IMPACT OF STATIN AND IDENTIFICATION OF RISK FACTORS ASSOCIATED WITH THE DEVELOPMENT OF CHRONIC KIDNEY DISEASE IN TYPE 2 DIABETIC PATIENTS: A RETROSPECTIVE COHORT STUDY IN THE UNITED ARAB EMIRATES

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LIST OF ABBREVIATIONS

ACC/AHA	American College of Cardiology/American Heart Association
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ADA	American Diabetes Association
ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation
AGI	Alpha-Glucosidase Inhibitors
AKI	Acute Kidney Injury
ALLIANCE	Aggressive Lipid-Lowering Initiation Abates New Cardiac Events
BRB	Blood-Retinal Barrier
BUN	Blood Urea Nitrogen
CAD	Coronary Artery Disease
CDC	Centers for Disease Control and Prevention
CDC	Chronic Disease Cohort
CI	Confidence Interval
CIN	Contrast-Induced Nephropathy
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CREDENCE	Canagliflozin on Renal and Cardiovascular Outcomes in Participants with Diabetic Nephropathy
CRP	C-reactive protein
CRS	Cardiorenal Syndrome
CVD	Cerebrovascular Disease
DALY	Disability-Adjusted Life Years
DDP-4	Dipeptidyl Peptidase-4
DKD	Diabetic Kidney Disease
DM	Diabetes Mellitus
DME	Diabetic Macular Edema
EASD	European Association for the Study of Diabetes
eGFR	Estimated Glomerular Filtration Rate
ESC/EAS	European Society of Cardiology/European Atherosclerosis Society
ESC	European Society of Cardiology
ESRD	End-Stage Renal Disease
FDA	U.S. Food and Drug Administration

GCC	Gulf Cooperation Council
GFR	Glomerular Filtration Rate
GLP-1	Glucagon-like Peptide 1
HbA1c	Glycated hemoglobin
HDL	High-Density Lipoprotein
IL	Interleukin
JUPITER	Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin
KDOQI	Kidney Disease Outcomes Quality Initiative
LDL	Low-Density Lipoprotein
MDRD-4	Modification of Diet in Renal Disease Study Equation
MENA	Middle East and North Africa
MODY	Maturity-Onset Diabetes of the Young
NPDR	Nonproliferative Diabetic Retinopathy
PANDA	Pravastatin in Dialysis Patients
PDR	Proliferative Diabetic Retinopathy
PVD	Peripheral Vascular Disease
RA	Receptor Agonists
SCr	Serum Creatinine
SGLT2	Sodium-Glucose Cotransporter 2
SPARCL	Stroke Prevention by Aggressive Reduction in Cholesterol Levels
SUA	Serum Uric Acid
T2DM	Type 2 Diabetes Mellitus
TNT	Treating to New Targets
UA	Uric Acid
UACR	Urine Albumin to Creatinine Ratio
UAE	United Arab Emirates
UAER	Urinary Albumin Excretion Rates
UKPDS	United Kingdom Prospective Diabetes Study
USA	United States of America
VADT	Veterans Affairs Diabetes Trial

LIST OF APPENDICES

KESAN STATIN DAN PENGENALPASTIAN FAKTOR RISIKO YANG BERKAITAN DENGAN PERKEMBANGAN PENYAKIT BUAH PINGGANG KRONIK DALAM KALANGAN PESAKIT DIABETES JENIS 2: SATU KAJIAN KOHORT RETROSPEKTIF DI ARAB EMIRIAH BERSATU

ABSTRAK

Penyakit buah pinggang kronik (CKD) merupakan satu cabaran kesihatan dunia yang signifikan, dengan implikasi yang sukar dicapai kepada kedua-dua pesakit dan sistem penjagaan kesihatan. Kajian ini bertujuan untuk menyediakan analisis menyeluruh mengenai insiden CKD pada tahap 3-5, meneliti impak terapi statin dan intervensi antihiperglisemik, serta mengenal pasti faktor ramalan signifikan, sekaligus memberikan pandangan penting tentang dinamika kompleks perkembangan CKD dalam kalangan individu dengan diabetes mellitus jenis 2 (T2DM). Kajian ini merupakan kajian kohort retrospektif di pusat tunggal berdasarkan data yang diperoleh dari rekod perubatan elektronik (EMR) dalam populasi Arab Emiriah Bersatu (UAE) dengan diabetes mellitus, yang berdaftar di klinik pesakit luar di Hospital Tawam di Al Ain, UAE, antara Januari 2011 dan Disember 2021. Pesakit T2DM berumur $\geqslant$ 18 tahun yang mempunyai tahap HbA1c $\geqslant$ 6.5% dan menggunakan salah satu terapi statin adalah kriteria rangkuman. Kajian ini menggunakan dua kumpulan kohort, iaitu satu kumpulan terdiri daripada pesakit yang menerima terapi statin dan satu lagi kumpulan terdiri daripada pesakit yang tidak menerima terapi statin. Pensampelan bertujuan digunakan dalam pengambilan pesakit ini. Pesakit diabetes mellitus jenis 1 (T1DM), yang telah menjalani terapi gantian buah pinggang kekal, dengan kurang dari satu tahun pemantauan dan data yang hilang atau tidak lengkap, telah dikecualikan dari kajian ini. Faktor-faktor yang menyumbang kepada perkembangan CKD

