Profiling undiagnosed diabetes in a working age Kazakh population

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DECLARATION:

I hereby declare that the Capstone project is my original work, and it has been written by me in its entirety. I have duly acknowledged all the sources of information that have been used in the Capstone project. In addition, this Capstone project has also not been submitted for any degree in any university previously.

Abstract

Undiagnosed diabetes (UDM) is a major public health concern. Almost half of all diabetic patients are unaware of their condition, which puts them at higher risk of mortality and serious comorbidities. Timely detection of UDM should decrease the social and economic costs associated with diabetes worldwide and can be achieved through establishing its risk profile, which differs for each country. Diabetes also shows varying degrees of insulin resistance (IR) and β-cell function possibly affecting the disease progression. UDM has been understudied in Kazakhstan, and this research aims to update the current understanding of its prevalence, cardiovascular risks and glucose metabolism profile in the local population. Total of 476 people were included in the analysis. The prevalence of UDM was 11.97% (95% CI, 9.20-15.24%), and it was represented by a significantly older population and worse cardiovascular risk profile. Stepwise-forward logistic regression identified systolic blood pressure, older age and total cholesterol as significant predictors of UDM. Using HOMA-IR and HOMA-β scores, k-means clustering defined three distinct UDM phenotypes. Phenotypes with β-cell dysfunction were more prevalent and showed higher risk for cardiovascular disease, which has possible implications for personalized treatment in diabetes care.

Introduction

The term diabetes mellitus (DM) is broadly applied to a group of diseases, all characterized by inability to either produce or effectively use insulin, which leads to a state of chronic hyperglycemia (Chan et al., 2020). Estimated 536.6 million people live with diabetes today, a number that is only predicted to rise to 643 million by 2030 (Sun et al., 2021).

Type 2 diabetes mellitus (T2DM) accounts for roughly 90% of all diabetes cases (International Diabetes Federation [IDF], 2023). Although the exact pathogenesis of T2DM is not entirely clear, it usually occurs at an older age in obese or overweight patients. Individuals with T2DM develop impaired insulin secretion by pancreatic β-cells along with suboptimal response to insulin, or insulin resistance, in peripheral tissues (Kahn et al., 2013).

T2DM is universally diagnosed using glycated hemoglobin (HbA1C) test scores, which gives information on a patient's average blood glucose levels over the past 3 months with A1C results over 6.5% indicating diabetes. Other widely used diagnostic tools include fasting blood glucose (over 126 mg/dL) and glucose tolerance test (over 200 mg/dL) (Centers for Disease Control and Prevention, 2022).

Alarmingly, almost half of all people with T2DM are unaware of their condition as reported by IDF (Ogurtsova et al., 2021). Studies on the prevalence of undiagnosed diabetes mellitus (undiagnosed DM, UDM) give different estimates depending on regional differences and diagnostic methods. In 2021, 87.5% of all UDM patients worldwide were located in low and middle-income countries where citizens are more likely to prioritize other health issues or have poor access to healthcare services (IDF, 2021). In high-income countries, 28.8% of diabetes patients are undiagnosed compared to a global average of 44.7% (IDF, 2021).

Timely detection of UDM is essential for decreasing mortality, health complications, as well as social and economic costs associated with diabetes. In 2017, the economic burden of UDM stood at $31.7 billion in the USA only, with the cost of $4250 per case (Dall et al., 2019). These estimates are extrapolatory: since the presence of undiagnosed disease can not be reported in the patients' medical data, a proxy population of T2DM patients within 2 years of diagnosis is usually used for calculations pertaining to UDM (Zhang et al., 2009). Patients with UDM are significantly more likely to receive ambulatory care and have emergency hospital visits for cardiovascular disease and hypertension compared to those without diabetes (Dall et al., 2019). Another large study with over 15 thousand participants reported a significant incidence of UDM in intensive care unit admissions: 9.3% of all and 26% of diabetic patients respectively (Carpenter et al., 2015). It is worth noting that hyperglycemia can result from a stress response, and not necessarily be an indication of UDM (Vedantam et al., 2022), which makes it challenging to drive solid conclusions about UDM's impact on healthcare use. Few studies investigated the management of hyperglycemic inpatients without diagnosed diabetes (Epa et al., 2020; Farmer et al., 2022). They conclude that upon discovering elevated glucose levels during ICU admission, no subsequent check-ups to confirm the presence of diabetes or prediabetes are done in most cases. This results in missed opportunities for early initiation of preventative measures or treatment.

Another challenge in diabetes-care comes from the implicit course of the disease at the beginning. It is known that after the initial onset of diabetic hyperglycemia, most T2DM patients show no apparent symptoms of the disease, which can last for many years before patients get clinically diagnosed. The exact amount of time between the onset of diabetes and diagnosis is still being debated; however, estimates range from 4 to 20 years on average (Ellis et al., 2010; Harris et

al.,1992; Sagesaka et al., 2018). During this asymptomatic stage patients are at risk of developing different health complications and comorbidities. Notably, one in three diabetic patients (35%) already had micro- and macrovascular complications at the moment of their diagnosis, as shown in a study by the Danish Diabetes and Endocrine Academy (n=6958) (Gedebjerg et al., 2018). Among these, ischemic heart disease was the most common, followed by retinopathy, cerebral atherosclerosis, neuropathy and nephropathy. Recent population-based study in Norway (n = 52856) reported poorer cardiovascular risk profiles in undiagnosed patients compared to those with known diabetes (Bjarkø et al., 2022). In the Verona study (n=806), almost half (49.5%) of newly diagnosed patients had chronic complications of T2DM, with neurological ones being more prevalent (Bonora et al., 2020). Similarly, the United Kingdom Prospective Diabetes Study (n=4209) reported a staggering 50% complications rate at baseline (King et al., 1999). These studies are likely to underestimate the real incidence of complications at diagnosis, since they were conducted on citizens of high-income countries and thus can not be generalized to a global population (Heydari et al., 2010).

Taking these into account, it is not surprising that heart diseases are the leading cause of death among the patients with T2DM. Coronary heart disease (CHD) contributes to this statistic the most (Dall et al., 2019). Controlling individual cardiovascular risk factors was shown to be effective in managing CHD in diabetic patients (ElSayed at al., 2023). It includes assessing and managing their weight, blood pressure, lipid profile and lifestyle choices such as smoking and alcohol consumption. According to the latest Standards of Care in Diabetes, these cardiovascular risk factors should be assessed at least annually in all people with T2DM (ElSayed at al., 2023).

