Asian Journal of Research № 11 (11), 2017
IMPACT FACTOR
SJIF 4,1
IFS 2,7

ISSN 2433-202x
JOURNAL DOI 10.26739/2433-202x
www.journalofresearch.asia
info@journalofresearch.asia

A PATIENT-CENTERED APPROACH TO MANAGEMENT OF PATIENTS WITH TYPE 2 DIABETES MELLITUS

Feruza Abrarovna Takhirova, Zairkhodja Sabirovich Akbarov
Center for the Scientific and Clinical Study of Endocrinology named after Ya.Kh. Turakulov, Uzbekistan Public Health Ministry
For correspondence: Takhirova, Diabetology Department, Ya.Kh. Turakulov Center for the Scientific and Clinical Study of Endocrinology, Uzbekistan Public Health Ministry, 56 Mirzo Ulugbek Street, Tashkent, 100125, Republic of Uzbekistan;
E-mail: feruza.endo@mail.ru;

http://dx.doi.org/10.26739/2433-202x
Issue DOI http://dx.doi.org/10.26739/2433-202x-2017-11-11
Article DOI http://dx.doi.org/10.26739/2433-202x-2017-11-11-10

Abstract: We report on the study of the ACE and TCF7L2 gene polymorphisms in Uzbek patients with type 2 diabetes mellitus (T2DM). In the patients, frequencies of negative genotypes of the genes above were found higher than in the apparently healthy ethnically matching subjects. The similar pattern was found among the diabetics with myocardial infarction in medical history. Multifactor estimation of myocardial infarction risk factors was performed resulting in generation of a calculator of myocardial infarction risk in Uzbek T2DM patients with due regard to genetic markers.

Keywords: type 2 diabetes mellitus, patient-centered approach, personalized medicine, myocardial infarction, prediction, calculator

Diabetes mellitus is a chronic disease affecting all life spheres of a human being. According to IDF (International Diabetes Foundation) Diabetes Atlas Eighth Edition, there were 425 million people with diabetes registered in 2017 worldwide.

ISSN 2433-202x
JOURNAL DOI 10.26739/2433-202x
www.journalofresearch.asia
info@journalofresearch.asia

Reportedly, incidence of diabetes in Uzbekistan in 2016 was 0.83% of adult population; thus, there were 182 865 people diagnosed with diabetes; though data from epidemiological studies indicate that true incidence of diabetes in Uzbekistan is 7.9% .

Type 2 diabetes mellitus (T2DM) may make up about 90% of cases of diabetes (IDF Diabetes Atlas Eighth Edition, 2017). This type of diabetes primarily occurs from abnormal life-style and predominantly affects the able-bodied part of population. Recently, principles of personalized medicine have been used for early prediction of diabetes and its complications.

According to current definitions, the personalized medicine is a broad and rapidly advancing field of health care based on the integrated, coordinated and patient-centered approach to analysis of onset and progression of any disorder (Chan I.S., 2011), or the medicine comprising personalized treatment facilities on the basis of genomics, findings from tests of predisposition to any disease, preventive measures, integration of diagnostics and treatment, and treatment monitoring (Jain, 2002).The personalized medicine is particularly relevant to the management of patients with diabetes mellitus; a patient-centered approach with due regard to a patient's age, presence of severe complications, hypoglycemia risk and life expectancy is considered as the most adequate one (Silvio E. Inzucchi, 2015).

Ischemic heart disease (IHD) is one of the most common causes of death among the diabetics, and diabetes is associated with the unfavorable prognosis in IHD (Koskinas KG, 2016). Total hospital and midterm mortality after myocardial infarction has reduced, but long-term prognosis remains poor so far (O'Donoghue ML, 2012). Myocardial infarction (MI) is known to occur in T2DM patients 3 times more frequently than in the non-diabetics (Booth GL, 2006).

In view of the above, the work was initiated to develop a patient-centered approach to early prediction of myocardial infarction (MI) in male Uzbek patients with type 2 diabetes mellitus (T2DM).

Materials and methods

245 Uzbek male T2DM patients and 64 ethnically matched non-diabetic healthy men were recruited for the study. The patients' ethnical identity (Uzbek one in the case) was established on the basis of ethnical identity of their parents and grandparents.