peringkat 3-5 dalam kalangan pesakit diabetes dikenal pasti menggunakan analisis regresi Cox dan model risiko bersaing Fine dan Gray, yang mengambil kira kejadian bersaing yang mungkin mempengaruhi perkembangan CKD. Kajian ini melibatkan kohort 1,003 individu. Kajian ini telah memerhatikan sejumlah 388 subjek yang mengalami CKD peringkat 3-5 di sepanjang tempoh pemantauan dengan purata 11.7 tahun. Ini menghasilkan insiden kumulatif sebanyak 38.7%, bermaksud kadar insiden sebanyak 38 kes setiap 1,000 orang-tahun. Data menunjukkan korelasi yang jelas antara penggunaan statin dan perkembangan CKD. Pengguna statin intensiti tinggi lebih berkemungkinan untuk mengalami CKD peringkat 3-5 berbanding pengguna statin intensiti rendah/sederhana (44.3% berbanding 37.9%) dan individu yang tidak menggunakan statin (44.3% berbanding 30.9%). Sebaliknya, pesakit yang menggunakan biguanida kurang berkemungkinan untuk mengalami CKD peringkat 3-5 (37.9% berbanding 52.8%; $p = 0.001$), manakala pengguna insulin lebih berkemungkinan untuk mengalami CKD peringkat 3-5 (54.2% berbanding 34.1%; $p < 0.001$). Faktor risiko yang dikenal pasti bagi perkembangan CKD peringkat 3-5 termasuk peningkatan usia (HR: 1.005, 95% CI: 1.002-1.009, $p = 0.026$), hipertensi (HR: 1.69, 95% CI: 1.032-2.8, $p = 0.037$), penyakit jantung (HR: 1.49, 95% CI: 1.16-1.92, $p = 0.002$), peningkatan kreatinin serum (HR: 1.006, 95% CI: 1.002-1.010, $p = 0.003$), penurunan eGFR (HR: 0.943, 95% CI: 0.938-0.947, $p < 0.001$), dan penggunaan beta-blocker (HR: 1.39, 95% CI: 1.12-1.73, $p = 0.003$). Sebagai kesimpulan, penyelidikan kami menekankan perhubungan kompleks antara pelbagai faktor dalam permulaan CKD peringkat 3-5. Hasil kajian ini menekankan kepentingan peranan strategi perubatan diperibadikan, terutamanya berkaitan dengan terapi statin dan ubat-ubatan lain, dalam populasi berisiko tinggi. Selain itu, faktor risiko yang dikenalpasti dalam kajian ini boleh memberikan panduan untuk pengesanan awal dan

intervensi yang tepat pada masanya, dengan matlamat untuk memperbaiki keadaan pesakit dan mengoptimumkan pengurusan CKD.

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ABSTRACT

Chronic Kidney Disease (CKD) represents a significant worldwide health challenge, with far-reaching implications for both patients and healthcare systems. This study aims to provide a comprehensive analysis of CKD incidence at stages 3-5, examines the impact of statin therapy and other antihyperglycemic interventions, and identifies key predictive factors, offering valuable insights into the complex dynamics of CKD progression in individuals with type 2 diabetes mellitus (T2DM). This was a single-centre retrospective cohort study based on data derived from electronic medical records (EMR) of United Arab Emirates (UAE) populations with diabetes mellitus, registered at outpatient clinics at Tawam Hospital in Al Ain, UAE, between January 2011 and December 2021. This study utilized two cohort groups, one of which consisted of a group of patients who were receiving statin therapy and another group of patients who were not receiving statin therapy and purposeful sampling was used in the recruitment of these patients. T2DM patients aged $\geqslant$ 18 years who had serum HbA1c level $\geqslant$ 6.5% and using one of the statin therapies were included. Patients with type 1 diabetes mellitus (T1DM), who had undergone permanent renal replacement therapy, with under 1 year of follow-up and missing or incomplete data were excluded from the study. Factors contributing to the progression of CKD stages 3–5 in diabetic patients were identified using Cox regression analysis and the Fine and Gray competing risk model, which accounts for competing events that may influence

CKD development. This study included a cohort of 1,003 individuals. We observed 388 subjects developed CKD stages 3–5 across an average monitoring duration of 11.7 years. This resulted in a cumulative incidence of 38.7%, translating to an incidence rate of 38 cases per 1000 person-years. The data revealed a clear correlation between the use of statin and the progression of CKD. High-intensity statin users were more likely to develop CKD stages 3-5 compared to low/moderate intensity users (44.3% vs 37.9%) and no statin users respectively (44.3%% vs 30.9%). Conversely, patients using biguanides were less likely to develop CKD stages 3-5 (37.9% vs. 52.8%; $p = 0.001$), whereas insulin users were more likely to develop CKD stages 3-5 (54.2% vs. 34.1%; $p < 0.001$). Advancing age (HR: 1.005, 95% CI: 1.002-1.009, $p = 0.026$), hypertension (HR: 1.69, 95% CI: 1.032-2.8, $p = 0.037$), heart disease (HR: 1.49, 95% CI: 1.16-1.92, $p = 0.002$), elevated serum creatinine (HR: 1.006, 95% CI: 1.002-1.010, $p = 0.003$), decreased eGFR (HR: 0.943, 95% CI: 0.938-0.947, $p < 0.001$), and beta-blocker use (HR: 1.39, 95%: CI 1.12-1.73, $p = 0.003$) were identified as significant risk factors for stages 3-5 CKD progression. In conclusion, this study underscores the complex interplay between various factors in the onset of CKD stages 3–5. The findings emphasize the pivotal role of personalized treatment strategies, particularly concerning statin therapy and other medications, in populations at high risk. Furthermore, the identified risk factors offer valuable guidance for early detection and timely intervention, aiming to improve patient outcomes and optimize the management of CKD.

CHAPTER 1

INTRODUCTION

1.1 Introduction to Type 2 Diabetes Mellitus (T2DM)

T2DM is a complex metabolic disorder, which is defined mainly by insulin resistance and gradual decline in the capacity of pancreatic β-cells to secrete insulin and produce glucose. T2DM is accountable for 90-95% of all diabetes situations and has become a global health concern because of its high incidence and complications (Ajjan & Orme, 2015). It is known that the disease manifests itself depending on the genetic factors and the impact of such factors as diet, lack of physical activity, and obesity. T2DM clinical symptoms may not be apparent for years and in fact, most patients are diagnosed with the disease when they are already in their Middle Ages. Hyperglycemia is a chronic condition that over time leads to both microvascular and macrovascular complications such as retinopathy, neuropathy, nephropathy, cardiovascular disease, and stroke, and these should be detected and managed as early as possible (Al Dahmani et al., 2021).