The heterogeneous nature of diabetes should also be considered when deducing the risk of cardiovascular complications. In the past few years, scientists started to recognize distinct phenotypes of T2DM largely based on individuals' profile of insulin resistance (IR) and β-cell dysfunction (Bloomgarden & Drexler, 2019). Both are recognized as fundamental for the development of T2DM, however the etiology of each of these pathogenic states is not entirely understood. Reserve of β-cells and the degree of IR varies in different populations for undefined reasons (Saha et al., 2022).

The functional assessment of β-cells and insulin response in peripheral tissues can be done using Homeostatic Model Assessment scores, HOMA-β and HOMA-IR, respectively. In a recent study in Yemen, cardiovascular risk profiles differed in newly diagnosed T2DM patients when they were assigned phenotypes based on their HOMA scores. Particularly, patients with low β-cell function displayed overall higher risk for cardiovascular disease (Gunaid et al., 2018). It might be paramount to perform this kind of subtyping on T2DM patients for our understanding of diabetes as we can then assess the difference in disease progression, complications rate and response to drugs for different IR and β-cell dysfunction profiles. It is worth noting that ethnicity has also been implicated in the differential incidence and pathogenesis of T2DM (Kodama et al., 2013). For instance, compared to Caucasians, type 2 diabetes in East Asians was characterized by poor β-cell function rather than insulin resistance. Reasons for such divergence are still unclear, however understanding them might prompt new therapeutic approaches and interventions (Yabe et al., 2015).

Last year, the 75th World Health Assembly outlined five new global targets for diabetes. The first target specifically focuses on reaching 80% diagnosis rate for people living with all types of DM (World Health Organization [WHO], 2022). In the light of this goal, it is necessary to identify groups that might benefit from the screening measures.

Studies on predictors of undiagnosed DM were conducted in a number of countries with the focus on both sociodemographic and physiological factors. Among shared findings is an association of high BMI, male sex, older age, hypertension, high triglyceride and HDL-C levels with UDM (Apidechkul et al., 2022; Du et al., 2020; Heltber et al., 2018; Islam et al., 2022; Mou et al., 2021; Pengpid & Peltzer, 2022). Being a Central Asian country, Kazakhstan may share genetic characteristics of both European and Eastern Asian populations (Sikhaeya et al., 2018) and can serve as a new vantage point into exploring the ethnic differences in T2DM progression, insulin sensitivity and insulin secretion. Yet, there is limited research on the UDM's prevalence and risk profile in Kazakhstan.

Recently published study (n=4753) reported 8% prevalence of T2DM in Kazakhstan; patients without known diagnosis constituted 54% of total T2DM cases (Orazumbekova et al., 2022). Being men, living in the city, having higher waist circumference and an older age were associated with higher odds of being undiagnosed. However, these estimates might be outdated since they are based on a survey conducted in 2015 to 2017.

This research aims to describe UDM in Kazakhstan based on the data collected from Khoja Akhmet Yassawi International Kazakh-Turkish University in Turkestan. This includes calculating its prevalence in the local population, identifying cardiovascular risk factors associated with UDM and exploring its unique profile of insulin resistance and β-cell function. Findings from the study can inform future public health policies and interventions, as well as add to the existing literature on differences in diabetes progression in different countries.

Specific aims:

1) To assess the prevalence of UDM

2) To identify cardiovascular risk factors associated with UDM

3) To investigate characteristics of insulin resistance and β-cell dysfunction in UDM patients in the general adult population in Kazakhstan.

Materials and Methods

Study design and participants

Data was initially collected at the Clinical Diagnostic Center of the Khoja Akhmet Yassawi International Kazakh-Turkish University during 2019 and 2020 from the university employees undergoing routine medical checkup. Original dataset excluded participants with established diabetes diagnosis and kidney disease. Inclusion criteria were the age between 27 and 69 and consent to participate in the study.

Participants were given a patient survey card that briefly described the study and its aims. It also contained an informed consent form and pars officialis (passport) followed by demographic data and self-administered questionnaires on lifestyle. In particular, the Fagerstrom test was included to identify participants' smoking status and the Alcohol Use Disorders Identification Test (AUDIT) was used to define the active drinkers. Physical activity was ranked using the results of the International Physical Activity Questionnaire (IPAQ). Patients' personal medical history was included in the card along with the results of anthropometric and laboratory studies. All examinations were conducted by the trained staff of the Clinical Diagnostic Center. Laboratory methods included the Fasting Blood Sugar Test, measuring triglycerides (TG), total cholesterol (TC), high-density lipoprotein (HDL), and low-density lipoprotein (LDL) cholesterol levels. Full details of the data collection process were described in Saruarov et al., 2023.

Using the available data, Framingham Risk Score (FRS) for myocardial infarction and coronary death was calculated for each patient. FRS assesses an individuals' 10-year risk of developing a cardiovascular disease based on sex, age, HDL, TC and smoking habits. FRS results below 10% (> 0.1) suggest low risk of CVD, while the range of 10–20% (0.1-0.2) and > 20% (>0.2) indicate intermediate and high risk, respectively (Wilson et al., 1998).

Patients with the BMI below 25.0 were identified as "Healthy". Those in the BMI range of 25.0-29.9 were placed in the "Overweight" category, whereas "Obese" patients had BMI of 30.0 and above.

Standard formulas (1), (2) were used to calculate HOMA scores.Participants were diagnosed with Insulin resistance (IR) if they showed HOMA-IR ≥ 2.5. β-cell dysfunction was reported for patients with HOMA-β ≤ 50. Based on the recommendations from World Health Organisation (WHO, 2020), UDM was defined as having a Fasting Blood Glucose concentration of ≥ 7.0 mmol/L.

$$\text{HOMA-IR} = \frac{Fasting\ Insulin\ (IU/mL) \times Fasting\ Glucose\ (mmol/L)}{22.5} \quad (1)$$

$$\text{HOMA-}\beta = \frac{20 \times Fasting\ Insulin\ (IU/mL)}{Fasting\ Glucose\ (mmol/L) - 3.5} \quad (2)$$

Statistical analysis

Statistical analysis was performed using the STATA 17.0 software program for MacOS. Descriptive statistics were used to assess the distribution of variables in the entire study sample and among subgroups of people with undiagnosed DM and no DM . Categorical data were presented in the form of percentages. Continuous data were presented using median and the interquartile range (IQR) as it was tested to show non-normal distribution. For categorical variables, Pearson's chi-square was selected as a test of difference between undiagnosed DM and no DM, while Mann Whitney U-test and Kruskal-Wallis test - in case of 3 and more comparison groups - were used on numerical data. All tests were two-tailed (except for Kruskal-Wallis by definition) and used $\alpha=0.05$ as the nominal level of significance.