The patients were eligible for the study if they were Uzbek males, older than 45 years of age, diagnosed with T2DM. Criteria of ineligibility included

ISSN 2433-202x
JOURNAL DOI 10.26739/2433-202x
www.journalofresearch.asia
info@journalofresearch.asia

female sex, age > 45 years, a non-Uzbek ethnical identity and presence of type 1 diabetes mellitus.

Non-obese (BMI < 30 kg/m^2) Uzbek males, older than 45 years of age, having neither arterial hypertension (AP<140/90 mm Hg) nor IHD (angina pectoris or MI) without considerable retinopathies and acute health problems were eligible for the study as apparently healthy subjects.

Obese women of a non-Uzbek ethical identity, younger than 45 years of age, diagnosed with arterial hypertension and retinopathy, having acute health problems and first- degree relatives with T2DM were considered as ineligible for the study.

All patients underwent routine complete medical checkup which included taking of a medical history, the physical examination and appropriate laboratory investigations. Evaluation of the patients included

- a questioning in compliance with the specifically developed examination record
- an anthropometric assessment of physical fitness with measurement of body mass and height, and calculation of body mass index
- functional methods of examination including ECG and echocardiography
- a biochemical investigation by measuring concentrations of cholesterol, triglycerides, HDL-C, LDL-C, fibrinogen, and creatinine as well as by evaluation of prothrombin index and hematocrit
- a genotype testing (ACE and TCF7L2 genes)
- an office visit to ophthalmologist for direct funduscopy

Statsoft STATISTICA 7.0, a software system (Statsoft, Russia), was used for statistical data processing. The results from genetic tests were processed by means of an online statistics calculator used for estimation of statistic parameters in the case-control studies (http://gen-exp.ru/calculator_or.php). The multifactor assessment of findings from the study was performed by means of a method for standardization of intensive parameters by Shigan E.N., based on Bayesian probability (Shigan E.N.).

Results and discussion

The *ACE* gene polymorphism in Uzbek male patients with type 2 diabetes mellitus (T2DM patients) and ethnically matched healthy subjects

The *ACE* gene insertion/deletion (I/D) polymorphism was studied in a sample of Uzbek men, consisting of 100 T2DM patients and 64 healthy subjects. Frequencies of I and D alleles were 49.2±4.4% and 50.8±4.4%, respectively (P>0.05). Frequencies of the *ACE* genotypes, such as II, ID and

ISSN 2433-202x
JOURNAL DOI 10.26739/2433-202x
www.journalofresearch.asia
info@journalofresearch.asia

DD were 25.0±5.4, 48.4 ±6.2 and 26.6 ±5.5%, respectively. The ID genotype was more frequent than the II genotype (P<0.01) and the DD genotype (P<0.05) (Table 1). In this study, the *ACE* gene genotype distribution did not deviate from Hardy-Weinberg equilibrium.

Table 1. Frequencies of the *ACE* alleles and genotypes in male T2DM patients and ethnically matched healthy subjects

Genetic marker		Allele and genotype frequency, %/abs		*P* value
		Healthy subjects (n=64)	T2DM patients (n=100)	
	I allele	49.2±4.4/53	25.5±3.1/51	<0.001
	D allele	50.8±4.4/65	74.5±3.1/149	<0.001
	II genotype	25.0±5.4/16	15.0±3.6/15	>0.05
	ID genotype	48.4±6.2/31	21.0±4.1/21	<0.001
	DD genotype	26.6±5.5/17	64.0±4.8/64	<0.001
	P 1-2	>0.05	<0.001	
	P 3-4	<0.01	>0.05	
	P 3-5	>0.05	<0.001	
	P 4-5	<0.05	<0.001	

Among T2DM patients frequencies of I and D alleles were 25.5±3.1 and 74.5±3.1%, respectively (P<0.001). Frequencies of the *ACE* gene II, ID and DD genotypes were 15.0±3.6, 21.0±4.1 and 64.0±4.8%, respectively; the DD genotype frequency was higher than those of the II genotype (*P*<0.001) and ID genotype (*P*<0.001).