T2DM has become a pandemic disease which affects hundreds of millions of people all over the world. T2DM has been influenced by several factors such as increased prevalence of obesity, reduced physical activity, and growing population of people with advanced age. T2DM has been described by WHO as a major health concern, contributing to 90-95% of diabetes, and the recent estimation showed that 422 million people are affected by the disease globally. The condition is most common in LMICs where there has been increased growth and development characterized by urbanization and changes in lifestyles that have boosted the emergence of T2DM (Al Mamari et al., 2023).

T2DM has far-reaching consequences for the world's population resulting in high morbidity, mortality, and economic costs. Diabetic complications include cardiovascular disease, renal failure, and neuropathy, which negatively affect the patient's quality of life and increases health care consumption (AlSayed et al., 2021). However, the management of T2DM continues to be a clinical challenge because of the disease's multifactorial nature and its interrelation with other chronic diseases. International organizations are still urging the governments and health care systems to adopt multi-faceted approaches that include prevention, early diagnosis and proper management of T2DM since it is on the rise (Alzahrani, 2018).

T2DM is characterized by peripheral tissue insulin resistance predominantly in the muscles and adipose tissue, increased glucose output by the liver and impaired insulin secretion by the pancreatic β-cells. High blood sugar and high cholesterol levels in T2DM cause oxidative stress, impaired blood vessels and inflammation, all of which contribute to diabetic complications. Notably, T2DM is defined to increase the risk of cardiovascular events by two to four times and plays a major role in the occurrence of chronic kidney disease globally (Bajaj et al., 2015).

1.1.1 Global Overview of T2DM

T2DM is considered as one of the largest health concerns globally. Both the World Health Organization as well as the International Diabetes Federation have recognized diabetes as a chief source of morbidity and mortality. T2DM has developed as a global health alarm in recent decades due to the rise in aged population, obesity and decline in physical activity (Beshyah et al., 2014). As per the data obtained in 2011 from IDF, the complications of diabetes were the leading cause of 4. 6 million deaths and the costs of healthcare for diabetes have reached approximately $465 billion or coarsely one-tenth of overall global health-care expenses. This economic load is

expected to increase in the future because of the rising cases of T2DM in LMICs, which take the heaviest weight of this disease due to inadequate health care means (Beshyah et al., 2015).

T2DM is a global disease, but the incidence rates differ greatly, and the highest rates are recorded in the Middle East and North Africa (MENA) and Southeast Asia. The disease is known to be a major cause of early mortality because of the complications that are associated with it; these complications include both the microvascular and macrovascular diseases. T2DM is a global health concern that needs to be managed through the identification of the disease and its risk factors, changes in behavior and the use of medication. Global recommendations also stress the importance of a coordinated care model that addresses glycemic control with cardiovascular risk in order to decrease the prevalence of CKD and CVD (Beshyah & Deeb, 2012).

T2DM involves insulin resistance whereby the body's cells are unable to respond to insulin appropriately and a relative insufficiency of insulin. This in turn results in chronic hyperglycemia which is characterized by complications that affect different organs in the body. T2DM is a multifactorial disease that results from a combination of genetic, environment and lifestyle factors. The hereditary factor is very important, as more than 50 genes are involved in the control of glucose homeostasis and insulin response. However, factors like diet, physical activity, and obesity are the key influential factors that define disease development and its progression (Beshyah et al., 2022).

Presently, T2DM affects about 537 million adults worldwide and is expected to affect 783 million by 2045, which shows the increasing trend of this disease. It is present all over the world in both the developed and the developing countries, but the

middle-income countries have the highest incidence rates due to factors such as urbanization, change in lifestyles and aging population. The economic costs of T2DM are high, the direct costs being mainly attributed to the costs of treating complications of the disease which constitute a large part of the total health care expenditure. T2DM has become one of the leading causes of mortality and morbidity globally and the global health care system is shifting towards prevention and early diagnosis and efficient management of T2DM (Beshyah, 2023).

The health organizations worldwide have embarked on numerous campaigns for checking the rising rates of diabetes. These campaigns have involved encouraging people to exercise, enhancing the approach to quality health services and increasing the number of people getting proper checkups for diabetes and receiving proper treatment at the early stages. However, T2DM remains a serious problem in among the population of world, specifically in the areas with controlled access to health care and elevated prevalence of fatness (Beshyah et al., 2022).

T2DM is now an alarming global health concern as its cases have risen sharply over the recent few decades. According to recent global statistics, approximately more than 463 million adults have suffered from diabetes, and the recognized figure may reach up to 700 million by 2045 as mentioned by IDF Diabetes Atlas, 2019. The economic consequences are massive, with the health care costs for diabetes estimated at about $760 billion per year global which is equivalent to approximately 10% of global health care expenses. The economic consumptions of diabetes do not only comprehend the direct medical expenditures but also failure of production, and constant disability, indicating that diabetes causes a great burden to families and countries across the globe (Beshyah et al., 2023).

T2DM is a metabolic disorder marked by insulin resistance and impaired insulin secretion by beta-cells resulting in persistent hyperglycemia. In the long run, this leads to the damage of the different organs and systems of the body, especially the circulatory system and the kidneys. This pathophysiological progression has made diabetes to be among the major causes of cardiovascular diseases (CVD) and chronic kidney disease (CKD) in the world. Furthermore, obesity, physical inactivity, and the increasing rate of aging populations are other factors that have led to increased T2DM incidence making it a global health concern (Bloomgarden, 2023).

T2DM has a negative impact on patients' quality of life because the disease is chronic, and patients have to deal with numerous complications. Most of the patients live with medications and changes in their lifestyle and frequent checkups for the rest of their lives. These comorbidities: CKD and cardiovascular disease increase the cost of health care and require specialized attention among T2DM patients. These issues point to the need for the incorporation of diabetes in primary care healthcare to improve early treatment and patient outcomes (Bonnet et al., 2024).

