The Impact of HbA1c Level on The Risk of End Stage Renal Disease in T2DM Patients with or Without Hypertension: What is The Therapeutic Target?

**Abstract:**

Objectives:

This protocol is planned to determine the relationship between good control of hyperglycemia and the prevention of renal failure and/or kidney damage. While the relationship between poor control of high blood pressure in Type II Diabetes Mellitus (T2DM) and progression to kidney failure is clear, the ideal blood glucose marker measurement, glycosylated haemoglobin (HbA1c) target level to protect the kidneys is, as yet, unknown and there is an obvious need to identify this ideal HbA1c target. The design of this protocol will also investigate whether coexistence of high blood pressure would exacerbate kidney damage in T2DM.

Methods:

This protocol will examine different treatment intensity options to control hyperglycaemia and hypertension (if it is present) until a specific HbA1c target is reached in each group to identify the relation between level of glycaemic control and progression into chronic kidney disease.

Participants will be from the Middle East & North Africa region (MENA), especially Egypt, Saudi Arabia, Kuwait and UAE.

Those patients should have been confirmed with diagnosis for at least 10 years, with an HbA1c level of ≥ 8% with no history of cardiovascular events or diabetic foot disease. Patients with or without a confirmed coexistence of high blood pressure will be eligible to participate in this study.

Conclusion:

This study is designed to determine a clear-cut target HbA1c and recommendations for healthcare providers, and insurers to provide the best level of care for subjects living with T2DM. Despite the numerous publications that studied this important topic, none of them were aiming in the primary end point to determine the HbA1c target with the best kidney functions or less likely progressing to renal failure.

**key words:** T2DM OR type 2 diabetes mellitus, non-insulin dependent diabetes mellitus, ESRD (End Stage Renal Disease), CKD (chronic kidney disease), CRI, (chronic renal insufficiency), renal failure, Hypertension, high blood pressure, systolic hypertension, elevated blood pressure, Glycated haemoglobin, HbA1c (HbA1c)

**Introduction:**

The reason for conducting the study in this region is the high prevalence of T2DM in the MENA region, in **figure 1,** you will see the prevalence of T2DM in MENA countries in the year 2008, and the International Diabetes Federation expected that number of diabetic patients will be doubled by the year 2030. They also stated that one of each 5 diabetic patients has two or more diabetes related complications. (1)

**Figure 1:** Prevalence of diabetes in Middle East and North Africa region, represented by 4 countries as defined by the World Bank arranged in increasing prevalence of diabetes;

Another study showed that highest prevalence of diabetes in the world was in the middle East, with an average prevalence of 12.2%, it compared the prevalence change in each country from the year 2000 to the year 2014 to reflect on the importance to find a way of better management and minimizing the potential complications. (2) see **figure 2**.

**Figure 2: Middle East and North Africa countries ranked by prevalence of type 2 diabetes in 2000 and 2014 in %.**

It has been demonstrated in previous research that diabetic kidney disease (DKD) is the main predisposing factor leading to kidney failure, and that poor control of diabetes can enhance the progression to kidney failure, even before the development of retinopathy, which is usually the first microvascular complication to appear in diabetic patients. (3) Despite the good control of hyperglycaemia, about 20% of diabetic patients will develop diabetic kidney disease, but that should not prevent us from maintaining good control of diabetes. (4,5) Clinical trials data have demonstrated that early aggressive blood glucose control can achieve normal glucose levels and also delay the deterioration of kidney function and the development of microalbuminuria and decrease the estimated glomerular filtration rate (eGFR) in type 2 Diabetes Mellitus (T2DM) patients to a certain extent. (6,7) While many guidelines state that aggressive treatment of diabetes from diagnosis to a target HbA1c of 7% or less can protect the kidneys and reduce the progression to diabetic kidney disease, some other studies concluded that both very low HbA1c of <6% or very high >9% will increase the risk of death. (8,9)

Hypertension has been shown to be a predisposing factor leading to kidney failure in patients with type 2 diabetes, and this has been demonstrated in many publications, including the ADVANCE study where more than 11,000 diabetic patients were randomized to either placebo or ACE inhibitors treatments (Perindopril-indapamide) regardless of their blood pressure baseline, with a median follow up of 4.3 years. Treatment with ACE inhibitors reduced the risk of renal events by 21%- through reduction of the rate of development of microalbuminuria and macroalbuminuria. (10)