Comparing data on allelic and genotypic polymorphisms in two groups, we found out that the D allele frequency was significantly higher and I allele frequency was significantly lower in T2DM patients than in healthy subjects (P<0.001). DD genotype occurred 2.4 times more frequently (P<0.001) in the patients than in healthy subjects, while the ID genotype frequency was 2.3 times higher (P<0.001) in healthy subjects than in T2DM patients.

Our findings demonstrated that frequencies of protective I allele and II genotype were lower in T2DM patients than in healthy subjects, while in the patients negative D allele and DD genotype occurred more frequently than in healthy subjects. Used for estimation of the relative risk for T2DM onset, the odds ratio (OR) for the DD genotype carriers was 5.4 (95%CI 2.05-7.64). D allele and DD genotype predominance in T2DM patients in our study suggests that the carriers of the allele and the genotype are predisposed to T2DM. This is consistent with the data about predisposition to T2DM among

ISSN 2433-202x
JOURNAL DOI 10.26739/2433-202x
www.journalofresearch.asia
info@journalofresearch.asia

carriers of DD genotype in the Arab population of Jerba Island in Tunisia (Thouraya B., 2009).

Known as determining onset and progression of pathologies, significantly higher frequencies of D allele and DD genotype in male Uzbek T2DM patients in our study imply high predictive value of these two genetic markers for T2DM onset.

The *ACE* gene polymorphism in Uzbek T2DM patients by IHD presence and severity

In the study on the *ACE* gene polymorphism, 146 Uzbek male patients over 45 years of age with duration of T2DM more than 10 years were grouped as those with myocardial infarction (MI) in the medical history (n=54), those with IHD but without MI (n=40) and those without IHD (n=52), the latter group served as the control one. Our study focused on *ACE* gene I and D alleles, and II, ID and DD genotypes.

As per findings of the patients' genotype testing, frequencies of *ACE* gene DD genotype in patients with MI in the medical history, those with IHD but without MI and those without IHD were 48.1%, 42.50% and 32.7%, respectively, while frequencies of II genotype in these groups were 14.8%, 17.5% and 30.8%, respectively (Table 2). ID genotype, a heterozygous one, occurred much the same in the three groups of patients (37, 40 and 36.6%, respectively).

Table 2. The *ACE* gene allelic and genotypic distribution by IHD presence and severity

Genetic marker	Allele and genotype frequency, %/abs			
	T2DM patients with IHD and MI (n=54)	T2DM patients with IHD but without MI (n=40)	T2DM patients with IHD (n=94)	Control group (n=52)
I allele	37.5±4.94/36	37.5±5.4/30	35.1± 3.5/66	49.0±4.9/51
D allele	62.5±4.94/72	62.5±5.4/50	64.9±3.5/122	51.0± 4.9/53
II genotype	14.8± 4.8/8	17.5±6.0/7	16.0±3.8/15	30.8±6.4/16
ID genotype	37.0±6.57/20	40.0±7.7/16	38.3±5.0/36	36.6±6.7/19
DD genotype	48.1±6.8/26	42.5±7.82/17	45.7±5.1/43	32.7±6.5/17

The predominance of DD genotype and low frequency of II genotype in T2DM patients with MI in medical history suggest significance of the *ACE* gene ID polymorphism for MI onset in Uzbek T2DM patients [P=0.04 according to Pearson fitting criterion (χ^2=4.36) in the additive inheritance, OR

ISSN 2433-202x
JOURNAL DOI 10.26739/2433-202x
www.journalofresearch.asia
info@journalofresearch.asia

1.91; 95%CI 0.87-4.2 and *P*=0.05 according to Pearson fitting criterion (χ^2=3.85) in the dominant inheritance, OR 2.56; 95%CI 0.98-6.64).

Similarly, when analyzing our findings for a combined group of diabetics with IHD including those with IM and without MI in the medical history, and data on patients without IHD, we found that DD genotype frequency was higher in the patients with IHD than in the one without the disease, while II genotype occurred less frequently in this group [*P*=0.4 according to Pearson fitting criterion (χ^2=4.39) in the dominant inheritance, OR 2.56, 95%CI 0.98-6.64].