T2DM management has transitioned from simple glycaemia control to cardiovascular and renal risks assessment and management. This shift is backed by clinical trials results that are shifting focus towards early intervention and the use of drugs that have cardio renal benefits. Current guidelines for T2DM treatment are based on a complex intervention strategy that includes lifestyle changes, pharmacological management and periodic assessment of glycemic status, cardiovascular risk and renal function (Cherney et al., 2023).

As postulated in the literature, insulin resistance is mainly caused by factors such as mitochondrial dysfunction, loss of receptors, and sequence variations. This results in a reduced ability to transport and metabolize glucose and the accumulation

of free fatty acids in the body leading to oxidative stress and inflammation. These processes are described in figure 3.1 given below, which should be placed here to illustrate the basic processes involved in the development of T2DM (Chopra et al., 2023).

T2DM has been a considerable problem in the Arab world as well as in the Gulf States including United Arab Emirates (UAE). There are specific highest prevalence rates in the world, principally because of the quick urbanization practices in these areas. For example, in the UAE, the cases of the T2DM have been projected to be about 16%. 3% are in the case of adults with ages between 20 to 79 years and this is overhead of the global mean value. This higher prevalence is also signaled in adjoining gulf countries because of the shared risk factors such as high obesity levels, low physical exercises and practices and intensified consumption of energy abundant but poor nutrient foods (Dahmani et al., 2024).

1.1.2 Regional Prevalence and Specific Challenges in the UAE

T2DM is among the one of the common chronic diseases that occurred in the people of Middle East, particularly in the GCC countries and UAE. The ultimate reasons that have been observed behind the high prevalence include the genetic transformation, limited exercise, poor diet plans, and abundance of obesity. For instance, In the UAE it is projected that 19% of the adult population has been diagnosed with T2DM but a large population are still undiagnosed. The corresponding areas have been subjected to rapid economic growth as well as urbanization that has altered the lifestyle of the people as they consume more fast foods, with minimum physical activities and have high indices of obesity which are considerable risk factors for T2DM (de Boer et al., 2020a).

The wide spread of T2DM in the Arab world and gulf states is strongly caused by a combination of genetic transfer from the grandparents to the children in series and inter cost marriages. There are some concerning factors related to cultural and lifestyle as well for predisposition to T2DM. There are seven out of 20 countries with the highest prevalence of diabetes in the Middle East and North Africa (MENA) region. And surprisingly the factors such as obesity, lack of exercise, and high calorie diet are found to be the common causes leading to the T2DM in this region. Number of the literatures has also identified that a large number of people have not yet been tested for the T2DM and those proportions that have been diagnosed are receiving inadequate care, hence increasing complications at an early age (de Boer et al., 2020b).

1.1.2(a) T2DM in the Arab World and Gulf States

The Arab world especially the Gulf States are among the regions with high prevalence of T2DM in the world. As per IDF, in 2011, diabetes prevalence was estimated at 9.1% of the population in MENA region, and the figure is projected to rise to about 59% in 2030. 7 million people (de Boer, Khunti, et al., 2022). Currently, Saudi Arabia, Kuwait, Qatar, and UAE are some of the countries with high prevalence of diabetes due to factors such as urbanization, increased economic development, and changes in dietary habits (de Sá et al., 2022).

T2DM is a costly and burdensome disease in the Gulf States. For example, in Saudi Arabia, diabetes is responsible for about 13.9 percent of all of health care expenditure (Diab, 2018).. The health care cost for diabetes has also been increased by over 500 percent over the last two decades, that is because the disease is suiting more prevalent and managing these complications is now became difficult. The economic burden as the consequence of the above facts is further intensified by demographic

transition in the region through expanded life probability, high fatness and physical inactive routine (Diab, 2018).

Some of the socio-cultural and economic factors in this context, are also responsible for the high occurrence of T2DM in the Gulf States such as Saudi Arabia, Kuwait and Qatar is said to be between 17% and 25%. The high prevalence rate in the highlighted regions is additionally worsened by high prevalence of hypertension, smoking and hyperlipidemia which are among the truly prevalent comorbid situations associated with diabetes. The Arab world also has problems related to the access to quality health care services and the acquaintance of the population regarding prevention as well as management of T2DM, that also leads to the risen rate of complications of T2DM (Dutta, 2015).

The T2DM burden is rising and exerting the continues pressure over the healthcare systems in the Gulf States. That is because the disease is now became the common in the population and many resources are expected to be accommodated for the patient needs including the frequent check-ups, medication, and management of the critical complications related to the disease. There is also a lack of adequate education and prevention programs for T2DM with regards to the modifiable risk factors (Elbarbary et al., 2016).

T2DM is more common in the Arab world especially the GCC countries and it is ranked among the highest in the world. This region has experienced a high incidence of T2DM due to economic growth, urbanization, and change in diet from high fiber to high calorie foods and reduced physical activity. T2DM is even more prevalent in Saudi Arabia, Kuwait, and the UAE, with more than 20% of adults affected; the situation is expected to worsen as people live longer, and physical activity levels decrease (Elfakey & Al-Ghamdi, 2016).

Other cultural factors that have been found to increase the risk factors for T2DM include large body size is considered healthy in the gulf states, and consanguineous marriages are also common. In addition, the high growth rate of urbanization and economic development in these countries has resulted into other factors that promote T2DM such as obesity and sedentary lifestyles. The healthcare systems in these countries are also under pressure as they have to cope with the increasing incidence of diabetes complications such as cardiovascular diseases and CKD that are expensive to manage and treat (Guedes & Pecoits‐Filho, 2022).

1.1.2(b) Unique Demographics and Risk Factors in the UAE

If we consider the UAE population, it has some peculiarities as it is young and consists of a large number of foreign residents from all over the world. However, rate of T2DM is significantly higher among the young population specially among the Emiratis. The factors that have been identified as influencing this high prevalence include a high calorie intake and a genetic susceptibility to insulin resistance largely. Additionally, with the growth of urbanization and economic advancement in the UAE, there was an alteration in people's diet and reduction in the physical activity (Al Dahmani et al., 2021).