In another study of type T2DM and hypertension, it was demonstrated that if T2DM and hypertension exist together in the same patient, there is an increased risk of end stage renal disease (ESRD) and cardiovascular disease by 2-4 fold, so it is important to understand the correlation between both diseases. (11) Many publications have been published on the relationship between good control of HbA1c (with or without hypertension) and deterioration to kidney failure, but few of them have sought to identify the range of HbA1c that we should be targeting to offset poor renal outcomes. (12) Microalbuminuria was the first established marker for renal outcome and has been utilized in clinical trials testing the effects of SGLT2 inhibitors and GLP-1 on the glycemic control and deterioration to ESRD. (13)

Perkovic *et al* have analyzed the ADVANCE study from a different perspective and stated that macroalbuminuria and doubled serum creatinine level are surrogate end points, but they provided an early warning on the reliability of albuminuria as a confirmed renal outcome and still debatable because some diabetic patients have developed progressive kidney disease without having albuminuria. In a 2-arm comparison between intensive glucose lowering versus standard glucose lowering, there was a 65% reduction of the progression into end stage renal disease in the intensive glucose lowering arm. Since the total number of events that occurred in both groups was low, the number needed to treat (NNT) over 5 years to prevent one incident of ESRD was 410 patients, it seems a high number and does not justify the intention of the study, however, in a subpopulation at high renal risk, the NNT over 5 years to prevent one incident of ESRD was only 85, more acceptable. (14)

The DISCOVER study was a global prospective observational study where patients were recruited from over 38 countries. Results demonstrated a positive relationship between HbA1c and microvascular complications. Chronic kidney disease had a prevalence of 5% and albuminuria at 4.3%, suggesting urgent modification of risk factors in addition to the good control of hyperglycemia is needed. (15)

To estimate the prevalence of hypertension in people living with diabetes in Jordan, a cross-sectional study was performed in the outpatient’s diabetes clinics and included 1000 patients with diabetes. The study used a questionnaire to determine whether participants were aware of having high blood pressure and then measured their blood pressure. It was found that almost 72% of patients in the study had hypertension of above 130/80. Hypertension was associated with age, Body Mass Index (MBI) and duration of diabetes (p=0.001). It also demonstrated that half of the patients were aware of having hypertension, but failed to control their high blood pressure, which prove that T2DM is a predisposing factor for developing hypertension. (16)

A Japanese study tested four different groups of patients to estimate the HbA1c level that could protect against diabetic nephropathy, and concluded that in all groups, maintenance of HbA1c lower than 7% (together with targeting BMI of <25) was beneficial in delaying the progression into end stage renal disease. (17)

In another HbA1c variability study conducted in Japan, Patients were monitored for a median of 9.5 years, they tested HbA1c from two angles, mean HbA1c and standard deviation HbA1c. it showed that patients with increased HbA1c-mean and HbA1c-SD had a significantly increased risk of developing diabetes-related complications, which were listed as our six study endpoints. After full adjustment of the model, increased HbA1c-mean was associated with a significantly increased risk of a UACR > 300 mg/g and advanced retinopathy, while increased HbA1c-SD was associated with a significantly increased risk of a UACR > 300 mg/g, doubling of serum creatinine, and all-cause mortality and CVD mortality. (18) This can only add to previous study referenced above and confirms that increased HbA1c will always lead to ESRD.

To conclude, poor glycaemic control and uncontrolled hypertension are risk factors for the development of ESRD. There is an urgent need to establish clear HbA1c targets to offset the risk of substantial morbidity and mortality.

**Rationale:**

With diabetic nephropathy as one of the most serious complications of type2 diabetes, it is important to understand the causality in diabetic patients and how to prevent or delay such serious outcomes.

The aim of this protocol is to determine the precise target in terms of controlling hyperglycaemia, here there will be a need to show that HbA1c -as a major marker for diabetes control- of lower than <7% would prevent and/or delay the progression to end stage renal disease. The primary end points will be monitored until we reach to a certain number of events that will be specified in the statistical analysis plan, in other words, this is an event driven study.

Additionally, the protocol will study subgroups of patients having other comorbidities at the recruitment time e.g., hypertension.

**Objectives:**

* Identify the HbA1c arm with the highest mean eGFR at the end of the study.
* To identify a well-defined HbA1c target to offset risk of DKD.
* Collect data which relates HbA1c levels to kidney disease.

**Hypothesis:**

As continuous control of hyperglycaemia is inversely proportional to progression to ESRD, it is expected that good glycaemic control will benefit the kidney, but the HbA1c target level is, as yet, unknown.