Association of individual cardiovascular risk factors with undiagnosed diabetes was assessed using univariate logistic regression. To examine the effect of multiple risk factors, stepwise forward regression was implemented. This algorithm incrementally adds new variables to the model based on their statistical significance. Performance of the final model was evaluated using receiver operating characteristic (ROC) plot. ROC plots display the relationship between the sensitivity and specificity of the models. Area under the curve (AUC) for ROC plot can then be used as a metric for model performance, where higher values indicate better accuracy. To address the overfitting problem, common for stepwise-built logistic regression models, k-fold cross validation was performed ($k=10$) with mean AUC calculated for all folds.

To investigate different phenotypes of insulin resistance and β-cell function in participants with undiagnosed diabetes, k-means clustering was performed using Python's scipy.stats package. Distribution of cardiovascular risk factors in created clusters was assessed using descriptive statistics, along with the Sankey diagram and violin plot built by Python's Plotly and Seaborn packages. Sankey diagrams are used to visualize the flow from one set of values to another. Violin plot shows the estimated probability density of each value and is similar to boxplots.

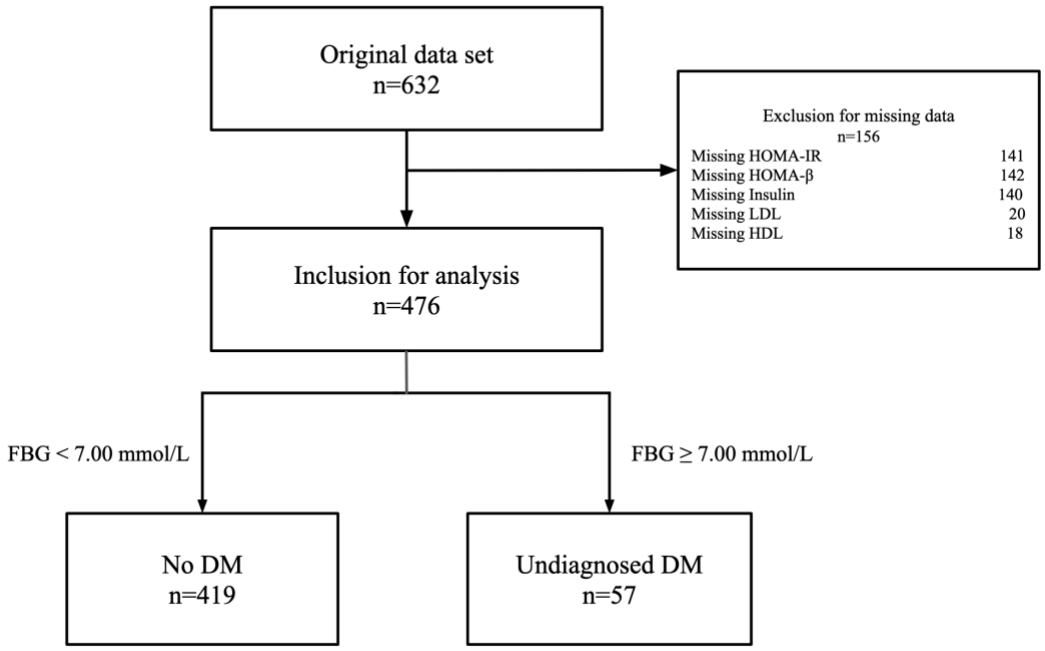
Ethics approval and consent to participate

Data collection was approved by the Commission on Clinical Ethics of the Faculty of Medicine of Khoja Akhmet Yassawi International Kazakh-Turkish University (No. 27/1; 23 September 2019) "for studies involving humans". The purpose and methods of the study were personally explained to all the participants prior to the study, along with the information on results storage and processing. Informed consent was obtained in the written form. Data analysis was approved by the Institutional Research Ethics Committee at Nazarbayev University School of Medicine. Dataset used in this study was anonymized prior to analysis with no possibility of identifying any of the participants.

Results

The process of sample selection is depicted in Figure 1. Data was initially available for 632 participants, but after excluding cases with missing values, overall sample size was 476. Based on the values of Fasting Blood Glucose test, participants were then assigned to either "Undiagnosed DM" or "No DM" comparison groups.

Figure 1
Sample selection process



Note. LDL= low-density lipoprotein cholesterol. HDL=high-density lipoprotein cholesterol. FBG = Fasting Blood Glucose. DM = Diabetes mellitus.

The baseline characteristics of the overall sample (n=476) are provided in Table 1. Most of the participants were women (71.85%; 95% CI 67.58-75.85%) and ethnic Kazakhs (88.66%; 95% CI 85.46-91.36%). Median age for the sample was 51 years old (IQR 41.00-59.25). High prevalence of abdominal obesity and elevated BMI is of note. Abdominal obesity was observed in 71.01% of the cases (95% CI 66.71-75.04%), whereas only 26.47% of patients had BMI in the healthy range (95% CI 22.71-30.63%). Most participants experienced low levels of physical activity in their everyday life (75.00%). Around one in ten people were smokers (12.18%; 95% CI 9.38 - 15.47%) and every fourth participant regularly consumed alcohol (25.84%; 95% CI 21.96-30.02%). Based on the Framingham scores, more than 17% of the sample were at medium to high risk of experiencing myocardial infarction and coronary death in the next 10 years. β-cell failure was more frequently observed (33.40%; 95% CI 29.18-37.83%) compared to insulin resistance (25.42%; 95% CI 21.57-29.58 %). Median total cholesterol of 4.90 mmol/L (IQR 4.40-5.47) falls into the healthy range which is below 5.20 mmol/L. Systolic and diastolic blood pressure were measured at median 120.00 (IQR 110.00-140.00) and 80.00 (IQR 70-90.00) mm Hg respectively.

