM) and an earlier age for peak prevalence. The health impact in these countries will be greater as the prevalence of DM is projected to rise in the coming decades.[8] Furthermore, there is evidence of increased risk for developing CKD in the diabetic Latin population.[9,10] Research about the impact of T2DM in the Latin population has been published, notwithstanding scarce studies have reported the prevalence of CKD in T2DM population in Latin America. Colombia has reported a prevalence of 17% of CKD in a T2DM population. Chile has reported that CKD is related to a T2DM etiology in 35% of patients,[11,12] whereas the reported prevalence of CKD in T2DM in the United States (a high-income country) has been 15%.[13] To the best of our knowledge, there is no evidence regarding specific survival for CKD in patients with T2DM. However, De Cosmo et al (2016) reported that 33.2% of an Italian cohort of patient with T2DM developed CKD after a 4-year follow up.[14] Understanding survival and risk factors for developing CKD in T2DM will aid in early detection of this complication. Since early management has been associated with better prognosis, further investigation of this high-health burden diseases is requeired.[15]

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The main objective of the present study is to determine the associated factors and survival time for CKD. As secondary outcomes we aim to obtain: survival for eGFR <30 mL/min/1.73m^2, incidence and incidence rate of CKD in a Latin population with T2DM in the primary level of care. With these objectives we expect to stablish a baseline of risk factors, incidence and survival time for CKD in the diabetic Latin population.

1. Subjects, materials and methods

1.1. Setting, population and data recovery

This is a retrospective clinical cohort study from a diabetes clinic of primary level of care in Chimbacalle (Quito, Ecuador), which followed a cohort of patients with T2DM from 2007 until 2017; sociodemographic, lifestyle and biochemical analyses information were obtained from the medical records and clinical assessments performed by trained personal. The minimum sample size was estimated in 385 patients, based on the unknown prevalence of the diseases of interest, for an alpha of 0.05 and a statistical power of 0.80.

All patients who had complete information regarding the following parameters were included in the study: T2DM diagnosis (according to American Diabetes Association criteria),[16,17] a minimum of two laboratory tests measurement within a year of diagnosis (total cholesterol –TC-, high density lipoproteins –cHDL-, low density lipoproteins –cLDL-, triglycerides –Tg-, glycated haemoglobin –HbA1c-, creatinine), previous assessment records for retinopathy, ankle-brachial index values (ABI), at least one electrocardiogram (EKG), being older than 18 years old and having signed a written consent. The exclusion criteria were: Type 1 Diabetes Mellitus diagnosis, incomplete data in clinical records, pregnancy, previous diagnosis of CKD or current dialysis treatment and the ones who did not sign a written consent. To avoid reverse causation bias, patients who developed CKD within 2 years of starting follow up were excluded from the study. Due to this reason 26 patients were excluded from a sample of 539. The final sample for the study was 513 patients (Fig. 1).

The management of the patients in this diabetes clinic regarding to cost, use of lipid lowering drugs and exercise have been described elsewhere.[18] All patients in the cohort were receiving a renal protective medication (ARA or ACEI).

1.2. CKD assessment

CKD was diagnosed according to the "Kidney Disease: Improving Global Out-comes KDIGO 2012" criteria (duration more than 3 months, eGFR <60 mL/min/1.73m^2 and evidence of structural or functional kidney damage)[1]; glomerular filtration was estimated using the CKD-EPI formula[19] and HTN was defined according to the eight Joint National Committee criteria.[20]

1.3. Statistical analysis

The values of the different variables are presented as the average values of the 10 year follow up. The population was classified according to the CKD status: with CKD and without CKD. Proportions and measures of central tendency were calculated for categorical and numerical variables respectively. When comparing the cohort, either by sex or by CKD status, numerical variables were compared using the mean difference (T-student), chi squared and odds ratios (OR) were calculated for categorical variables.

Survival time was stablished to be the amount of years from the diagnosis of T2DM (index time) and diagnosis of CKD (occurrence of the event of interest), death or end of follow up (December 31st, 2017), whichever occurred first. Secondary analyses used eGFR <30 mL/min/1.73 m^2 as the event on interest for survival analysis. Survival analysis for CKD and eGFR <30 mL/min/1.73 m^2 was estimated using life tables. Kaplan-Meier was used to obtain the survival for CKD according to the following binary variables: sex, smoking history, HTN, Body Mass Index (BMI, >or equal 25), altered electrocardiogram (defined according to the Minnesota Code Manual of Electrocardiographic Findings),[21] age at T2DM diagnosis (>65 years), peripheral artery disease (PAD, ABI <0.9), TC (>200 mg/dL), cHDL (< 40 mg/dL in males and <50 mg/dL in females), cLDL (>100 mg/dL), Tg (>150 mg/dL), HbA1c (≥7%). Additionally, hazard ratios (HR) and confidence intervals of 95%, for the first, second, third and fourth decade of CKD disease were calculated. Statistically significant analyses were assessed as a $p < 0.05$. SPSS Statistical Analysis Software (IBM SPSS, version 23) was used for the