The null hypothesis is that HbA1c level is thought to be around 7% to achieve the highest average of eGFR and kidney protection. So, at the end of the trial, eGFR will be similar in both groups.

**Methodology:**

**Study description:**

The study will be an open label randomized clinical trial. It will also look at different therapeutic targets and allow the drop out of not more than 10%, and termination of participation of any patient from the study at the discretion of the physician if they see it appropriate. The randomization will prevent any bias from happening and ensure fair allocation of eligible patients into different study arms. As the study is open label, the end points will be objective and not subjective, in other words, there will not be any patient’s preference or quality of life questionnaires, again to avoid potential bias.

**Study Population:**

*Inclusion & Exclusion criteria*:

Inclusion and exclusion criteria will be based on the hypothesis and objective of the study. Screening of patients will carefully investigate these criteria and make sure each successfully screened patient will meet the eligibility criteria as per the protocol and any deviation will lead to termination of patient participation and will not be counted in the analysis (see table 1).

|  |  |
| --- | --- |
| ***Inclusion Criteria*** | ***Exclusion Criteria*** |
| * Patients with longstanding diabetes >10 years (with or without hypertension) will be recruited.
 | * Patients who are participating in another clinical trials, currently or in the past 90 days.
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| * Age between 40 - 65 years old.
 | * Patients with history of coronary artery disease.
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| * Patients on two or three types of medications and with HbA1c of >8%.
 | * Previous incident of diabetic kidney disease.
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| * Recruitment from different countries in the Middle East.
 | * Previous incident of strokes or Transient Ischaemic Attacks.
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| * eGFR should be >60 ml/min/1.73 m2 at screening time
 | * Any foot disorders related to their current diabetes.
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**Table 1:** Inclusion & Exclusion criteria

**Intervention and Analysis:**

Patients who meet eligibility criteria of the study will be randomly and equally assigned to one of the patient arms demonstrated above. The study will initiate therapy with the same regimen in all groups, then adjust the doses and/or add more medications according to the planned goal of control of HbA1c as per the study design below. (see figure 3)

An event driven study with open label randomization to four treatment arms, as follows.

* Study arm 1a: Patients with T2DM alone and A1c target of 6.5% - 7%
* Study arm 1b: Patients with combined T2DM & Hypertension and A1c target of 6.5% - 7%
* Study arm 2a: Patients with T2DM alone and A1c target of 7% - 7.5%
* Study arm 2b: Patients with combined T2DM & Hypertension and A1c target of 7% - 7.5%

Randomization will be prepared in a central store as sealed envelopes, then eligible patients will be assigned randomly using Interactive Voice Response System.

**Study design:**

Patients will be assigned to one of several study arms, according to the intensity of management of hyperglycaemia, in each arm we should allow doses to increase every 3 months until we reach the desired HbA1c target for each arm, then once the HbA1c target is achieved, the latest medications and doses used will be maintained until progression to end stage renal disease. The main 2 study arms according to the target HbA1c will be 1) Between 6.5% - 7.%. 2) Between 7% - 7.5%, in addition to two more arms for patients who have also high blood pressure at the baseline, as other comorbidity with T2DM. HbA1c will continue to be monitored every 6 months until the end of the study.

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**Figure 3:** this diagram illustrates the study design and the randomization to each arm of the study. Also, it shows the two subcategories of each arm (with or without baseline hypertension), until each patient group reaches their desired or planned HbA1c target.

**Suggested interventions:**

* Medications of study arm 1a: SGLT2i (Dapagliflozin 10mg) + DPP4i (Vildagliptin + metformin 50/1000 X2) + basal insulin (+/- GLP1 in jection)
* Medications of study arm 1b: SGLT2i (Dapagliflozin 10mg) + DPP4i (Vildagliptin + metformin 50/1000 X2) + basal insulin (+/- GLP1 injection) + ACEi
* Medications of study arm 2a: SGLT2i (Dapagliflozin 10mg) + biguanide (metformin 2gm/day) + basal insulin (+/- GLP1 injection or Galvus)
* Medications of study arm 2b: SGLT2i (Dapagliflozin 10mg) + biguanide (metformin 2gm/day) + basal insulin (+/- GLP1 injection or Galvus) + ACEi

HbA1c will be measured every 3 months and adjust doses up or down when needed or add a new medication (GLP1 injection) to achieve the desired HbA1c target of each treatment arm, then it will be measured every 6 months onward in the maintenance phase.