Table 1
Baseline characteristics of the sample

Variables		n	%
Total		476	100.00
Sex	Male	134	28.15
	Female	342	71.85
Age groups	20-29	8	1.68
	30-39	96	20.17
	40-49	111	23.32
	50-59	142	29.83
	60-69	119	25.00
Ethnicity	Kazakh	422	88.66
	Other	54	11.34
Smoking	Yes	58	12.18
	No	418	87.82
Alcohol intake	Yes	123	25.84
	No	353	74.16
Physical activity	Low	357	75.00
	Medium	75	15.76
	High	44	9.24
BMI	Healthy	126	26.47
	Overweight	162	34.03
	Obese	188	39.50
Abdominal obesity	Yes	338	71.01
	No	138	28.99
Framingham Risk [a]	Low	393	82.56
	Medium	41	8.61
	High	42	8.83
Insulin resistance	Yes	121	25.42
	No	355	74.58
β-cell dysfunction	Yes	159	33.40
	No	317	66.60

Note. BMI = body mass index.
[a] Refers to the Framingham 10-year risk of myocardial infarction (MI) and coronary death (CD)

Table 1 (continued)

Variables		Median	IQR
Age	(years)	51.00	41.00-59.25
BMI	(kg/m^2)	28.54	24.66-32.46
Waist circumference	(cm)	95.00	83.00-102.00
Hip circumference	(cm)	104.00	99.00-113.00
SBP	(mm Hg)	120.00	110.00-140.00
DBP	(mm Hg)	80.00	70.00-90.00
TC	(mmol/L)	4.90	4.40-5.47
LDL	(mmol/L)	2.25	1.92-2.63
HDL	(mmol/L)	1.19	1.10-1.35
TG	(mmol/L)	2.05	1.36-2.45
Framingham Risk [a]		0.90	0.20-4.33
Fasting blood glucose	(mmol/L)	5.60	5.00-6.40
Insulin	(uIU/mL)	7.48	4.90-9.86
HOMA-IR		1.80	1.27-2.51
HOMA-β		71.45	40.17-119.31

Note. BMI = body mass index. SBP = systolic blood pressure. DBP = diastolic blood pressure. TC= total cholesterol. HDL = high-density lipoprotein cholesterol. LDL = low-density lipoprotein cholesterol. TG = triglycerides.

[a] Refers to the Framingham 10-year risk of myocardial infarction (MI) and coronary death (CD)

Table 2 compares the characteristics of participants in both groups. Undiagnosed DM accounted for 11.97% (95% CI, 9.20-15.24%) of the cases. Unweighted prevalence of UDM stratified by age, sex and BMI groups is presented. The proportion of men and women was not significantly different in comparison groups (p = 0.988). However, participants with undiagnosed DM were significantly older with the median age of 60 compared to 50 in the "No DM" group (IQR 54-65 and IQR 40-58 respectively). Undiagnosed DM also reported the largest proportion of obese patients (66.7%) with only 3.5% falling into the healthy BMI range.

Notably, UDM patients reported poorer values for almost every category of cardiovascular risk factors. In order of significance, they had higher proportion systolic (median 140.00 versus 120.00 mm Hg) and diastolic (median 90.00 versus 80.00 mm Hg) blood; larger waist circumference (IQR 96.00-108.00 versus IQR 81.50-101.00 cm) and total cholesterol measurements (median 5.50 versus 4.85 mmol/L); lower HDL cholesterol (IQR 1.05-1.18 versus IQR 1.12-1.36 mmol/L); much more frequent abdominal obesity (94.74% versus 67.78%); higher LDL cholesterol (median 2.61 versus 2.17 mmol/L); larger hip circumference (median 107.00 versus 104.00 cm) and higher triglyceride levels (median 2.35 versus 2.03 mmol/L). Gender, alcohol consumption and smoking were the only cardiovascular risk factors that were not significantly different in two comparison groups.

Undiagnosed DM patients also had significantly higher median Framingham Risk score (4.20 versus 0.80), despite the smaller proportion of low-risk individuals compared to the "No DM" group (70.18% versus 84.25% respectively).

Table 2

Baseline characteristics of the comparison groups

Variables		No DM		Undiagnosed DM		p-value*
		n	%	n	%	
Total		419	100.00	57	100.00	-
Sex	Male	118	28.16	16	28.07	0.988
	Female	301	71.84	41	71.93	
Age groups	20-29	8	1.91	0	0.00	<.001
	30-39	96	22.91	0	0.00	
	40-49	104	24.82	7	12.28	
	50-59	123	29.36	19	33.33	
	60-69	88	21.00	31	54.39	
Ethnicity	Kazakh	370	88.31	52	91.23	0.514
	Other	49	11.69	5	8.77	
Smoking	Yes	50	11.93	8	14.04	0.649
	No	369	88.07	49	85.96	
Alcohol intake	Yes	114	27.21	9	15.79	0.065
	No	305	72.79	48	84.21	
Physical activity	Low	310	73.99	47	82.46	0.234
	Medium	67	15.99	8	14.04	
	High	42	10.02	2	3.51	
BMI	Normal	124	29.59	2	3.51	<.001
	Overweight	145	34.61	17	29.82	
	Obese	150	35.80	38	66.67	
Abdominal obesity	Yes	284	67.78	54	94.74	<.001
	No	135	32.22	3	5.26	
Framingham Risk [a]	Low	353	84.25	40	70.18	0.029
	Medium	32	7.64	9	15.79	
	High	34	8.11	8	14.03	
Insulin resistance	Yes	96	22.91	25	43.86	0.001
	No	323	77.09	32	56.14	
β-cell dysfunction	Yes	109	26.01	50	87.72	<.001
	No	310	73.99	7	12.28	

Note. BMI = body mass index.