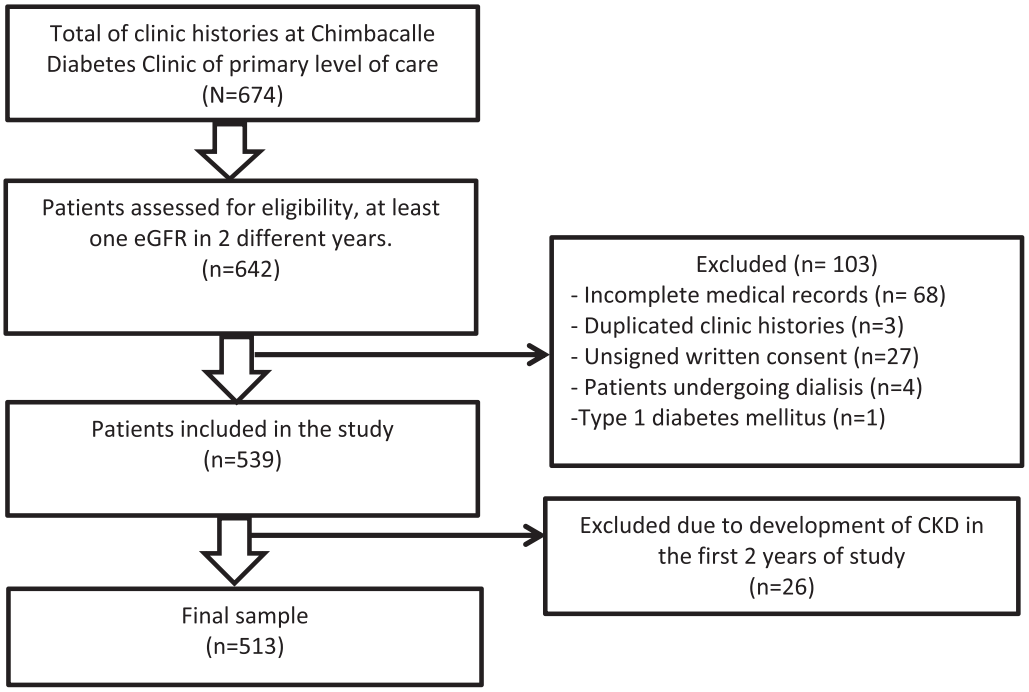

Fig. 1. Flow diagram of sample selection.

statistical analysis.

1.4. Ethics

The Bioethics Committee at the Central University of Ecuador approved this study as part of one of the Biomedicine Investigation Institute projects of the same institution (resolution no. 279-CE-UCE-2015).

2. Results

From the 513 patients included in the study, 410 (79.9%) were female and 507 (98.8%) identified themselves as Latins. The mean age was 65.69 years (SD: 11.739, range: 31–92, median: 66) and the mean years of disease was 13.34 years (SD: 7.190, range: 3–40). In this cohort the difference between sexes was statistical significant for the variables: BMI, Total Cholesterol, c-HDL, presence of albuminuria, presence of PAD, abnormal EKG and smoking status (Table S1). During the 10 years of follow up 207 (40.4%) of patients developed CKD. The incidence rate was 32.07 per 1000 person-years of follow-up.

When comparing the groups with CKD and without CKD the mean difference for age at last control, age at diagnosis of T2DM, years from diagnosis until last control and years of disease until event were statistical significant (Table 1). For the binary variables we found a statistical significant increased risk for developing CKD with the following variables: HTN (OR: 3.07, 95%CI: 1.94–4.86, *p*: <0.001), albuminuria (OR: 3.07, 95%CI: 2.01–4.70, *p*: <0.001), retinopathy (OR: 2.61, 95%CI: 1.66–4.13, *p*: <0.001), triglycerides >150 mg/dL (OR: 1.47, 95%CI: 1.03–2.10, *p*: 0.04), HbA1c ≥7% (OR: 1.5, 95%CI: 1.03–2.18, *p*: 0.04) and age at T2DM diagnosis >65 years (OR: 2.71, 95%CI: 1.61–4.55, *p*: <0.001) (Table 2).

Table 1
Mean difference of clinical and metabolical characteristics according to different chronic kidney disease status in patients with Type 2 Diabetes Mellitus.