A certain demographic factor that is responsible behind the incidence of T2DM includes high population density of refugees with several genetic predisposition, prompt urbanization and adaptation to poor food habits. The UAE has its abnormalities, for example, an increased obesity rate that is one of the key predictors of T2DM, as well as initial manifestation of diabetes problems due to delayed diagnosis and treatment. The cultural practices such as fasting during the month of Ramadhan and culture that controls movement specifically for women, also improves the risk and better the management of T2DM in the UAE (Hussein & Aljuhani, 2022).

Studies conducted by different authors have agreed that genetic factors are the primary cause of T2DM in the region of UAE. Consanguineous marriages are more common in this region, and this has strongly influenced the high occurrences of genetic mutations causing diabetes. Furthermore, the conventional diet in this region is rich in carbohydrates and sugar along with low physical activities have stemmed in high dominance of obesity, which is a compelling conjecturer of T2DM. The transformation from a physically active and rural-based life to a supplementary sedentary and urbanized lifestyle has heightened the diabetes problem in the region (Jairoun et al., 2024).

There have been observed several barriers in the UAE regarding the management of T2DM epidemic including the late diagnosis as one of the serious problems, privileged access to specialized health care, and lack of awareness about the deadly disease. A large proportion of people are timely diagnosed with T2DM at a developed stage, and thus, there is a demand for top screening and early detection. Furthermore, there is a significant lack of health improvement knowledge about T2DM, with numerous people even having no idea about the risk factors responsible for the related complications. Because of this minimum awareness, higher occurrences of undiagnosed diabetic patient is resulted and consequently the accompanying complications such as kidney failure cardiovascular diseases and neuropathy are resulted (Jameson, 2017).

These factors include genetic predisposition, lifestyles, and the general health care system of the expatriates which may influence the occurrence of T2DM and its complications. Potential risk factors for T2DM in the UAE include high obesity levels, high levels of metabolic syndrome, and genetic disposition to insulin resistance. Socioeconomic status and urbanization also have significant contributions because

people with higher income levels are likely to have less physically active lifestyles and consume more calories than they burn (Jörgens et al., 2014).

It is for this reason that the UAE government has realized the importance of having an overall population health approach to T2DM. They include encouraging people to adopt healthy diets, exercising more, and screening for T2DM. Such interventions are important in the prevention of disease and avoiding development of complications that may be associated with poorly controlled the UAE, similar to other Gulf countries, has its own peculiarities in the treatment of T2DM because of the demographic and genetic background. The UAE has a young population; however, there is an increasing incidence of T2DM in young adults, which is worrisome since they will have longer duration of exposure and early onset of complications. Predisposing factors that include high consanguinity rate in the population increase the vulnerability to diabetes and its complications, including CKD (Kalra, 2007).

The process of urbanization in the UAE has been very fast and this has resulted in a change of the lifestyle of the people from active ones to more of a sedentary one and they have also adopted to eating more of processed foods, sugars and fats. These factors have led to a high prevalence of obesity, which is a well-known predictor of T2DM. Furthermore, the UAE has one of the highest obesity levels in the world with 69% of the population being either overweight or obese. This trend is worrisome especially given the fact that obesity is a well-established risk factor for the development of T2DM and CKD (Khalil et al., 2013).

Although T2DM is common in many populations, there are still many shortcomings in the management of the disease in the healthcare system. These are delays in diagnosis, inadequate screening for complications and lack of uniformity in treatment regimens. There is also a need to have more public health interventions that

would help to create awareness on diabetes and encourage people to adopt healthier behaviors to reduce the incidence of the disease and its complications (Larijani, 2012).

It has been found out that several factors have been found to have a very close relationship with the development of diabetes with the help of a number of epidemiologic and experimental studies. These risk factors can be put under the category of reversible and irreversible risk factors. These are factors which cannot be changed and include age, gender, ethnicity and family history. Of these, the age factor can be said to be especially influential (Meeking, 2011).

T2DM risk is age-related because the body's ability to secrete insulin decreases over time and insulin sensitivity is also reduced. This is made worse by the fact that such people are more likely to develop other diseases such as hypertension and obesity which are associated with diabetes. In developed countries, age is believed to be the most important risk factors for chronic diseases such as diabetes. Further, gender differences play a significant role in the development and the worsening of T2DM. Diabetes is more prevalent in men than in women and the disease is more common in younger men than in women of the same age, although postmenopausal women are also at high risk because of hormonal changes that influence insulin sensitivity and fat deposition. Ethnicity is another factor, some people of color namely South Asians, African Americans, and Hispanics have a higher risk of T2DM due to their genetics (Nagendra & Mondal, 2024). This predisposition is usually compounded by variations in fat patterning and metabolism to diet. Another determinant is family history since a close relation to the diabetic patients increases the probability of acquiring the disease implying the genetic influence (Navaneethan et al., 2023).

The risk factors that are changeable are considered as potential targets for prevention and modification. Obesity is another modifiable risk factor, and central

obesity is considered to be more dangerous than general obesity. Obesity is defined as a high BMI especially when accompanied by increased accumulation of Visceral Adipose Tissue (VAT) since it causes insulin resistance and impaired glucose metabolism which are the main causes of T2DM. It is understood that obesity and insulin resistance are closely linked, and obesity-induced inflammation and free fatty acid levels worsen insulin signaling pathways. Diet and physical activity also have their significance in the management of the condition. Consumption of foods rich in refined carbohydrates, saturated fats, and sugars are the main causes of obesity and insulin resistance, which are major causes of T2DM (Pozzilli & Napoli, 2021).

On the other hand, exercise enhances the body's ability to use insulin, helps in weight loss and prevents the onset of diabetes. But people's inactivity, which is more typical for people living in big cities and following a civilized lifestyle, plays a major role in the development of the disease. Also, other modifiable risk factors include the following: smoking and excessive use of alcohol. Studies have revealed that smoking causes the insulin resistance and heightened abdominal fat mass, whereas the alcoholism widely results in the weight gain as well as poor glucose tolerance, both of which are correlated with T2DM (Rees et al., 2017).