[a] Refers to the Framingham 10-year risk of myocardial infarction (MI) and coronary death (CD)

* Chi-square test

Table 2 (continued)

Variables		No DM		Undiagnosed DM		p-value*
		Median	IQR	Median	IQR	
Age	(years)	50.00	40.00-58.00	60.00	54.00-65.00	<.001
BMI	(kg/m^2)	27.89	24.04-32.34	30.93	28.89-35.38	<.001
Waist circumference	(cm)	94.00	81.50-101.00	101.00	96.00-108.00	<.001
Hip circumference	(cm)	104.00	98.00-112.50	107.00	102.00-116.00	0.005
SBP	(mm Hg)	120.00	110.00-140.00	140.00	140.00-150.00	<.001
DBP	(mm Hg)	80.00	70.00-90.00	90.00	90.00-90.00	<.001
TC	(mmol/L)	4.85	4.40-5.40	5.50	4.80-5.90	<.001
LDL	(mmol/L)	2.17	1.85-2.61	2.61	2.20-2.91	<.001
HDL	(mmol/L)	1.21	1.12-1.36	1.10	1.05-1.18	<.001
TG	(mmol/L)	2.03	1.32-2.42	2.35	1.67-2.58	0.007
Framingham Risk [a]		0.80	0.20-3.45	4.20	0.90-8.70	<.001
Fasting Blood Glucose	(mmol/L)	5.40	4.90-6.10	8.50	7.80-11.89	<.001
Insulin	(uIU/mL)	7.67	5.11-9.98	6.05	3.93-9.56	0.014
HOMA-IR		1.76	1.23-2.42	2.32	1.57-4.05	<.001
HOMA-β		82.08	49.25-127.78	19.66	12.68-33.09	<.001

Note. BMI = body mass index. SBP = systolic blood pressure. DBP = diastolic blood pressure. TC= total cholesterol. HDL = high-density lipoprotein cholesterol. LDL = low-density lipoprotein cholesterol. TG = triglycerides.

[a] Refers to the Framingham 10-year risk of myocardial infarction (MI) and coronary death (CD)

* Mann-Whitney U test

The results of univariate logistic regression are presented in Table 3. Odds ratios (OR) as well as corresponding 95% CIs and p-values are included for each variable. Same metrics are reported for the stepwise-built multiple logistic regression model (Table 4). Univariate analysis found association of UDM with most of the candidate variables, excluding gender, physical activity, smoking and alcohol consumption. For stepwise regression, the software identified systolic blood pressure, age and total cholesterol to be significant predictors of undiagnosed diabetes in our sample. Figure 2A displays the ROC plot for the model, while Figure 2B shows the results of 10-fold cross-validation. Area under the curve (AUC) is included for both figures.

Using k-means clustering, the machine identified 3 distinct phenotypes of UDM patients (Figure 3). Cluster 0 was characterized by the presence of both IR and β-cell dysfunction. Individuals with β-cell dysfunction, but no IR were concentrated in Cluster 1, which was also the largest cluster. Cluster 2 contained cases with solely IR. Table 5 provides a detailed summary of these clusters. Overall, there was no significant difference in cardiovascular risk distribution among the three, except for the age.

Table 3

Association of individual cardiovascular risk factors with undiagnosed diabetes

Variables		Undiagnosed diabetes			
		OR	95% CI		p-value
Female (vs. male)		1.00	0.54	1.86	0.99
Age		1.11	1.07	1.14	0.01
Smoking		1.20	0.54	2.69	0.65
Alcohol intake		0.50	0.24	1.06	0.07
Physical activity (vs. low)	medium	0.79	0.36	1.74	0.56
	high	0.31	0.12	0.07	0.12
BMI		1.12	1.06	1.17	<.001
Abdominal obesity		8.56	2.63	27.86	<.001
Waist circumference		1.06	1.03	1.08	<.001
Hip circumference		1.04	1.01	1.06	0.003
SBP		1.05	1.03	1.07	<.001
DBP		1.10	1.06	1.14	<.001
TC		2.41	1.69	3.43	<.001
LDL		1.98	1.35	2.91	<.001
HDL		0.11	0.03	0.41	0.001
TG		1.59	1.08	2.36	0.02

Note. BMI = body mass index. SBP = systolic blood pressure. DBP = diastolic blood pressure. TC= total cholesterol. HDL = high-density lipoprotein cholesterol. LDL = low-density lipoprotein cholesterol. TG = triglycerides.

Table 4.

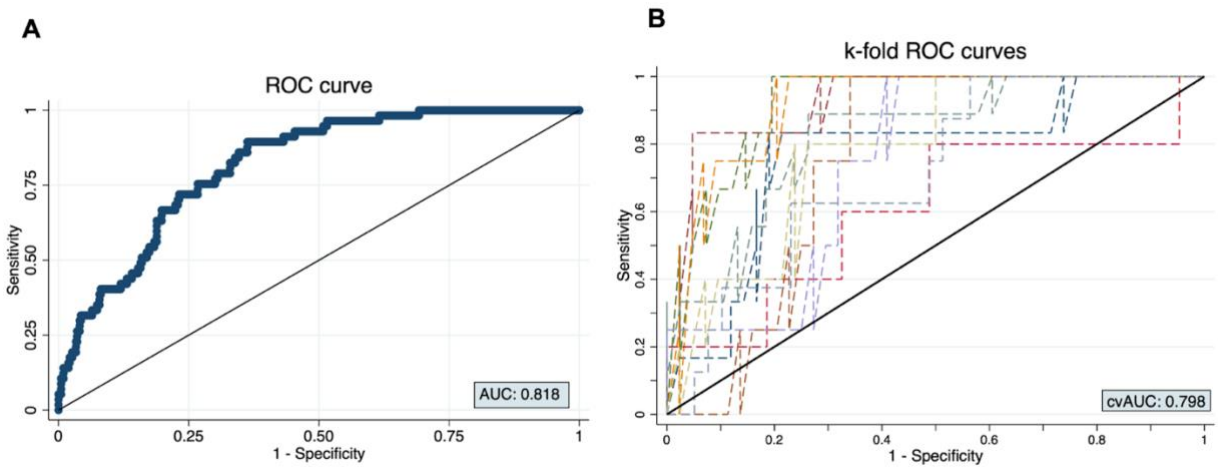
Model: Association of stepwise forward selected CV risk factors with undiagnosed diabetes

Predictors	Undiagnosed diabetes			
	OR	95% CI		p-value
SBP	1.03	1.01	1.05	< .01
Age	1.06	1.02	1.10	0.01
TC	1.65	1.14	2.40	0.01
HDL	0.38	0.10	1.39	0.14
Alcohol (vs. no alcohol)	0.56	0.25	1.25	0.15

Note. SBP = systolic blood pressure. TC= total cholesterol. HDL = high-density lipoprotein cholesterol.