Our findings on the distribution of I and D alleles demonstrated predominance of D allele in patients with MI [*P*=0.02 according to Pearson fitting criterion (χ^2=5.4) in the multiple inheritance, OR 1.92, 95%CI 1.10-3.35] and higher frequency of I allele in patients without MI [*P*=0.02 according to Pearson fitting criterion (χ^2=5.41) in the multiple inheritance]. In this study, the *ACE* gene genotypic distribution did not deviate from Hardy-Weinberg equilibrium.

The *TCF7L2* gene polymorphism in Uzbek male T2DM patients and ethnically matched healthy subjects

Alleles and genotypes of the *TCF7L2* gene rs7903146 polymorphism were studied in 54 Uzbek male T2DM patients and 46 ethnically matched healthy subjects. Among T2DM patients, frequencies of CC, TT and CT genotypes were 9.3, 51.9 and 38.8%, respectively. Frequencies of C and T alleles were 28.7% and 71.3%, respectively. Among ethnically matched healthy subjects, CC, TT and CT genotypes were registered in 4.3, 34.8 and 60.9%, respectively. Frequencies of C and T alleles were 34.8% and 65.2%, respectively (Table 3).

Table 3. Frequencies of the *TCF7L2* gene alleles and genotypes in Uzbek male T2DM patients and ethnically matched healthy subjects

	Genetic marker	**Allele and genotype frequency, %/abs**		***P* value**
		Healthy subjects (n=46)	**T2DM patients (n=54)**	
	C allele	34.8±4.9/32	28.7±4.3/31	>0.05
	T allele	65.2±4.9/60	71.3±4.3/77	>0.05
	CC genotype	4.3±3.0/2	9.3±3.9/5	>0.05
	CT genotype	60.9±7.2/28	38.9±6.6/21	<0.05
	TT genotype	34.8±7.0/16	51.9±6.8/28	<0.05
	P 1-2	<0.001	<0.001	
	P 3-4	<0.001	<0.001	
	P 3-5	<0.001	<0.001	
	P 4-5	<0.05	>0.05	

ISSN 2433-202x
JOURNAL DOI 10.26739/2433-202x
www.journalofresearch.asia
info@journalofresearch.asia

Frequencies of the *TCF7L2* CT genotype in the group of apparently healthy subjects were significantly higher than those in the group of T2DM patients ($P<0.05$). In contrast to apparently healthy subjects, in T2DM patients the *TCF7L2* TT genotype occurred more frequently than CC and CT genotypes (OR 2.33; 95% CI 1.04-5.25).

Frequencies of the *TCF7L2* T allele in T2DM patients and healthy subjects were significantly higher than those of C allele ($P<0.001$). The intergroup comparison of frequencies demonstrated no significant differences between frequencies of C and T alleles both among T2DM patients and healthy subjects ($P>0.05$).

Thus, predominance of the *TCF7L2* TT genotype registered in Uzbek T2DM patients suggests an association of the genotype with the increased T2DM risk.

The *TCF7L2* gene polymorphism in Uzbek T2DM patients by IHD presence and severity

In our study on the *TCF7L2* gene rs7903146 polymorphism by IHD presence and severity, 108 Uzbek male patients over 45 years of age with duration of T2DM more than 10 years were grouped as those with IHD and myocardial infarction (MI) in the medical history (n=40), those with IHD but without MI (n=42) and those without IHD (n=26), the latter group served as the control one. Our study focused on the *TCF7L2* gene C and T alleles and CC, CT and TT genotypes.

As per findings of the patients' genotype testing, frequencies of CC genotype in patients with IHD and MI in the medical history, those with IHD but without MI and those without IHD were 15.4±7.1%, 11.9± 5.0% and 2.5±2.47%, respectively, while frequencies of CT genotype in these groups were 38.5±9.5%, 52.4±7.7% and 27.5±7.1%, respectively. TT genotype occurred more frequently in patients with IHD and MI (70.0±7.2%) than in those without IHD (46.2±9.8%) and in those with IHD but without MI (35.7±7.4%). T allele occurred more frequently in patients with IHD and MI (83.8±4.1%) than in the controls (65.4±6.6%, $P<0.05$), while C allele was registered less frequently (16.3±4.1%) in the patients with IHD and MI than in the controls (34.6±6.6%, $P<0.05$) (Table 4).