The metabolites analysis within a biological system has showed a greater understanding about how the sex and the age modify the metabolite profiles as well as susceptibility and advancement of diseases such as T2DM. It has been examined that with age, there occurs transformations in the metabolite's levels, which are indicative of variations in the metabolic pathways correlated with age related diseases including diabetes. A study conducted on longitudinal plasma samples from the Wisconsin Registry for the prevention of Alzheimer has indicated that metabolomics is largely affected by the age factor. The study has also discovered that there are over a thousand

metabolites and over fifty percent of these are associated to age, therefore displaying that metabolite levels change as the age advances (Rossing et al., 2022a). These age-related adjustments such as the weakening in mitochondrial function as well as raised oxidative stress are critical for understanding how aging controls the development of T2DM. By studying the corresponding changes, researchers have defined a higher risk metabolomic profile, that will help in the prevention of the disease at the early stage. Additionally, age factor remains one of the extremely significant predictors for the chronic diseases, and analyzing the dynamics of the metabolome can discover reasons that influence disease risk (Sam & Meeran, 2009).

The studies of the differences in the metabolite profiles also showed that men and women can have different sensitivities to T2DM and other metabolic disorders. The above-mentioned study also reported that sex is another factor that affects metabolite concentrations and hence, people of different sexes have different metabolomic profiles. These metabolomic changes are greatly affected by hormonal differences especially estrogen in women. For instance, postmenopausal women have altered metabolite profiles because of a reduced level of estrogen leading to T2DM and cardiovascular diseases. The findings of sex-specific biomarkers are necessary to enhance the accuracy of diabetes risk prediction and management. For example, some metabolites such as LPC 18:2 were found to be more effective in predicting the risk of impaired glucose tolerance and T2DM in women as compared to men, therefore stressing the need for sex-specific approach in diabetes research (Schott, 2012).

Some other related research supports the above conclusions. The PIVUS and ULSAM investigations investigated the metabolomic patterns in people with and without T2DM, and the results revealed certain metabolites that are linked to the condition. For instance, 3-hydroxyundecanoyl-carnitine was found to be upregulated

in urine samples, which may be related to alteration in the fatty acid metabolism depending on age or gender. In another study, the researchers established a positive correlation between BCAAs such as leucine, isoleucine, and valine with T2DM and a negative correlation between glycine and T2DM. The dissimilarity in the BCAA catabolism between the sexes might be the reason for the sex-specific risk factors for T2DM. A study on UAE nationals showed that compared to obese T2DM patients, metabolites were significantly different in non-diabetic controls; sex and age should be taken into consideration when analyzing metabolomic data. Such findings clearly point out the need for more regional studies especially in the Middle Eastern region or any other population like that of UAE where genetic, lifestyle and demographic factors are likely to interact (Shouqair et al., 2021).

Though cross-sectional studies have contributed to the understanding of the subject, they do not allow for the measurement of changes in the metabolite profiles in time. Prospective studies including the Baltimore Longitudinal Study of Aging (BLSA) are critical to analyzing how metabolic modifications in aging promote disease development. The BLSA analyzed which plasma metabolites were related to gait speed, a marker of physical function in older adults, and connected these metabolites to disability and mortality. Such types of studies are quite important for obtaining the thorough picture of the correlation between the aging process, metabolites levels, and the risk related to the diseases. They suggest an excellent picture of the roles these factors play in the growth and the advancement of T2DM, admitting the recognition of at-risk populations and the use of preventative measures that would decrease the risk of the development of T2DM. Specified the fact that the UAE population has its individual specific demographic and genetic features, which impacts the levels of metabolites, it is significant to investigate the influence of these

variable quantities in order to design a specific anticipation and treatment measures and improve the overall health of the people (Silveiro, 2022).

The demographic characteristics of the population in the UAE and the committed lifestyle perform a major role in growing T2DM rates. The population is comparatively youthful, as is marked by the youthful median population, but there is an expanding prevalence of diseases that are conventionally associated with aged populations. The key influencing factors for T2DM in the UAE involve obesity, which is elevated among women and physical inactivity, which has ascended with the practices of urbanization and upgrading of the living standards (Sridhar & Yarabati, 2000).

Furthermore, there are numerous issues related to the UAE demographic profile, that is the elevated proportion of foreign residents. The emigrant population is categorized by distinct health behaviors and risks, which constitutes the work of public health representatives challenging. For instance, the research has showed that some indigenous groups in the emigrant communities are more susceptible to T2DM than others, incorporating South Asians. This implies that there is a necessity to develop and apply specific public health intermediations that will fit the requirements of the people (Tang & Sharma, 2018).

Additionally, the data on the UAE demonstrates an extraordinary frequency of childhood obesity, which means an elevated future burden of T2DM. Preventative measures including early recognition and fit lifestyles among the young people as well as timely screening among the high-risk classes are a handful of strategies that can help in decreasing this increasing epidemic. There is also a necessity for culturally responsive education and anticipation programs since conventional health promotion

messages may not be helpful for whole groups of the UAE varied population (Tong & Adler, 2022).

These factors justify why it is mandatory to create aimed approaches to the UAE population concerning T2DM control and avoidance. These confronts will require a multi-sectoral effort that involves government policies, health care systems, and the community to combat the rising prevalence of T2DM in the region (Abegaz, 2024).