Figure 2

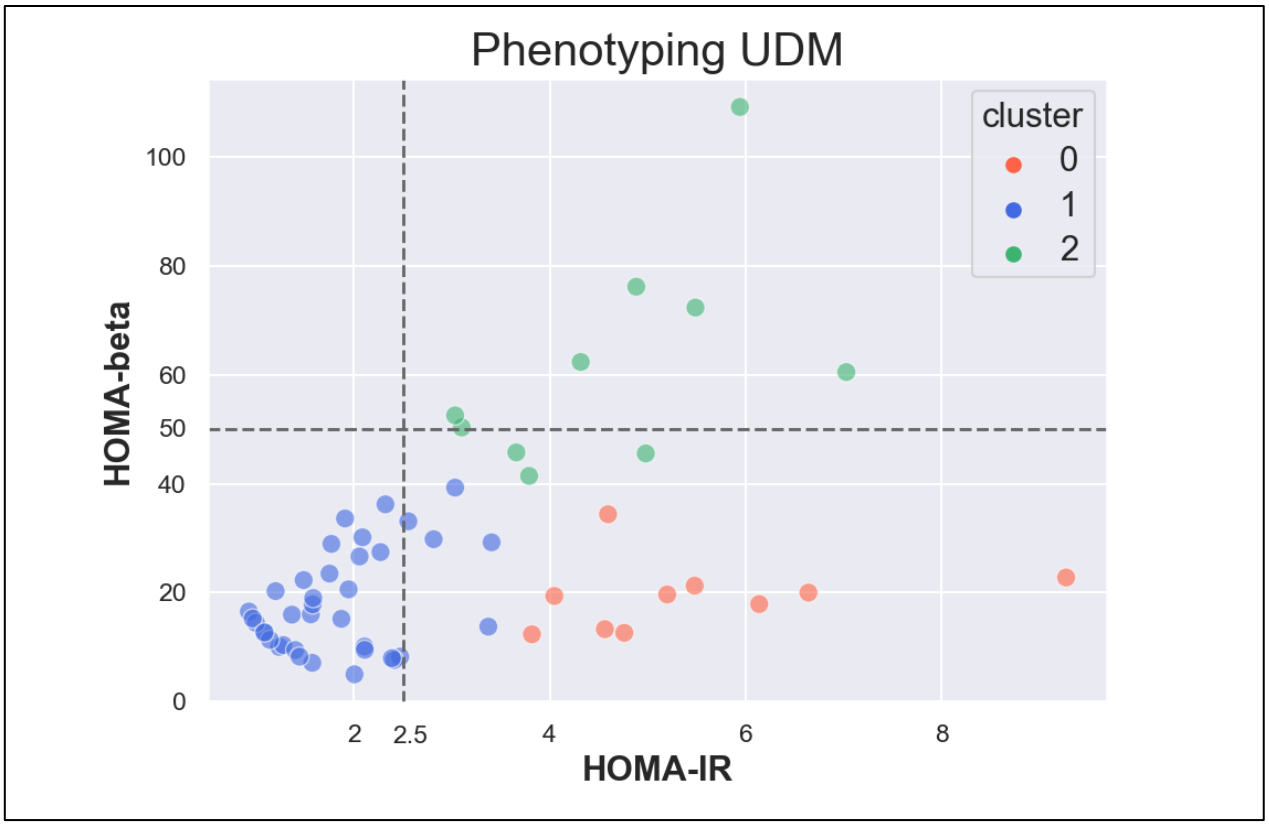
Receiver operating characteristic (ROC) plots for the model



Note. A: Naive ROC curve. B: ROC plot for 10-fold cross-validation. Dashed lines represent the ROC curve for each fold. AUC= area under the curve

Figure 3

k-means clustering of undiagnosed diabetes patients



Note. Cluster 0 = insulin resistance (IR) and β-cell dysfunction. Cluster 1=β-cell dysfunction. Cluster 2 = IR. Dashed lines indicate HOMA thresholds for IR and β-cell dysfunction. Colored dots represent each individual in the UDM group.

Table 5
Description of UDM clusters

Variables		Cluster 0: IR, BCD		Cluster 1: BCD		Cluster 2: IR		p-value*
		n	%	n	%	n	%	
Total		10	100.00	37	100.00	10	100.00	-
Sex	Male	5	50.00	9	24.32	2	20.00	0.230
	Female	5	50.00	28	75.68	8	80.00	
Age	40-49	2	20.00	0	0.00	5	50.00	<.001
	50-59	6	60.00	10	27.03	3	30.00	
	60-69	2	20.00	27	72.97	2	20.00	
Ethnicity	Kazakh	9	90.00	34	91.89	9	90.00	0.971
	Other	1	10.00	3	8.11	1	10.00	
Smoking	Yes	3	30.00	4	10.81	1	10.00	0.280
	No	7	70.00	33	89.19	9	90.00	
Alcohol intake	Yes	2	20.00	5	13.51	2	20.00	0.810
	No	8	80.00	32	86.49	8	80.00	
Physical activity	Low	10	100.00	31	83.78	6	60.00	0.073
	Medium	0	0.00	4	10.81	4	40.00	
	High	0	0.00	2	5.41	0	0.00	
BMI	Normal	1	10.00	0	0.00	1	10.00	0.314
	Overweight	2	20.00	13	35.14	2	20.00	
	Obese	7	70.00	24	64.86	7	70.00	
Abdominal obesity	Yes	9	90.00	36	97.30	9	90.00	0.500
	No	1	10.00	1	2.70	1	10.00	
Framingham Risk [a]	Low	6	60.00	25	67.57	9	90.00	0.081
	Medium	4	40.00	5	13.51	0	0.00	
	High	0	0.00	7	18.92	1	10.00	
Insulin resistance	Yes	10	100.00	5	13.51	10	100.00	<.001
	No	0	0.00	32	86.49	0	0.00	
β-cell dysfunction	Yes	10	100.00	37	100.00	3	30.00	<.001
	No	0	0.00	0	0.00	7	70.00	