Variables	With chronic kidney disease	Without chronic kidney disease	*t*[a]	*p***
	n = 207 (*40.4%*)	*n = 306* (*59.6%*)		
Age at last control[b], mean (SD)	70.52 (11.08)	62.42 (11.04)	−8.141	<0.001
Age at diagnosis of T2DM, mean (SD)	54.75 (11.93)	50.74 (10.97)	−3.918	<0.001
Years from T2DM diagnosis until last control[b], mean (SD)	15.77 (7.98)	11.69 (6.08)	−6.571	<0.001
Years from T2DM diagnosis until event or end of follow up, mean (SD)	13.89 (8.44)	11.69 (6.11)	−3.222	0.001
BMI (kg/m^2), mean (SD)	29.05 (4.54)	29.29 (5.07)	0.547	0.59
Total cholesterol (mg/dl), mean (SD)	182.37 (33.93)	182.50 (37.40)	0.038	0.97
c-HDL (mg/dL), mean (SD)	60.47 (15.85)	58.56 (11.85)	−1.476	0.14
c-LDL (mg/dL), mean (SD)	87.85 (24.88)	91.02 (25.93)	1.379	0.17
Triglycerides (mg/dL), mean (SD)	176.58 (77.56)	168.60 (81.33)	−1.110	0.27
HbA1c %, mean (SD)	7.79 (1.32)	7.58 (1.51)	−1.601	0.11
GFR (mL/min/1.73m^2), mean (SD)	45.88 (12.97)	77.67 (13.47)	26.618	<0.001

Abbreviations: SD, standard deviation; T2DM, Type 2 Diabetes Mellitus; CKD, chronic kidney disease; BMI, body mass index; c-HDL, high density lipoprotein cholesterol; c-LDL, low density lipoprotein cholesterol; HbA1c, glycated haemoglobin; GFR, glomerular filtration rate.

[a] T of student.

** Statistically significant when p < 0,05.

[b] Last control of 2017.

The median survival time for CKD was found to be 20.52 years and for eGFR <30 mL/min/1.73 m^2 it was 40 years, without adjusting for cofounders. The HR for the first, second, third and fourth decade of disease were: 1.84 (95% CI: 1.43–2.26), 4.72 (95% CI: 3.76–5.68), 7.19 (95% CI: 4.87–9.52), 8.18 (95% CI: 3.30–13.06) for CKD respectively. The HR for eGFR <30 mL/min/1.73 m^2 was 0.07 (95% CI: −0.01-0.15) in the first decade, 0.63 (95% CI: 0.29–0.98) in the second decade, 1.35 (95% CI: 0.35–2.34) in the third decade and 1.54 (95% CI: −0.59-3.66) in the fourth decade. The survival curves for these outcomes can be seen in Figs. 2 and 3. The survival curves for CKD stratified by sex did not show a significant difference between the sexes.

When analyzing the survival for CKD according to different binary variables we found a significant difference with HTN, albuminuria, age at diagnosis of T2DM >65 years, Tg >150 mg/dL and HbA1c ≥7% (CKD presents earlier with HbA1c <7%) (Table 3). The rest of the binary variables did not show a statistical significant difference in the survival of CKD.

3. Discussion

In the present study a T2DM cohort showed a median survival time of 20.52 years for developing CKD, the risk was higher as the decades with T2DM increased. The main factors associated with CKD were those related to renal damage (microalbuminuria, HTN), HbA1c% and the age at diagnosis of T2DM. According to the U.K. Prospective Diabetes Study the incidence of CKD in patients with T2DM is 29% in 15 years follow up. This is a low percentage comparing to the incidence in this 10-year follow up study (40.4%).

Risk factors associated with CKD development in T2DM have been widely studied. A study performed in Thailand found similar differences in the means of CKD and non-CKD diabetic populations including the variables: age, high blood pressure, presence of retinopathy, duration of diabetes and HbA1c %.[6] Retinopathy and nephropathy are recognized as microvascular complications of diabetes. Although an association between retinopathy and CKD was found when analyzing CKD vs non-CKD patients in this study, retinopathy did not show a statistical significance when analyzing survival time for CKD according to this variable. Park, et al (2019) found that when retinopathy is stratified (proliferative and non-proliferative) there is a significant influence in CKD progression.[22] In the present study retinopathy was not stratified into different categories.