1.2 The Link Between Type 2 Diabetes Mellitus and Chronic Kidney Disease and Its Renal Complications: Pathophysiology, Epidemiology, and Risk Factors

Diabetes mellitus (DM) is a metabolic disease where blood glucose levels rise (Sapra & Bhandari 2021). Metabolic abnormalities are responsible for insulin resistance or low insulin levels. Low insulin levels lead to inadequate function of target tissues such as skeletal muscle and adipose tissue (Kharroubi 2015). Beta and alpha cells of the pancreas constantly change the secretion of hormones and dependence on glucose in the environment. When there is no balance between glucagon and insulin, inadequate glucose levels, hypoglycemia or hyperglycemia occur. In DM, insulin is absent or has a disturbing effect and this leads to hyperglycemia (Sapra & Bhandari 2021). The symptoms of DM and their severity depend on the duration of the disease and its type. In the early stages of type 2 DM (T2DM), some patients will not develop symptoms, while some will develop symptoms such as polyphagia, weight loss, blurred vision, etc. If DM is not controlled, it can lead to coma and even death (Kharroubi 2015). DM can be classified into type 2 diabetes mellitus, type 1 diabetes mellitus, gestational diabetes mellitus (Kharroubi 2015), maturity-onset diabetes of the

young (MODY), neonatal diabetes, secondary causes due to the use of steroids, endocrinopathies, etc. (Sapra & Bhandari 2021).

The prevalence of DM varies in all populations globally (Spanakis & Golden 2013). Geographical differences and ethnicity affect the prevalence of T2DM. For example, the prevalence of T2DM is higher among residents in Dubai than in other parts of the United Arab Emirates (UAE) (al Awadi et al. 2020). Additionally, a previous study found an association between, the prevalence of DM and the urban population rather than among the rural population (Khan, Gruebner & Kraemer 2014). Furthermore, the prevalence of DM is different in men and women. There was a greater increase in the prevalence of DM in men than in women in the period from 1980 to 2014 except in some parts of the world such as North Africa and the Middle East (Tramunt et al. 2019). Obesity, diet, and physical activity are associated with an increased prevalence of DM. Lack of physical activity, poor eating habits, and a high prevalence of obesity have led to a large increase in the number of DM cases worldwide. One of the most influential risk factors for T2DM is obesity. Childhood obesity increases adolescent body mass index which also poses a risk of developing T2DM (Chobot et al. 2018). Severe and prolonged stress is also a risk factor for the development of DM. Recurrent stress over time leads to disturbances in homeostasis and disrupts glucose, lipids, immunity, appetite, and circadian alignment (Merabet et al. 2022). Also, risk factors for the development of DM are environmental factors, viruses, and genetic factors. The global prevalence of DM increased from 211.2 million in 1990 to 476.0 million in 2017, with an increment of 129.7%. The standardized prevalence rate increased from 4,738.5 to 5,886.9. The prevalence of T2DM increased from 4,576.7 (1990) to 5,722.1 (2017), while the prevalence of T1DM increased from 161.7 (1990) to 164.8 (2017) (Lin et al. 2020).

As the pathogenesis of DM is complicated, the control and therapy of DM must be combined with the consideration of the individual circumstances of the patient to achieve successful glycemic control (Zhao et al. 2020). Successful self-monitoring includes blood glucose monitoring, physical activity, diet modification, and drug therapy. Therapies used for DM mainly consist of insulin, non-insulin hypoglycemic drugs, and insulin analogs. Insulin is one of the main and irreplaceable drugs for DM patients who have an absolute or relative lack of insulin secretion, as it plays a critical role in maintaining glycemic control and preventing complications associated with uncontrolled blood sugar levels (Zhao et al., 2020). Due to the complex physiology of DM, many interventions are required for treatment to be successful. Patient engagement and education are essential for DM management. Patients who manage their diet on their own, monitor their blood glucose levels, and exercise regularly have better results. Lifelong treatment is generally necessary to prevent DM complications (Sapra & Bhandari 2021).

The risks of macrovascular events, stroke, myocardial infarction, stroke, and mortality are closely related to hyperglycemia occurring in T2DM. The main feature of T2DM is a decline in the function of beta-cells and a worsening of insulin resistance (Fonseca 2009). Macrovascular complications of DM are diseases of the coronary arteries, cerebrovascular network, and peripheral arteries (Zimmerman 2016). Patients with T2DM have an increased probability of developing microvascular disease with an extended period of the disease. Recent research has clarified the incidence and prevalence of microvascular complications in patients with type 2 diabetes mellitus (T2DM). A study by Abebe et al. (2024) reported an overall prevalence of 26.5% for diabetic microvascular complications, with neuropathy being the most common (13.2%), followed by nephropathy (12.4%) and retinopathy (6.4%) (Abebe et al.,

2024). These findings align with a 2021 study, which found that chronic kidney disease (CKD) was the most common complication at the time of T2DM diagnosis, affecting 12.3% of patients (Khunti et al., 2021).

According to Abebe et al. (2024), several factors are significantly associated with the development of microvascular complications, including advancing age, poor glycemic control, hypertension, anemia, positive proteinuria, prolonged T2DM duration, and hypercholesterolemia. Additionally, a 2024 study by Alam et al. found that microvascular complications were strongly linked to lack of regular physical activity, obesity, irregular use of anti-diabetic medications, hypertension, and disease duration (Alam et al., 2024). These findings underscore the importance of early identification and management of risk factors to prevent or delay the onset of microvascular complications in patients with type 2 diabetes.

An attribute of chronic kidney disease (CKD) is the retention of toxic uremic metabolites that adversely affect many organs. Approximately 50% of people developed CKD due to impaired glucose homeostasis (Shehab Eldin et al. 2007; Lorenzo et al. 2009; Sahakyan et al. 2011). Insulin resistance occurs in the early stages of CKD and worsens with worsening renal function (Dengel et al. 1996; Kato et al. 2005; Kobayashi et al. 2005; Nerpin et al. 2008). Dyslipidemia such as hypercholesterolemia and hypertension mainly occurs in patients with CKD (Satirapoj et al. 2010). Total cholesterol, low HDL, high LDL cholesterol, and high non-HDL cholesterol are significantly associated with an increased risk of renal failure in CKD patients. (Schaeffner et al. 2003). Dyslipidemia is the most common complication that occurs in patients suffering from CKD and is caused by renal dysfunction. This further causes the progression of renal impairment and deterioration of renal function, the main feature of which is a progressive reduction in the estimated glomerular filtration

rate (eGFR) (Jungers et al. 1997). Dyslipidemia is generally regarded as a consequence of chronic kidney disease (CKD) rather than its primary cause. However, research by Geng et al. (2024) and Kim and Lee (2023) highlights the complex and reciprocal relationship between dyslipidemia and CKD. CKD alters lipid metabolism, leading to distinctive lipid profiles marked by elevated triglycerides, reduced HDL cholesterol, and variable LDL cholesterol levels (Ferro et al., 2024). According to the Korean Society of Lipids and Atherosclerosis (2023), these abnormalities are particularly pronounced in dialysis patients and individuals with advanced CKD.