For the control of hypertension, the goal is to achieve a blood pressure of <130/80 mmHg, we will start with ACEi and increase the dose until we reach blood pressure target, if necessary, we may also add Calcium Channel Blockers.

The materials for intervention will be monitored/counted for all patients in every visit to insure they are adherent to their respective medications. Periodic telephone check may take place in between visits to see how they are adherent to their medications.

All patients’ groups participating in the study will be advised to perform physical exercise at least walking for 30 min per day and will be encouraged to keep an acceptable body weight through following a diet plan and perhaps change their eating habits.

All patients’ groups will be trained on glucose self-monitoring and measure their fasting and post prandial blood sugar levels at least 2-3 times a week and will be trained on how to adjust their basal insulin level accordingly.

Patients not able to achieve their planned HbA1c target for 3 or more consecutive visits, will be forced to exit the study, because this will only reflect their non-compliance to the assigned therapy.

**Schedule of enrolment, interventions and timelines:**



**Table 2:** The sequence of events and procedure of the study.

 **Sample Size & Power Calculation:**

At a 5% level of significance, in order to achieve 80% power and a difference of 12% (19,20,21) in the number of patients reaching the definition of ESRD, 241 eligible patients will be needed to be enrolled in each of the 2 arms. 250 patients per arm might be recruited to compensate for those patients not achieving the HbA1c goal.

***Justification of sample size calculation:***

In a meta-analysis of randomized Controlled Trials, B.Sinha and S.Ghosal, they made a conclusion that a target HbA1c of 7.1% - 7.7% will reduce the risk of both macrovascular and microvascular complications including end stage renal disease and macroalbuminuria, it showed reduction of 32% of ESRD, and reduction of 18% in the incidence of macroalbuminuria. (19) Zoungas and colleagues, conducted a meta-analysis of four major studies and reported that intensive glycaemic control can offer up to 20% reduction in the risk of the composite of end stage renal disease, macroalbuminuria and death. (20) In another Chinese study, they stated that patients with HbA1c of <6% were associated with highest risk of end stage renal disease, followed by patients with an HbA1c of >7%, and concluded that the group of patients with HbA1c between 6%-6.9% were associated with the lowest risk of ESRD. (21)

It is now obvious that lower HbA1c target is associated with a better outcome in terms of macroalbuminuria and end stage renal disease. According to different studies and meta-analysis, they concluded that risk reduction of ESRD ranges between 20%-32% and sometimes reach to 40%, and risk reduction of macroalbuminuria ranges between 18% and 30%. So, our sample size calculation is based on an average difference of 12% between the 2 arms in this study.

The study can be event driven study, where a specific numbers of end points should occur to conclude the study, as we cannot wait for all subjects to develop CKD, it may last for decades. The protocol is to set an average time of 5 or 6 years as the length of the study, then we can evaluate the end points by then.

**Data Collection:**

Patients’ data will be collected on a CRF (case report form) which will most likely be in an electronic form (eCRF) to make life of investigators and study teams easier. Periodic and random monitoring will be performed on regular bases, where queries will be generated -when needed- and will be sent to study investigators to answer. When data is clean, it can be submitted to data management centre.

**Study Outcomes:**

Since the protocol is open label, none controlled study, all outcomes will be quantitative in nature (numerical) and no patient questionnaires will be used to avoid bias. (see table 3)

|  |  |  |
| --- | --- | --- |
| 1. ***Primary endpoints***
 | 1. ***Secondary endpoints***
 | 1. ***Safety endpoints:***
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| * Median number of patients with eGFR below 20 mL/min/1.73m2 in each arm.
 | * Percentage of patients who needed incident dialysis in each arm.
 | * Reporting any serious adverse events (SAEs) that might occur.
 |
| * Percentage of patients who developed MACE\* (major adverse cardiovascular events) in each arm.
 | * Reporting the common adverse events (AEs) related to any of the interventional drugs e.g., hypoglycaemia, urinary tract infection, nausea, vomiting or cough.
 |
| * Median number of occurrences of macroalbuminuria (urine albumin excretion rate (AER)≥300 mg/d) in each arm.
 | * Percentage of hospitalization due to hypoglycaemia in each arm.
 |
| * Percentage of hospitalization due to any cause in each arm.
 | * Each of the common AEs will receive a code to facilitate reporting in the eCRF.
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**Table 3:** The study outcomes/endpoints, from primary, secondary and safety endpoints.