Many variables related to age showed an association with CKD, including: age at diagnosis, years of disease and age at last control. This might be attributable to the physiologic decline in renal function with age.[23] However, evidence has shown that the renal function decline with age is accelerated in patients with diabetic nephropathy (DN).[24] This means that the association of time and decreased eGFR is expected even in non-diabetic patients but T2DM patient may develop CKD sooner. The current investigation did not take into account the rate of function decline per year, so a comparison cannot be made. Rapid renal function decline (defined as a decrease of 4% of renal function per year) was not identified either, which shares several risks factors with the development of CKD.[25] The incidence of rapid decline has been reported to be 15.6% in a 10-year follow up. It would be expected that the survival time for developing CKD for this patients would be less than the one for normal function decline patients with T2DM. If these patients are present in the current study they may have acted as outliners reducing the survival time for CKD in the cohort. Further studies in this subgroup would help to identify them and understands their prognosis more deeply. Understanding that age and T2DM act as factors for the development of CKD, a shorter survival time for CKD in patients diagnosed with T2DM at 65 or more year of age was an expected result of the present work.

HTN and albuminuria have been known to be risk factors for diabetic nephropathy. HTN by itself is a cause of renal disease but when

Table 2
Crosstables and mean difference by subgroups of clinical and metabolical characteristics according to chronic kidney disease status in patients with Type 2 Diabetes Mellitus.

Variables	With chronic kidney disease	Without chronic kidney disease	With chronic kidney disease	Without chronic kidney disease	t^a	p^{**}
	n = 207	*n = 306*	*Mean GFR +/− SD*	*Mean GFR +/− SD*		
Arterial hypertension						
Yes	178	204	45.13 +/− 13.35	75.98 +/− 13.14	−22,710	<0.001
No	29	102	50.45 +/− 9.87	81.05 +/− 13.54	−14.03	<0.001
OR: 3.07 (1.94–4.86), *p*: <0.001**						
Albuminuria						
Yes	73	46	37.64 +/− 16.07	77.80 +/− 15.37	−13.5	<0.001
No	134	260	50.36 +/− 7.97	77.64 +/− 13.14	−25.58	<0.001
OR: 3.07 (2.01–4.70), *p*: <0.001**						
Retinopathy						
Yes, n (mean GFR +/− SD)	56	38	40.89 ±16.01	73.82 +/− 12.21	−11.29	<0.001
No, n (mean GFR +/− SD)	151	268	47.73 +/− 11.15	78.21 +/− 13.57	−24.8	<0.001
OR: 2.61 (1.66–4.13), *p*: <0.001**						
Triglycerides (mg/dL)						
>150	122	151	46.07 +/− 13.37	77.58 +/− 14.00	−18.86	<0.001
<150	85	155	45.60 +/− 12.45	77.75 +/− 12.97	−18.63	<0.001
OR: 1.47 (1.03–2.10), *p*: 0.04**						
HbA1c %						
≥7	143	183	44.50 +/− 13.65	79.75 +/− 14.52	−22.33	<0.001
<7	64	123	48.96 +/− 10.78	74.57 +/− 11.08	−15.13	<0.001
OR: 1.50 (1.03–2.18) *p*: 0.04**						
Age at diagnosis of T2DM (years)						
>65	43	27	48.99 +/− 9.13	73.56 +/− 9.68	−10.71	<0.001
<65	164	279	45.06 +/− 13.71	78.06 +/− 13.73	−24.45	<0.001
OR: 2.71 (1.61–4.55), *p*: <0.001**						

Abbreviations: SD, standard deviation; T2DM, Type 2 Diabetes Mellitus; CKD, chronic kidney disease; HbA1c, glycated haemoglobin; GFR, glomerular filtration rate, *OR*: odds ratio.

[a] T of student.

[**] Statistically significant when p < 0,05.