While dyslipidemia is, first and foremost, a complication associated with CKD, some evidence suggests that it may also accelerate CKD progression. Studies have identified correlations between specific lipid abnormalities and an increased risk of needing renal replacement therapy or experiencing faster declines in kidney function (Mitrofanova et al., 2023). This underscores the intricate interplay between CKD and lipid disorders, where CKD induces dyslipidemia, which in turn may worsen kidney damage and hasten disease progression. Furthermore, the decrease in eGFR is linked with cardiovascular disease independently of other risk factors. Therefore, it is of great importance that lipid regulation treatment in CKD patients with dyslipidemia is initiated as soon as possible (Hyre et al. 2007).

1.3 Diagnostic Challenges and Gaps in the UAE Context

The first problem that can be mentioned when speaking about the management of DKD in the UAE is the lack of timely diagnosis of the disease. A large number of patients receive a diagnosis of CKD when the disease is still in its later stages, and this makes the treatment quite challenging and reduces the life expectancy of the patient. This has been due to the fact that diabetic patients are not usually subjected to

screening for proteinuria and GFR on a regular basis. Also, there is a scarcity of nephrology care and many primary care practitioners are not knowledgeable or equipped to identify or manage DKD (Masuda et al., 2024).

There is also a lack of knowledge concerning the relationship between diabetes and kidney disease among the public. Some of the patients lack knowledge of the need to have their kidney function checked, thus they delay seeking medical attention. Also, further studies are required to identify the genetic and environmental risk factors for the development of DKD in the UAE population as they might not be similar to those in other countries (Morales et al., 2023).

The UAE has individual risk factors that have contributed to the high prevalence of T2DM. Diabetes has also become rampant in the country due to genetic factors and changes in the lifestyle of people. Overweight and obesity are common with approximately 29% of the adult population being classified as obese, which is a major T2DM risk factor. The subsequent changes in lifestyles, including the adoption of sedentary lifestyles, and increased consumption of calorie dense, nutrient poor diets add to the risk.

Due to the UAE's economic growth and increased urbanization, there have been changes in people's lifestyle such as sedentary lifestyle and increased consumption of processed foods rich in sugars and fats. These are accompanied by cultural factors that favor a sedentary lifestyle and the rising cases of risky factors like smoking. Besides, the high level of consanguinity within the UAE population also plays a role in increasing the genetic susceptibility to T2DM and its complications (Mottl & Nicholas, 2024).

Diabetic nephropathy, often referred to as diabetic kidney disease (DKD), is a specific subset of CKD caused by the chronic effects of diabetes on the kidneys. It is

characterized by persistent albuminuria, declining glomerular filtration rate (GFR), and an increased risk of cardiovascular complications. In the UAE, diabetic nephropathy poses several problems which include poor accessibility to routine screening, poor knowledge of CKD among patients and physicians, and irregular application of diagnostic guidelines. The first sign is usually not detected because early CKD is characterized by subtle symptoms, and the disease is diagnosed at a later stage when the treatment is less useful. This study also highlighted that there are no national guidelines for CKD screening in diabetic patients and this has led to delayed diagnosis and progression to ESRD. Packing these gaps via public health interferences with regards to alertness and screening is thus important (Mottl et al., 2022).

1.4 Management of T2DM in the Context of CKD.

T2DM patients diagnosed with CKD also are excellently cared for applying a combined approach with applications on glycemic control as well as renal product. It involves lifestyle adjustments, medication aid, and follow-up care for avoiding the advancement of CKD and excellent control of its complications (Ali et al., 2022). The controlling of T2DM in patients affected with CKD proposes some remarkable problems especially when it happens to glycemic control and its effects on the kidneys. Therapeutic interventions should be properly focused on glycaemia control, reduction of proteinuria, blood pressure control and slackening of the progression of renal disease. The managing of CKD and its difficulties involve early detection and treatment in order to pause the advancement of the disease (Shubrook & Neumiller, 2023).

1.4.1 Overview of Diabetes Management Strategies.

As it has already been identified that for T2DM specifically in patients with CKD, glycemic control is the fundamental approach for preventing or suspending the complications. Glycemic control is usually realized by both lifestyle interventions, including diet and exercise, and drug therapy. It is to keep the blood glucose levels as close to normal as possible for each individual patient and the target HbA1c level is generally considered to be below 7% for the majority of patients. However, the management of T2DM in patients with CKD is somewhat complicated because kidneys are involved in the metabolism and elimination of most glucose lowering drugs. When renal function is impaired, the risk of hypoglycemia becomes higher and adjustment of the dose or change of therapy may be needed to prevent complications. Other targets of T2DM management in CKD patients include blood pressure control, lipid management, and lifestyle modifications to lessen cardiovascular risk and kidney disease progression (SOLER, 2024).

T2DM requires management through diet, exercise, medications to control blood sugar levels and other medications to minimize the risk of complications. These are changes in behavior pattern that include consuming proper diet, exercising, and being at proper weight. Medical managing incorporates the consumption of antidiabetic drugs including insulin, metformin, sulfonylureas, GLP-1 receptor agonists and SGLT-2 inhibitors, for regulating the blood glucose levels and proposes renal and cardiovascular benefits. The choice of the drugs should also involve the cardiovascular risk factors, the renal function of the patients and the probable side effects (Tsai et al., 2022).

Corresponding to the instructions for the management of the CKD in patients, there are multiple approaches. They include blood pressure control, glycemic control