Note. BMI = body mass index.
[a] Refers to the Framingham 10-year risk of myocardial infarction (MI) and coronary death (CD)
* Chi-square test

Table 5 (continued)

Variables		Cluster 0: IR, BCD		Cluster 1: BCD		Cluster 2: IR		p-value*
		Median	IQR	Median	IQR	Median	IQR	
Age	(years)	54.00	50.00-56.75	64.00	59.00-67.00	51.00	43.50-57.25	<.001
BMI	(kg/m^2)	30.88	29.95-34.58	30.86	28.72-35.38	32.22	29.58-32.76	1.00
Waist circumference	(cm)	101.50	96.50-114.00	101.00	98.00-108.00	100.00	92.00-104.25	0.62
Hip circumference	(cm)	108.50	102.50-114.50	107.00	102.00-116.00	107.00	104.50-113.75	0.98
SBP	(mm Hg)	150.00	141.25-150.00	140.00	140.00-150.00	140.00	130.00-147.50	0.25
DBP	(mm Hg)	90.00	90.00-90.00	90.00	90.00-90.00	90.00	90.00-90.00	0.91
TC	(mmol/L)	4.85	4.52-5.50	5.60	5.10-5.90	5.55	4.80-6.13	0.17
LDL	(mmol/L)	2.66	1.97-2.89	2.61	2.44-2.91	2.33	2.09-2.70	0.38
HDL	(mmol/L)	1.12	1.04-1.22	1.09	1.05-1.17	1.12	1.08-1.17	0.68
TG	(mmol/L)	2.13	1.47-2.31	2.43	1.85-2.60	2.34	1.58-2.81	0.35
Framingham Risk [a]		4.55	2.77-9.47	4.90	1.80-8.70	0.80	0.11-1.35	0.09
Fasting blood sugar test	(mmol/L)	13.89	12.70-14.30	8.30	7.80-10.10	7.72	7.33-8.30	<.001
Insulin	(uIU/mL)	9.40	7.36-10.38	4.09	3.01-5.86	12.63	10.19-15.51	<.001
HOMA-IR		4.98	4.57-5.97	1.77	1.37-2.27	4.60	3.69-5.36	<.001
HOMA-β		19.52	14.44-20.95	15.96	10.10-26.64	56.51	46.88-69.83	<.001

Note. BMI = body mass index. SBP = systolic blood pressure. DBP = diastolic blood pressure. TC= total cholesterol. HDL = high-density lipoprotein cholesterol. LDL = low-density lipoprotein cholesterol. TG = triglycerides.

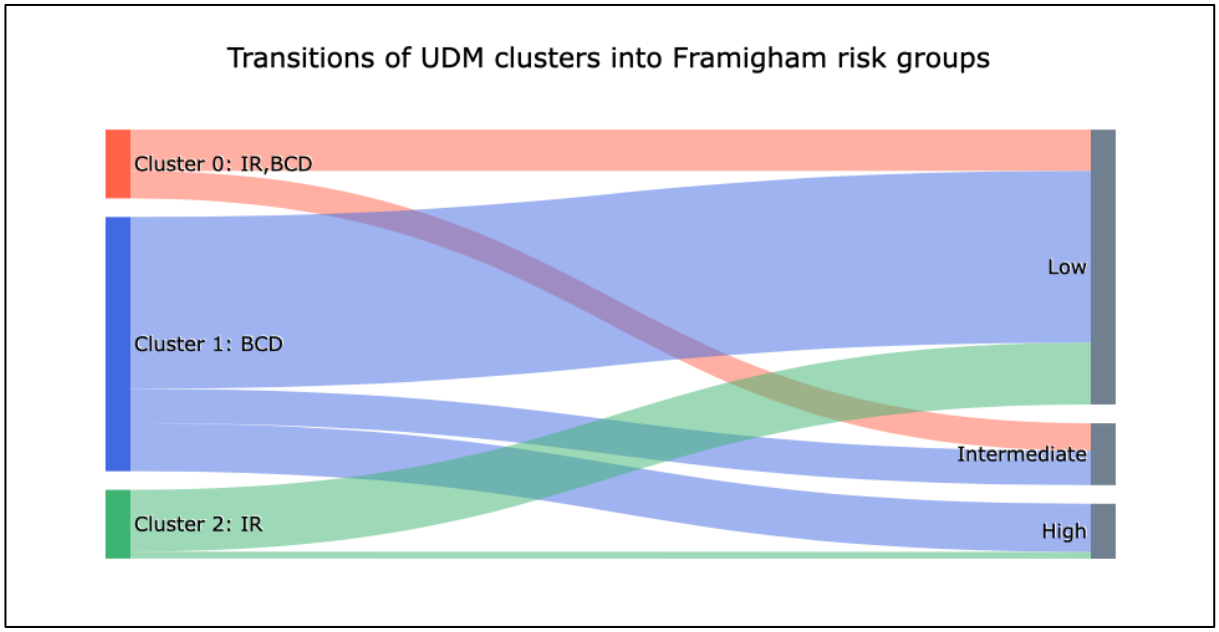
[a] Refers to the Framingham 10-year risk of myocardial infarction (MI) and coronary death (CD)

* Kruskal-Wallis test

Sankey diagram in Figure 4 shows the transitions of UDM clusters into Framingham Risk categories. Figure 5 provides the visual representation of distribution of Framingham Risk Score among these clusters. Overall, individuals in Cluster 0 (IR and β -cell dysfunction) and 1 (β-cell dysfunction) might be at higher 10-year risk of myocardial infarction and coronary death, although tests of difference (Table 5) showed no significant difference for these variables.

Figure 4

Transition of undiagnosed diabetes clusters into Framingham Risk categories



Note. Cluster 0 = insulin resistance (IR) and β-cell dysfunction. Cluster 1= β-cell dysfunction. Cluster 2 = IR.

Figure 5

Distribution of Framingham Risk score among clusters of undiagnosed diabetes patient

Note. Cluster 0 =insulin resistance (IR) and β-cell dysfunction. Cluster 1=β-cell dysfunction. Cluster 2 =IR.