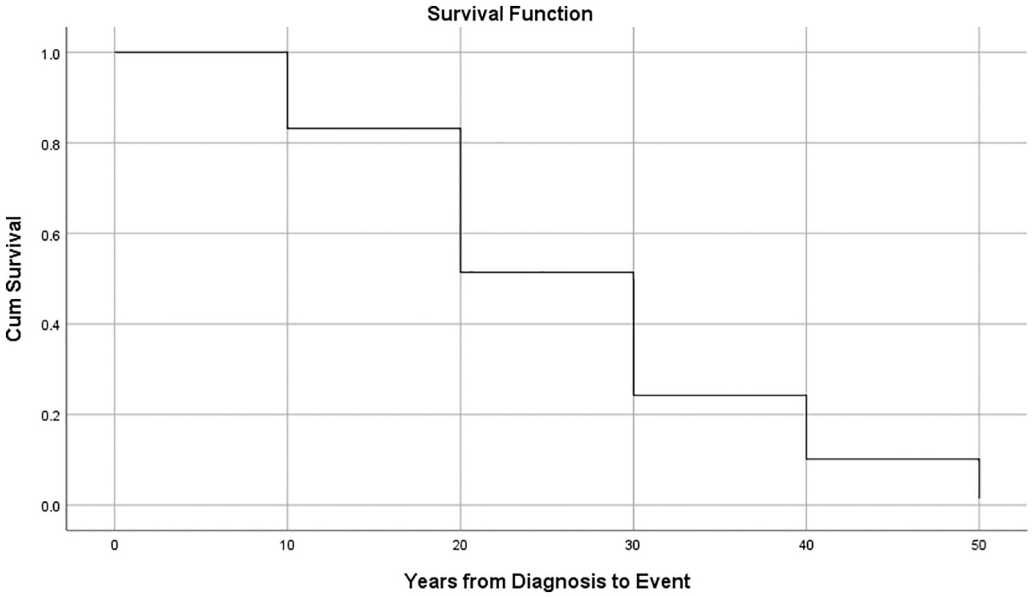

Fig. 2. Survival for eGFR <60 mL//min/1.73m^2 in patients with Type 2 Diabetes Mellitus by 10 year intervals.

associated with diabetes it has a synergistic effect.[26,27] Furthermore, higher blood pressure has been related to the presence of albuminuria in patients with T2DM, which is a risk factor for accelerated renal function decline.[28,29] In this study HTN and albuminuria were confirmed as risk factors for reduced eGFR, highlighting the important role of blood pressure control in patients with T2DM. Albuminuria has been related with changes in the glomerulus after chronic exposure to high glucose levels (endothelial damage, glycocalyx thinning and podocyte effacement).[30] Nevertheless, albumin in the urine as a risk factor for developing reduced eGFR in T2DM should be interpreted with caution. Current research has shown that even in the absence of albuminuria there is renal function decline in patients with T2DM.[31] This may

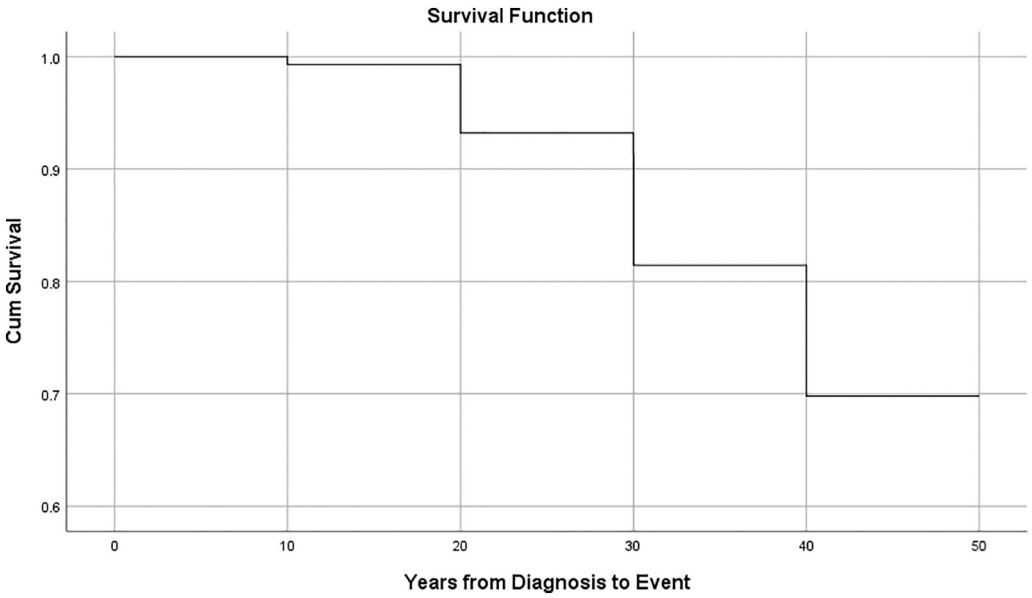

Fig. 3. Survival for eGFR <30 mL//min/1.73m^2 in patients with Type 2 Diabetes Mellitus by 10 year intervals.

Table 3
Survival years for chronic kidney disease according to different variables in patients with Type 2 Diabetes Mellitus.

	Years with T2DM diagnosis	Superior interval	Inferior interval	p^*
HTN				
Yes	19.886	18.401	21.371	0.02
No	28.271	22.015	34.526	
Albuminuria				
Yes	18.217	16.262	20.171	0.02
No	22.627	20.433	24.821	
Age at T2DM diagnosis (years)				
>65	11.740	10.217	13.263	<0.001
<65	22.130	19.295	22.367	
Triglycerides (mg/dL)				
>150	18.356	16.547	20.165	<0.001
<150	23.643	21.106	26.179	
HbA1c (%)				
≥7	21.762	19.982	23.542	0.004
<7	18.711	15.614	21.808	

Abbreviations: T2DM, Type 2 Diabetes Mellitus; HTN, arterial hypertension; HbA1c, glycated haemoglobin.

* Statistically significant when p < 0,05. All variables that are not in the table were not statistically significant.

represent early changes in the pathophysiology of nephropathy in patients with T2DM.