Our findings from the case-control study on distribution of the *TCF7L2* gene alleles and genotypes in Uzbek T2DM by IHD presence and severity

ISSN 2433-202x
JOURNAL DOI 10.26739/2433-202x
www.journalofresearch.asia
info@journalofresearch.asia

demonstrated that the *TCF7L2* gene TT genotype occurred more frequently in T2DM patients with IHD and MI in the medical history than in the controls, while frequency of CC genotype was lower in patients with IHD and MI than in the controls (P=0.02 according to Pearson fitting criterion, χ^2=5.92, in the multiple inheritance, OR 2.73, 95%CI 1.20-6.22).

The TT genotype predominance and low frequency of CC genotype in Uzbek T2DM patients with IHD and MI in medical history in our study suggests that the *TCF7L2* gene C/T polymorphism confers an increased MI risk in the patients (P=0.02 according to Pearson fitting criterion, χ^2=5.31, in additive inheritance, OR 2.72, 95%CI 0.98-7.59)

To sum up, the findings from our study demonstrated that among Uzbek T2DM patients, the *TCF7L2* gene TT genotype occurred more frequently in those with IHD and MI in medical history than in those without IHD; as the fact was confirmed by both multiple and additive inheritance models, this genotype can serve as a predictor of MI risk in this kind of patients.

Table 4. Frequencies of the *TCF7L2* gene alleles and genotypes in T2DM patients by IHD presence and severity

Genetic marker	**Frequency, %/abs**				
	Control group (n=26)	T2DM patients with IHD, but without MI (n=42)	T2DM patients with IHD and MI (n=40)	P 1-2	P 1-3
C allele	34.6±6.6/18	38.1±5.3/32	16.3±4.1/13	>0.05	<0.05
T allele	65.4±6.6/34	61.9±5.3/52	83.8±4.1/67	>0.05	<0.05
CC genotype	15.4±7.1/4	11.9± 5.0/5	2.5±2.47/1	>0.05	>0.05
CT genotype	38.5±9.5/10	52.4±7.7/22	27.5±7.1/11	>0.05	>0.05
TT genotype	46.2±9.8/12	35.7±7.4/15	70.0±7.2/28	>0.05	>0.05

Based on the findings above, we aimed at developing a method for early MI prediction in Uzbek patients with due regard to genetic markers. To achieve the aim we perform multifactor estimation of MI risk factors with due regard to DD genotype of the ACE gene I/D polymorphism and to TT genotype of the TCF7L2 gene C/T polymorphism.

Multifactor approach to estimation of myocardial infarction risk factors in Uzbek T2DM patients with due regard to genetic markers

A conception of risk factors is based upon identification of associations between clinical manifestations of a disease and a set of

ISSN 2433-202x
JOURNAL DOI 10.26739/2433-202x
www.journalofresearch.asia
info@journalofresearch.asia

physiological, biological and environmental factors. Effect of each factor alone or in combination with others increases risk of any disease onset. As a method of mathematical statistics and data analysis, which involves designing and writing computer programs that allow the computer hardware to interface with the programmer and the user, system programming can be used not only to make medical predictions for the period of time, but also to determine risk conferred by one or another complication comparing prognostic indices.

Estimation of relative risk parameters in male Uzbek T2DM patients demonstrated that among MI risk factors MI in family medical history comes the first (9.20) followed by left ventricular hypertrophy (7.87), age (5.80), the *ACE* gene DD genotype (4.22), arterial hypertension (4.11), diabetes duration (2.86), diabetic nephropathy (2.77), alcohol abuse (2.34), HbA1c≤7% (2.00), obesity (BMI> 25 kg/m^2) (1.88), stroke in family medical history (1.82), dislipidemia (1.54), the *TCF7L2* gene TT genotype (1.51), smoking (1.46) and hypercoagulation (1.26) (Fig.1). This type of rating is essential in a physician's practice to categorize the MI risk contingent among T2DM patients with chronic kidney disease (CKD) as a microangiopathy and myocardial infarction (MI) as a macroangiopathy.