* \* MACE: the composite of total death, myocardial infarction, coronary revascularization, stroke, and hospitalization because of heart failure.

**Statistical Analysis Plan:**

Simple descriptive statistics will initially be employed to summarize the outcome of each arm of the study. Two sample proportion tests will be used to assess for the significance of any differences between arms: 1a and 2a; 1b and 2b as well as overall difference between arms 1 and 2.

Bonferroni corrections will be used due to multiple testing. A 5% level of significance will be set, and test will be performed using IBM SPSS v28.0.

***Prespecified Eligibility for Analysis:***

Patients will be non-compliant for 3 or more visits and will not achieve their assigned HbA1c target, will be excluded from the study and will not be eligible for analysis.

**Study Assumptions:**

Total number of patients: 482

Recruitment period: 12 months

Accrual intervals: 9.3 patients per week

Follow-up intervals: 60 months

Median time to an event (best estimate): 7.5 years

A total of 482 patients will enter this two-treatment parallel-design study. The probability is 80 percent that the study will detect a treatment difference at a two-sided 5.0 percent significance level if the true hazard ratio is 1.555. This is based on the assumption that the accrual period will be 12 Months and the follow up period will be 60 Months and the median survival is 90 Months. The total number of events will be 158.

**Discussion:**

 As was described in the introduction, huge number of trials have been conducted by respected authors for the benefits of good control of hyperglycaemia and hypertension and how this control will benefit type II diabetes patients in the prevention and/or delay of microvascular complications, including the progression into end stage renal disease, which is the topic of this study.

There was no consistency in the literature for the level of HbA1c that we should target to get the maximum benefits. They all agreed that HbA1c above 8% is directly linked to renal failure and mortality.

And the majority also stated that target of less than 6% is also linked to higher mortality.

On the other hand, there was a consensus that target HbA1c of less tha n 7.5% is beneficial to protect against ESRD, but it was not very clear whether a target of 7% to 7.5% is better or worse than a target of 6.5% to 7%.

Hence came the need to specifically investigate those two target ranges through a randomized clinical trial with the primary objective to settle the ideal range of HbA1c target, which can protect the kidneys of type II diabetic patients.

**Strengths and Limitations of This Study:**

* It can be a landmark study for the Middle East T2DM patients due to lack of similar studies conducted in this population.
* The cost of medications and proposed lab tests in both groups might not be encouraging for independent institution to conduct it, it may need a collaborative study group to minimize the cost per each site.
* Almost half of the population in the Gulf Counsel Corporation (Saudi Arabia & Gulf countries) are expatriates and the probability of “lost follow up” is high due to people moving out back to their homes.

**Conclusion:**

Conclusion will be drawn after carrying out the study.

**Disclaimer (Artificial intelligence)**

Option 1:

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

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Details of the AI usage are given below:

1.

2.

3.

**Ethical Approval and Consent:**

As this is currently a protocol and the study will not be conducted now, the EC approval will not be needed at this phase. If someone would like to conduct this protocol, an informed consent should be created and submitted to the regulatory authorities and hospital committees together with copy of the protocol to seek their approval.