When analyzing the survival time for CKD related to HbA1c the results showed that an HbA1c <7% has a shorter survival time related to higher levels. Two facts guide us for explaining this result. First, as eGFR reduces HbA1c is less reliable as a glycemic control marker. Due to a reduced lifespan of erythrocytes CKD patients may show lower HbA1c values.[32] This means some patients with low eGFR may have been classified in the group of HbA1c <7%, biasing the results. Second, average HbA1c has not shown to be a good correlator to CKD as is HbA1c variability.[33,34] The present study did not assessed HbA1c variability and the survival analysis was based on the HbA1c average.

The median for developing CKD was far different from developing an eGFR <30 mL/min/1.73m^2 (20.52 years vs 40 years respectively). This may be explained due to the age of the population. As other investigators have suggested in the general population, older individuals have a reduced risk of reaching ESRD compared with younger individuals. This has been attributed to a higher likelihood of death in older patients. Also eGFR declines faster in older patients than in younger counterparts but when the eGFR goes below 45 mL/min/1.73m^2 this pattern reverses.[35] Other investigation shows that when CKD is established, about one-third of patients improve or stabilize its eGFR.[36] Our results suggest that these principles may also be applied to a Latin T2DM population.

Regarding triglycerides the obtained results showed that patients with CKD had higher levels of triglycerides. High triglycerides levels were also associated with a shorter survival time for developing CKD. An Italian retrospective study's researchers found that triglycerides higher or equal to 150 mg/dL as well as low c-HDL (less than 40 mg/dL in men and 50 mg/dL in women) increased the risk of developing CKD.[37] Even though our work did not show any relation of HDL with CKD, triglycerides were statistically significant related (risk factor and decreased survival time for CKD) and may be considered a promising marker related to eGFR decline in T2DM, due to its association with insulin resistance. Shang, J. et al (2019) found that the triglyceride glucose index could be a prognostic factor in predicting biopsy-proven diabetic nephropathy.[38] Further investigation regarding the cut-off points and predictive value of triglycerides is necessary.

The strengths of this study include a longitudinal design comprised of a clinical population of patients with T2DM, provided with comprehensive health care followed up by the same physician and during ten years. This study included mainly Latin population; it can be used as a basis for establishing a baseline of risk factors, prevalence and survival time for CKD in the diabetic Latin population. This is also a limitation as other populations may show different outcomes. Another study limitation is that it was performed in a center with free services and specialized diabetes management (including renal protective medication on all patients), so the results may only extrapolate to health centers with similar characteristics. The current study did not try to assess the causal factors of CKD in patients with T2DM; however some variables that might relate to CKD should be taken into account when analyzing the results (although the patients were receiving treatment for their comorbidities, certain comorbidities like HTN may influence the outcomes of the study). Finally the study presents a higher proportion of females; this may have biased the difference of PAD between sexes. However, there was not a sex difference in mean eGFR or in CKD presence between sexes.

The results of this investigation highlight the characteristics that

should guide the primary care physician to look for CKD in patients with T2DM. Time, either as age at diagnosis or time with the disease, is an important risk factor for developing CKD in these patients. This fact seems independent of the normal physiologic decline and indicates that CKD is an expected complication as the diabetic patient becomes older. More studies should be done regarding HbA1c reliability in this population and other predictors (like triglycerides) for reduced CKD in T2DM. The bibliography regarding survival time for CKD in patients with T2DM is scarce, not only on Latin populations but as a whole. Further studies regarding this topic would be useful.

This study concludes that half of the patients with T2DM in a Latin population will develop CKD in 20 years with the risk increasing each decade. However, the risk for developing an eGFR <30 mL/min/1.73m^2 is low and does not increase significantly through the decades with T2DM. Patients who develop CKD are more likely to have hypertension, albuminuria, retinopathy, longer time of disease and older age at diagnosis. Excluding retinopathy, the presence of these factors was also related to a shorter survival time for developing CKD; high triglycerides were also included in this group. Finally, average HbA1c is not a reliable marker for CKD and should be interpreted with caution. The conclusions provide us with the opportunity to identify more efficiently the patients which might be at the highest risk of developing CKD. It also supports the need for more investigation of other variables, like triglycerides, to predict CKD in patients with T2DM.

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Declaration of competing interest

The authors declare no conflicts of interest concerning the research, authorship, and/or publication of this manuscript.