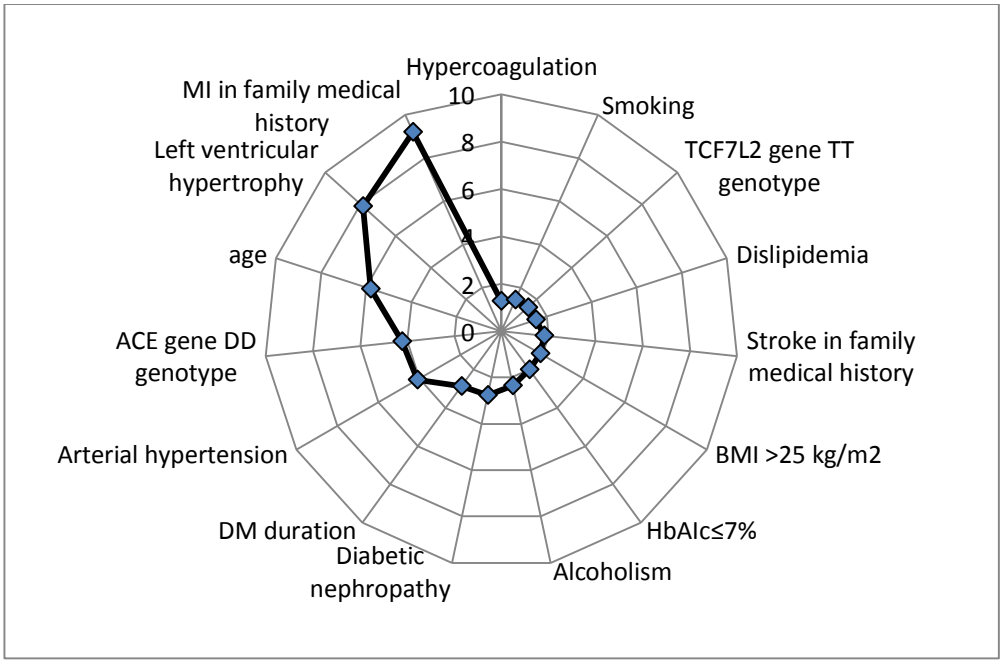

Figure 1. Multifactor estimation of MI risk in Uzbek T2DM patients with due regard to genetic markers

ISSN 2433-202x
JOURNAL DOI 10.26739/2433-202x
www.journalofresearch.asia
info@journalofresearch.asia

After estimation of MI relative risk parameters, ranges of risk for all factors above were determined. Maximum and minimum values for each factor were summed up; the sum was divided into three, each part corresponded to a MI risk degree. The whole MI risk range in type 2 diabetes mellitus scored from 41.0 to 155.8. That is, the higher a standardized intensive parameter due to the effect of factors under study, the higher MI risk in patients with type 2 diabetes mellitus. It seemed expedient to divide the whole risk range into subranges to categorize patients by various risk probability for the risk factors under study. Thus, there are three appropriately scored subranges of MI risk with relevant criteria.

1. The lowest MI risk subrange scoring 41.0-79.26 is for patients with favorable prognosis and minimum MI risk.

2. The moderate MI risk subrange scoring from 79.26 to 117.52 is for patients who have higher probability of MI and require focusing of physicians' attention.

3. The highest MI risk subrange scoring from 117.52 to 155.8 is for patients with unfavorable prognosis maximally affected by MI risk factors.

Based on the calculations above, a computer program titled "A calculator for myocardial infarction risk in Uzbek T2DM patients" was developed.

Below is the procedure any Uzbek T2DM patients should undergo. Presence or absence of MI risk factors should be identified in an outpatient setting or in a hospital. Medical history should include data on his age, diabetes duration, MI and stroke in family medical history, smoking and alcohol abuse. Derived from his weight and height the body mass index (BMI) normally should not exceed 25kg/m². The patient should have HbA1c measured for his carbohydrate metabolism to be assessed, diabetes is considered compensated if HbA1c is ≤7%. Measurement of arterial pressure and ECG are indispensable. The patient should be genotyped for two disease candidate-genes: *ACE* and *TCF7L2*. The *ACE* DD genotype and the *TCF7L2* TT genotype are MI risk factors in this kind of patients. To calculate MI risk in the patient, the data above should be entered into the computer program "A calculator for myocardial infarction risk in Uzbek T2DM patients" (Fig.2).