**References:**

1. Sherif S. Economic development and diabetes prevalence in MENA countries: Egypt and Saudi Arabia comparison. World Journal of Diabetes. 2015;6(2):304. doi:10.4239/wjd.v6.i2.304
2. El-Kebbi IM, Bidikian NH, Hneiny L, Nasrallah MP. Epidemiology of type 2 diabetes in the Middle East and North Africa: Challenges and call for action. World Journal of Diabetes. 2021;12(9):1401–25. doi:10.4239/wjd.v12.i9.1401
3. Bash LD, Selvin E, Steffes M, Coresh J, Astor BC. Poor glycemic control in diabetes and the risk of incident chronic kidney disease even in the absence of albuminuria and retinopathy. Archives of Internal Medicine. 2008;168(22):2440.
4. Wang J, Xiang H, Lu Y, Wu T, Ji G. New progress in drugs treatment of diabetic kidney disease. Biomedicine & Pharmacotherapy. 2021;141:111918.
5. G.L. Bakris, Recognition, pathogenesis, and treatment of different stages of nephropathy in patients with type 2 diabetes mellitus, Mayo Clin. Proc. 86 (5) (2011) 444–456.
6. KDOQI Clinical Practice Guideline for Diabetes and CKD: 2012 Update, Am. J. Kidney Dis. Off. J. Natl. Kidney Found., 60(5), 2012, pp. 850–886.
7. M.J. Davies, D.A. D’Alessio, J. Fradkin, W.N. Kernan, C. Mathieu, G. Mingrone, P. Rossing, A. Tsapas, D.J. Wexler, J.B. Buse, Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), Diabetes Care 41 (12) (2018) 2669–2701.
8. Y. Slinin, A. Ishani, T. Rector, P. Fitzgerald, R. MacDonald, J. Tacklind, I. Rutks, T.J. Wilt, Management of hyperglycemia, dyslipidemia, and albuminuria in patients with diabetes and CKD: a systematic review for a KDOQI clinical practice guideline, Am. J. Kidney Dis. Off. J. Natl. Kidney Found. 60 (5) (2012) 747–769.
9. E.S. Huang, J.Y. Liu, H.H. Moffet, P.M. John, A.J. Karter, Glycemic control, complications, and death in older diabetic patients: the diabetes and aging study, Diabetes Care 34 (6) (2011) 1329–1336.
10. de Galan BE, Perkovic V, Ninomiya T, Pillai A, Patel A, Cass A, et al. Lowering blood pressure reduces renal events in type 2 diabetes. Journal of the American Society of Nephrology. 2009;20(4):883–92.
11. Sun D, Zhou T, Heianza Y, Li X, Fan M, Fonseca VA, et al. Type 2 diabetes and hypertension. Circulation Research. 2019;124(6):930–7.
12. MacIsaac RJ, Jerums G, Ekinci EI. Effects of glycaemic management on diabetic kidney disease. World Journal of Diabetes. 2017;8(5):172.
13. MacIsaac RJ, Ekinci EI, Jerums G. ‘Progressive diabetic nephropathy. How useful is microalbuminuria?: contra’ Kidney Int. 2014;86:50–57.
14. Perkovic V, Heerspink HL, Chalmers J, Woodward M, Jun M, Li Q, MacMahon S, Cooper ME, Hamet P, Marre M, et al. Intensive glucose control improves kidney outcomes in patients with type 2 diabetes. Kidney Int. 2013;83:517–523.
15. Kosiborod M, Gomes MB, Nicolucci A, Pocock S, Rathmann W, Shestakova MV, et al. Vascular complications in patients with type 2 diabetes: Prevalence and associated factors in 38 countries (the Discover Study Program). Cardiovascular Diabetology. 2018;17(1).
16. Mubarak FM, Froelicher ES, Jaddou HY, Ajlouni KM. Hypertension among 1000 patients with type 2 diabetes attending a National Diabetes Center in Jordan. Annals of Saudi Medicine. 2008;28(5):346–51.
17. Nakanishi S, Hirukawa H, Shimoda M, Tatsumi F, Kohara K, Obata A, et al. Comparison of hba1c levels and body mass index for prevention of diabetic kidney disease: A retrospective longitudinal study using outpatient clinical data in Japanese patients with type 2 diabetes mellitus. Diabetes Research and Clinical Practice. 2019;155:107807.
18. Wu T-E, Su Y-W, Chen H-S. Mean hba1c and HbA1c variability are associated with differing diabetes-related complications in patients with type 2 diabetes mellitus. Diabetes Research and Clinical Practice. 2022;192:110069.
19. Sinha B, Ghosal S. A target hba1c between 7 and 7.7% reduces microvascular and macrovascular events in T2D regardless of duration of diabetes: A meta-analysis of randomized controlled trials. Diabetes Therapy. 2021;12(6):1661–76.
20. Zoungas S, Arima H, Gerstein HC, et al. Effects of intensive glucose control on microvascular outcomes in patients with type 2 diabetes: a meta-analysis of individual participant data from randomised controlled trials. Lancet Diabetes Endocrinol 2017. [https://doi.org/10.1016/S2213-8587(17)30104-3](https://doi.org/10.1016/S2213-8587%2817%2930104-3)
21. Liao LN, Li CI, Liu CS, Huang CC, Lin WY, Chiang JH, Lin CC, Li TC. Extreme Levels of HbA1c Increase Incident ESRD Risk in Chinese Patients with Type 2 Diabetes: Competing Risk Analysis in National Cohort of Taiwan Diabetes Study. PLoS One. 2015 Jun 22;10(6):e0130828. doi: 10.1371/journal.pone.0130828. PMID: 26098901; PMCID: PMC4476774.