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CRediT authorship contribution statement

Research idea and study design: F.B.G., K.T.C., F.C.T., M.E.M., O.V.B.; data acquisition: F.B.G., F.C.T., M.E.M., O.V.B.; data analysis/interpretation: F.B.G., K.T.C., F.C.T.; statistical analysis: F.B.G., K.T.C., F.C.T. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

References

1 DOF C, Graded N. Chapter 1: definition and classification of CKD. *Kidney Int Suppl.* 2013;3:19–62. https://doi.org/10.1038/kisup.2012.64.
2. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the global burden of disease study 2010. *Lancet.* 2012;380:2095–2128. https://doi.org/10.1016/S0140-6736(12)61728-0.
3. Couser WG, Remuzzi G, Mendis S, Tonelli M. The contribution of chronic kidney disease to the global burden of major noncommunicable diseases. *Kidney Int.* 2011;80:1258–1270. https://doi.org/10.1038/ki.2011.368.
4. Wyld MLR, Morton RL, Aouad L, Magliano D, Polkinghorne KR, Chadban S. The impact of comorbid chronic kidney disease and diabetes on health-related quality-of-life: a 12-year community cohort study. *Nephrol Dial Transplant.* 2020;12:1–9. https://doi.org/10.1093/ndt/gfaa031.
5. Wu B, Bell K, Stanford A, et al. Understanding CKD among patients with T2DM: prevalence, temporal trends, and treatment patterns— NHANES 2007–2012. *BMJ Open Diabetes Res Care.* 2016;4. https://doi.org/10.1136/bmjdrc-2015-000154.
6. Jitraknatee J, Ruengorn C, Nochaiwong S. Prevalence and risk factors of chronic kidney disease among type 2 diabetes patients: a cross-sectional study in primary care practice. *Sci Rep.* 2020;10:1–10. https://doi.org/10.1038/s41598-020-63443-4.
7 Shewaneh DD, Damtie S, Biadgo B, et al. Diabetic Nephropathy Gondar 2018.Pdf. *Ethiop J Heal Sci.* 2018;28:691–699. N(Dm).
8. Cho NH, Shaw JE, Karuranga S, et al. IDF diabetes atlas: global estimates of diabetes prevalence for 2017 and projections for 2045. *Diabetes Res Clin Pract.* 2018;138:271–281. https://doi.org/10.1016/j.diabres.2018.02.023.
9. Retnakaran R, Cull CA, Thorne KI, Adler AI, Holman RR. Risk factors for renal dysfunction in type 2 diabetes: U.K. Prospective diabetes study 74. *Diabetes.* 2006;55:1832–1839. https://doi.org/10.2337/db05-1620.
10. Young BA, Maynard C, Boyko EJ. Nephropathy, cardiovascular disease, and mortality in a national population. *Diabetes Care.* 2003;26:2392–2399.
11. Js Z. Epidemiología De La diabetes chilean epidemiology in diabetes mellitus. *Rev Clínica Las Condes.* 2016;27:146–151.
12 Perrasse AV, Abad SB, Faciolince S, Vallejo P, Hernández N, Maya C, et al. El control de la diabetes mellitus y sus complicaciones en Medellin, Colombia. 2006;20:2001–2003. https://www.scielosp.org/pdf/rpsp/2006.v20n6/393-402/es.
13. Duru OK, Middleton T, Tewari MK, Norris K. The landscape of diabetic kidney disease in the United States. *Curr Diab Rep.* 2018;18. https://doi.org/10.1007/s11892-018-0980-x.
14. De Cosmo S, Viazzi F, Pacilli A, et al. Predictors of chronic kidney disease in type 2 diabetes: a longitudinal study from the AMD annals initiative. *Med (United States).* 2016;95:4–10. https://doi.org/10.1097/MD.0000000000004007.
15 Foggensteiner L, Mulroy S, Firth J. In: Boner G, Cooper ME, eds. *Management of diabetic nephropathy*10.
16. American Diabetes Association (ADA). Standard of medical care in diabetes - 2017. *Diabetes Care.* 2017;40:s4–s128. https://doi.org/10.2337/dc17-S003. January.
17. Statements P. Standards of medical care in diabetes - 2012. *Diabetes Care.* 2012;35. https://doi.org/10.2337/dc12-s011.
18. Barrera-Guarderas F, Carrasco-Tenezaca F, De la Torre-Cisneros K. Peripheral artery disease in type 2 diabetes mellitus: survival analysis of an Ecuadorian population in primary care. *J Prim Care Community Health.* 2020:11. https://doi.org/10.1177/2150132720957449.
19. Bermúdez RM, Sanjuán JB, Samper AO, Castán JAB, García SG. Valoración de la nueva ecuación CKD-EPI Para la estimación del filtrado glomerular. *Nefrologia.* 2012;32:273–274. https://doi.org/10.3265/Nefrologia.pre2012.Jan.11340.
20. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults. *JAMA.* 2014;311:507. https://doi.org/10.1001/jama.2013.284427.
21 Prineas RJ, Crow RS, Zhang Z-M. Ch. 00: Front Matter. In: *Minnesota Code Man Electrocardiogr Find.* 2010:i–xiii.
22. Park HC, Lee YK, Cho A, et al. Diabetic retinopathy is a prognostic factor for progression of chronic kidney disease in the patients with type 2 diabetes mellitus. *PLoS One.* 2019;14:1–12. https://doi.org/10.1371/journal.pone.0220506.
23. Denic A, Glassock RJ, Rule AD. Structural and functional changes with the aging kidney. *Adv Chronic Kidney Dis.* 2016;23:19–28. https://doi.org/10.1053/j.ackd.2015.08.004.
24. Hobeika L, Hunt KJ, Neely BA, Arthur JM. Comparison of the rate of renal function decline in NonProteinuric patients with and without diabetes. *Am J Med Sci.* 2015;350:447–452. https://doi.org/10.1097/MAJ.0000000000000583.
25. Sheen Y-J. Risks of rapid decline renal function in patients with type 2 diabetes. *World J Diabetes.* 2014;5:835. https://doi.org/10.4239/wjd.v5.i6.835.
26. Giunti S, Barit D, Cooper ME. Mechanisms of diabetic nephropathy: role of hypertension. *Hypertension.* 2006;48:519–526. https://doi.org/10.1161/01.HYP.0000240331.32352.0c.
27. Bakris GL, Weir MR, Shanifar S, et al. Effects of blood pressure level on progression of diabetic nephropathy: results from the RENAAL study. *Arch Intern Med.* 2003;163:1555–1565. https://doi.org/10.1001/archinte.163.13.1555.
28. Tziomalos K, Athyros VG. Diabetic nephropathy: new risk factors and improvements in diagnosis. *Rev Diabet Stud.* 2015;12:110–118. https://doi.org/10.1900/RDS.2015.12.110.
29. Babazono T, Nyumura I, Toya K, et al. Higher levels of urinary albumin excretion within the normal range predict faster decline in glomerular filtration rate in diabetic patients. *Diabetes Care.* 2009;32:1518–1520. https://doi.org/10.2337/dc08-2151.
30. Gil CL, Hooker E, Larrivée B. Diabetic kidney disease, endothelial damage, and podocyte-endothelial crosstalk. *Kidney Med.* 2021;3:105–115. https://doi.org/10.1016/j.xkme.2020.10.005.
31. Vistisen D, Andersen GS, Hulman A, Persson F, Rossing P, Jørgensen ME. Progressive decline in estimated glomerular filtration rate in patients with diabetes after moderate loss in kidney functiond even without albuminuria. *Diabetes Care.* 2019;42:1886–1894. https://doi.org/10.2337/dc19-0349.
32. Little RR, Rohlfing CL, Tennill AL, et al. Measurement of Hba1C in patients with chronic renal failure. *Clin Chim Acta.* 2013;418:73–76. https://doi.org/10.1016/j.cca.2012.12.022.
33. Lee MY, Huang JC, Chen SC, Chiou HYC, Wu PY. Association of HbA 1C variability and renal progression in patients with type 2 diabetes with chronic kidney disease stages 3–4. *Int J Mol Sci.* 2018;19:1–12. https://doi.org/10.3390/ijms19124116.
34. Penno G, Solini A, Bonora E, et al. HbA1c variability as an independent correlate of nephropathy, but not retinopathy, in patients with type 2 diabetes: the renal

insufficiency and cardiovascular events (RIACE) italian multicenter study. *Diabetes Care*. 2013;36:2301–2310. https://doi.org/10.2337/dc12-2264.
35. O'Hare AM, Choi AI, Bertenthal D, et al. Age affects outcomes in chronic kidney disease. *J Am Soc Nephrol*. 2007;18:2758–2765. https://doi.org/10.1681/ASN.2007040422.
36. Eriksen BO, Ingebretsen OC. The progression of chronic kidney disease: a 10-year population-based study of the effects of gender and age. *Kidney Int*. 2006;69:375–382. https://doi.org/10.1038/sj.ki.5000058.
37. Russo GT, De Cosmo S, Viazzi F, et al. Plasma triglycerides and HDL-C levels predict the development of diabetic kidney disease in subjects with type 2 diabetes: the AMD annals initiative. *Diabetes Care*. 2016;39:2278–2287. https://doi.org/10.2337/dc16-1246.
38. Shang J, Yu D, Cai Y, et al. The triglyceride glucose index can predict newly diagnosed biopsy-proven diabetic nephropathy in type 2 diabetes: a nested case control study. *Medicine (Baltimore)*. 2019;98, e17995. https://doi.org/10.1097/MD.0000000000017995.