A calculator for myocardial infarction risk in Uzbek T2DM patients

MI risk factors

MI in family medical history **Diabetic nephropathy** **Stroke in family medical history**

Yes No Yes No Yes No

Left ventricular hypertrophy **Alcoholism** **Dislipidemia**

ISSN 2433-202x
JOURNAL DOI 10.26739/2433-202x
www.journalofresearch.asia
info@journalofresearch.asia

Yes No Yes No Yes No
ACE gene DD genotype **HbA1c≤7%** **TCF7L2 gene TT genotype**
Yes No Yes No Yes No
Arterial hypertension **Obesity (BMI >25 kg/m²)** **Smoking**
Yes No Yes No Yes No
Age **DM duration** **Hypercoagulation**
Under 50 years 1- 5 years Yes No
51-60 years of age 6-10 years
61-70 years of age 11-15 years
Over 70 years 16-20 years
Over 20 years

Calculate
Reset

Fig.2. Interface of "A calculator of myocardial infarction risk in Uzbek T2DM patients"

Making the program start and logging it in, a user can see the interface of "A calculator of myocardial infarction risk in Uzbek T2DM patients" with all MI risk factors and two icons ("yes" and "no") below each of them displaying on the desktop. Choosing the appropriate icon ("yes" denoting presence of a MI risk factor or "no" denoting its absence) and clicking it, the user can enter appropriate data for each MI risk factor The input of data for all MI risk factors completed, scores for MI risk degree (low, moderate or high) can be obtained by clicking the icon "Calculate" at the bottom. Clicking the icon "Recommendations", the user can get information about the recommendations for MI prevention in Uzbek T2DM patients.

As opposed to current methods used for MI risk prognosis, in addition to other MI risk factors, our method addresses genetic risk factors, such as *ACE* gene DD genotype and *TCF7L2* gene TT genotype, which are thought typical of Uzbek T2DM patients. Aside of that, a computer program "A calculator for myocardial infarction risk in Uzbek T2DM patients" helped simplify multifactor assessment of MI risk factors and estimation of risk as low, moderate or high. To our knowledge, there is no analogous computer program for MI prediction in Uzbek T2DM patients.

Estimation of potential MI risk degree in T2DM patients can facilitate appropriate well-timed interventions and help delay or prevent MI onset, or smooth its course with minimal or no complications. It makes possible for

ISSN 2433-202x
JOURNAL DOI 10.26739/2433-202x
www.journalofresearch.asia
info@journalofresearch.asia

practical healthcare specialist (i) to combine a patient's demographic and clinical characteristics for estimation of MI risk and prediction of MI progression in T2DM patients, and (ii) to perform appropriate interventions on early stages of the disease using the latest achievements in endocrinology and cardiology.

ISSN 2433-202x
JOURNAL DOI 10.26739/2433-202x
www.journalofresearch.asia
info@journalofresearch.asia