Discussion

Prevalence of undiagnosed diabetes

The crude prevalence of UDM was 11.97% (95% CI, 9.20-15.24%) which suggests that a large proportion of diabetes remains unreported among adults in Turkestan. Previous large study on the local population reported an average of 4.32% of newly diagnosed DM (Orazumbekova et al., 2020) which is significantly lower than in our study sample. This can in part be attributable to the limitations in our sampling approach: along with having a much smaller sample size, the study excluded those younger than 29 and was performed in one location. Considering that T2DM is more prevalent in older populations, it introduces bias to our estimations.

Association of cardiovascular risk factors with undiagnosed diabetes

Overall, patients in the "Undiagnosed DM" category had poorer cardiovascular risk profiles compared to those in "No DM" . Framingham score was also significantly higher for UDM patients, which puts them at large risk of experiencing myocardial infarction or coronary death in the next 10 years.

Stepwise forward regression identified systolic blood pressure, age and total cholesterol as significant risk factors for undiagnosed DM in our study population. The good predictive capacity of this model is confirmed by the ROC plot. AUC > 0.7 (0.818) shows moderate to high predictive power of the model. Cross-validation resulted in mean AUC = 0.798 which still falls into the moderate to high accuracy range.

People with high SBP were at larger risk of having undiagnosed DM. Hypertension and diabetes mellitus are known to coincide and interact in individuals. Observational studies have shown that elevated systolic blood pressure (SBP) is associated with future onset of type 2 diabetes, but whether this association is causal is not known (Aikens et al., 2017). Some literature suggests that high glucose levels may contribute to the development of hypertension by causing damage to the arterial walls (Levin et al., 2010). Antihypertensive therapy was shown to significantly reduce the risk of cardiovascular events in people with T2DM (Emdin et al., 2015; Costas et al., 2017).

Older age was another significant predictor of having UDM, which is consistent with the findings of previous large study conducted in Kazakhstan (Orazumbekova et al., 2022). Aging has been associated with the development of impaired glucose homeostasis and diabetes, altering the processes that regulate the pancreatic β-cell mass and insulin secretion, as well as with a decline in insulin sensitivity (Tuduri et al., 2022). Among possible explanations are the changes in physical activity and body composition (with muscle mass in particular) that come with senescence, although the exact mechanism is not entirely understood (Kalyani et al., 2014). The prevalence of diabetes in older adults is high, however they are often excluded from interventional studies, which has negative implications on diabetes management in this particular population and should be considered when designing health care policies (Kalyani et al., 2017).

Total cholesterol is the next variable significantly associated with UDM in our model. Cholesterol is known to play a key role in β-cell membrane function and homeostasis. Accumulation of high levels of cholesterol was shown to cause β-cells dysfunction and decreased insulin secretion (Perego et al., 2019; Fryirs et al., 2009). HDL has a possible, but not significant protective effect on UDM in our model, as suggested by its OR and 95% CI. Low level of HDL is one of the hallmarks of diabetic dyslipidemia and is often regarded as a risk factor for developing diabetes (Haase et al., 2015).

Although we can not determine the direction of found associations, these results suggest the benefit of receiving T2DM diagnosis for our population. Undergoing glucose lowering therapy and some form of glycemic control was consistently shown to have a positive effect on cardiovascular outcomes and all-cause mortality in T2DM patients (Ray et al., 2009; Tian et al., 2020). Moreover, modern guidelines on diabetes care usually include antihypertensive therapy and lipid management, apart from glycemic control (Boer et al., 2017). This is relevant for UDM patients in our study, since they were shown to be affected by high SBP and TC levels. Overall, our findings are consistent with the current view of the cardiovascular risk factors in T2DM patients.

Insulin resistance and β-cell dysfunction in patients with undiagnosed diabetes

We identified the presence of three distinct phenotypes in the undiagnosed diabetes population. The most notable observation is that a large proportion of cases had β-cell dysfunction rather than insulin resistance. This is consistent with the previous studies that reported higher prevalence of poor β-cell function for Asians (Yabe et al., 2015).

Our study also adds to the emerging perspectives on the existence of different phenotypes within T2DM. Traditional perception of pathogenesis in DM is that β-cell shrinkage supersedes insulin resistance (Cerf, 2013). However, our findings suggest that some individuals (cluster 0) have relatively normal β-cell function, while simultaneously displaying significant insulin resistance. This supports a personalization perspective of approaching diabetes treatment. To illustrate, prescribing drugs that specifically stimulate insulin production (such as semaglutides) might be more effective for patients with no IR, but low β-cell function; whereas, using biguanides - that improve peripheral insulin sensitivity - might be a better choice for individuals with IR only (Padhi et al., 2020).

Tests of difference failed to show significant difference in cardiovascular risk factors among these clusters, which can be attributable to the small sample size (Table 5). The only exception was age with individuals in cluster 1 (β-cell dysfunction) being significantly older. The age-dependent decline in β-cell proliferation has been observed in some studies, although the exact reason is not understood (Weir et al., 2016; Aguayo-Mazzucato, 2020). Visualizing data suggests that β-cell dysfunction might increase the risk of cardiovascular disease, as Framingham Risk scores were generally higher in clusters 0 and 1.

Limitations and future directions

Since the analysis was conducted on the existing, secondary data, this study was limited in its sampling approach. Original dataset included only individuals of working age that were all enrolled from one organization, which makes it hard to generalize our results on the entire population of Kazakhstan. Small sample size is another limitation. Moreover, people with diagnosed diabetes were absent from the dataset. In the future studies, it might be useful to compare the cardiovascular profile of individuals with and without diabetes diagnosis. Cross-sectional design of the study also prevents us from establishing the direction of identified associations. There are no standardized values for IR or beta-cell deficit; having selected other values, results of this work may have been different. Lastly, participants were assigned to the diabetes category based on a single measure of fasting blood glucose test, which may cause inaccuracies in the estimations. In the future, using multiple tests, including a more reliable HbA1C test is recommended to avoid over- or underestimation of UDM.

Conclusion

The results of the study indicate the high prevalence of UDM and its comorbidities, such as obesity and hypertension, in Kazakhstan. The overall poor cardiovascular profiles of individuals with undiagnosed DM highlight the need for this kind of regular assessment among the local population. Age and TC are significantly associated with a higher probability of UDM. We also performed the subtyping of UDM patients and assessed the cardiovascular risk of different insulin resistance and β-cell function phenotypes, adding to the emerging perspectives on heterogeneous nature of T2DM in different groups.

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