References

1. American Diabetes Association. (1999). Implications of the United Kingdom Prospective Diabetes study. *Diabetes Care*, 27-31.
2. Alberti G., Z. P. (2005). IDF. Epidemiology Task fores consensus group. The metabolic syndrome – a new worldwide definition. *Lancet*, 1059-1062.
3. Andre Gustavo P. Sousa, G. F. (2009). 30. Andre Gustavo P. Sousa, Guilherme FTCF7L2 Polymorphism rs7903146 is associated with Coronary Artery Disease Severity and Mortality. *Plos one*.
4. Booth GL, K. M. (2006). Recent trends in cardiovascular complications among men and women with and without. *Diabetes Care*, Jan; 29(1):32-7.
5. Cambien F., A.-G. F. (1998). Familial resemblance of plasma angiotensin-converting enzyme level: the Nancy study. *Am J Hum Genet*, 774-780.
6. Chan I.S., G. G. (2011). Personalized medicine: progress and promise. *Annu Rev Genomics Hum Genet*, 12:217-44.
7. Colagiuri S, C. C. (2002). Are lower fasting plasma glucose levels at diagnosis of type 2 diabetes associated with improved outcomes? U.K. prospective diabetes study. *Diabetes Care*, 1410-1417.
8. Conkbayir C, F. Y. (2017). Impact of Genetic Defects on Coronary Atherosclerosis among Turkish Cypriots. *Heart Surg Forum*, 223-229.
9. Fischer SCPM, P. S. (2018). Association of Multiple Genetic Variants with the Extension and Severity of. *Arq Bras Cardiol*, 16-23.
10. Fysekidis M., H. S. (2007). ACE I/D polymorphism predicts end stage renal disease and or mortality in type 1 diabetic patients except for those with already advanced nephropathy: the follov up of the Genesis/Genediab Studies. *The European Asociation for the study of Diabetes*, (стр. 157). Amsterdam.
11. Holman R, T. R. (1998). Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: United Kingdom prospective diabetes study for United Kingdom Prospective Diabetes Study Group. *British Medical Journal*, 713-720.
12. IDF. (2017). *Diabetes Atlas.*
13. International Diabetes Federation. (2017). Получено из idf.org: https://www.idf.org/about-diabetes/what-is-diabetes.html

ISSN 2433-202x
JOURNAL DOI 10.26739/2433-202x
www.journalofresearch.asia
info@journalofresearch.asia

14. International Diabetes Federation. (2017). *http://www.diabetesatlas.org/key-messages.html*. Получено из http://www.diabetesatlas.org/.

15. Jain, K. (2002). From molecular diagnostics to personalized medicine. *Exp Rev Mol Diagn*, 2(4):299-301.

16. Koskinas KC, S. G. (2016). Impact of Diabetic Status on Outcomes After Revascularization With Drug-Eluting Stents in Relation Outcomes After Revascularization With Drug-Eluting Stents in Relation of 6081 Patients. *Circ Cardiovasc Interv.*, 9(2) :e003255.

17. National Institute of Diabetes and Digestive and Kidney Diseases. (2001). *65. U.S. Renal Data System. USRDS 2001 Annual Data Report: atlas of end-stage renal disease in the United States.*

18. O'Donoghue ML, V. A. (2012). An Invasive or Conservative Strategy in Patients With Diabetes Mellitus and Non–ST-Segment Elevation Acute Coronary Syndromes. *J Am Coll Cardiol*, 60(2):106-111.

19. Parving H-H, O. R. (2000). *Diabetic nephropathy.* Philadelphia: W.B. Saunders.

20. Silvio E. Inzucchi, R. M. (2015). Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient-Centered Approach: Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*, Jan; 38(1): 140-149.

21. Shigan E.N. Modeling and hardware in assessment and prediction of public health. Moscow. 1983.-60p

22. Tamara S. Hannon MD, C. R. (2005). Childhood Obesity and Type 2 Diabetes Mellitus. *Pediatrics*, 473-480.

23. Thouraya B., R. B. (2009). Association of the insertion/deletion polymorphism of the angiotensin-converting enzyme gene with type 2 diabetes in two ethnic groups of Jerba Island in Tunisia. *Journal of the Renin-Angiotensin-Aldosterone System*, Vol.10.- P.35-40.

24. Turner R. C, M. H. (1998). Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus: United Kingdom prospective diabetes study (UKPDS: 23) for the United Kingdom Prospective Diabetes Study Group. *British Medical Journal*, 823-828.

25. Wu L.S., H. C. (2009). Association and interaction analyses of genetic variants in ADIPOQ, ENPP1, GHSR, PPARgamma and TCF7L2 genes for diabetic nephropathy in a Taiwanese population with type 2 diabetes. *Nephrol Dial Transplant*, 3360-3366.

ISSN 2433-202x
JOURNAL DOI 10.26739/2433-202x
www.journalofresearch.asia
info@journalofresearch.asia

26. Žaliaduonytė-Pekšienė D, L. V.-M.-P. (2017). Association of the genetic and traditional risk factors of ischaemic heart. *J Renin Angiotensin Aldosterone Syst.*, 15-28.