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Total cardiovascular risk among native population of Kyrgyzstan with diabetes mellitus type 2 and impaired glucose tolerance in high and low-altitude regions

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Abstract

Objective: In diabetes mellitus (DM) type 2, there is a very high risk of developing cardiovascular (CV) events. We aimed to study the total CV risk of the indigenous people of Kyrgyzstan with impaired carbohydrate metabolism (DM type 2 and impaired glucose tolerance, IGT), depending on the region of residence (low and high altitudes), and to develop targeted preventive measures.

Methods: Overall, 248 families (992 people) in the Naryn (high-altitude) (study group) and 260 families (1041 people) in the Chui region (low-altitude) (control group) were surveyed and 363 people with DM type 2 and IGT were identified, of which: 138 people in the study group and 225 people in the control group.

Results: In patients with DM type 2 and IGT, moderate CV risk was found in the low-altitude and high-altitude in men and women aged 46–65 years, the leading risk factor in men is BMI>25 kg/m^2; in women, hypertension (HT) and hypercholesterolemia. A high risk of CV complications was detected only in the low-altitude in men aged 46–65 years, the leading risk factor is HT. High and very high risk of CV complications are rarely found both in the low-altitude and in the high-altitude.

Conclusion: During stratification of total CV risk, 363 people with carbohydrate metabolism disorders (DM type 2 and IGT) of 2033 native population living in 2 regions of Kyrgyzstan revealed features of the total CV risk: BMI>25kg/m^2 for men of high-altitude and low-altitude, HT and hypercholesterolemia for women of high-altitude, and for men, low-altitude only HT. Both in the high-altitude and in the low-altitude, low and moderate CV risk are predominantly expressed, and high and very high CV risk are rare.

Key words: diabetes mellitus, impaired glucose tolerance, native population, low-altitude, high-altitude, factors of total cardiovascular risk

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Introduction

In diabetes mellitus (DM) type 2, a very high total cardiovascular (CV) risk of development and mortality from coronary artery disease (CAD) is by 2–4 times and acute myocardial infarction - by 6– 10 times higher than in the general population (1-8). In Kyrgyzstan in 2015, the number of deaths from DM at the age of 20-79 years was 2560.3 (in the world - 4960535.8) (9), in 2017 - 2482.9 (in the world 3990420.6), including from cardiovascular (43% of cases) and cerebrovascular (12%) pathology (10,11). For comparison, in Russia, these figures were 55-60% and 29% for CV and cerebrovascular pathology, respectively (12-15). Since DM type 2 is an independent risk factor of CV disease (16), the study of the total CV risk in DM is important (17-18). Risk factors can be modified by preventive measures and influence course

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of diseases, including diabetes (19).

The carbohydrate metabolism in highlanders has specific features: in high-altitude, the incidence of diabetes and average blood glucose levels are lower (7). Obesity, like DM type 2, hypertension (HT) and atherosclerosis, among the high-altitude of all age groups is 3 times less common than among the population of the low-altitude (20).

Previously, we studied the significance of the risk factors and the stratification of the 10- year risk of developing DM type 2 in the native population of the Chui (low-altitude) and Naryn (high- altitude) regions of Kyrgyzstan. The following features were identified: low risk prevails in both women and men, high risk in 4.6% of women and 2.1% of men in the Chui region and in 1.4% of women and 1% of men in the Naryn region, regardless of gender, and a very high risk does not occur (21).

The standardized mortality rate from circulatory diseases aged up to 65 years and older per 100,000 population (WHO, 2016) in Kyrgyzstan is high with a tendency to decrease: from 714.1 (2009) to 658.73 (2013); in Germany from 217.16 (2009) to 186.28 (2014); in Kazakhstan from 626.37 (2009) to 305.09(2014), in Russia from 682.98 (2009) to 613.31 (2011). Standardized mortality rate from CAD in Kyrgyzstan is also high with a similar tendency to decrease from 437.78 (2009) to 429.36 (2013); in Germany from 84.43 (2009) to 68.88 (2014); in Kazakhstan from 238.5 (2009) to 112.37 (2014); in Russia from 351.72 (2009) to 323.25 (2011). Standardized mortality rate from concurrent cerebrovascular diseases in Kyrgyzstan is high with a tendency to decrease from 234.13 (2009) to 175.43 (2013); in Germany from 37.62 (2009) to 30.07 (2014); in Kazakhstan from 180.41 (2009) to 113.81 (2014); in Russia from 220.67 (2009) to 187.0 (2011) (22).

In Kyrgyzstan, in the structure of causes of mortality of the population, circulatory system diseases take the leading places, although a slight decrease is observed: in general, this indicator was 50.5% (2013) and 50.4% (2014), 50.8% (2015), 50.8% (2016), including in Chui - 54.2% (2013), 53.7% (2014), 54.4% (2015) and 52.8% (2016) in Naryn - 42.7% (2013), 42.4% (2014), 42.0% (2015) and 44.6% (2016) regions (23-25).

The incidence of CV disease, including diabetes, is increasing in Kyrgyzstan: if in 2008 there were 28,694 patients (783.3 per 100 thousand), then in 2014 there were 46,468 (1157.0 per 100 thousand) patients with diabetes and its prevalence at the age of 20–79 years in Kyrgyzstan is 5.2 (3.7– 10.4). An increase in the number of patients with diabetes is also noted by region: 7580 people in Chui (1230.1) and Naryn-2032 (1130.0) regions (23-25). Research has shown that among risk factors, HT among residents of the Chui region was registered in 34.1% of respondents, higher in women than in men (36.7 vs. 30.5%, 95% CI 0.01–0, 11; p=0.021). With age, there was a regular increase in the prevalence of HT, reaching in the age group of 60 years and over - 75.2%, however, the following pattern is revealed: at the age of 40 years, the prevalence of HT is somewhat higher in men, and after 50 years the incidence of elevated blood pressure prevails in women (26).

If we compare the data of our previous studies, where the prevailing risk factors of development of diabetes, irrespective of the region of residence and sex were irregular consumption of vegetables and fruits, visceral obesity and overweight, the factors of total CV risk among native population of Kyrgyzstan with DM type 2 and IGT are not well established (21).

According to the data of Mashalayeva et al. (27), the most common risk factors of CAD among the surveyed residents of the low-altitude and high-altitude regions of Kyrgyzstan are HT (82% and 69.49%) with the significantly higher levels of systolic (145.17±13.89 mm Hg vs 131.6±15.9 mm Hg, respectively), and diastolic (90.25±4.77 mm Hg vs 84.72±7.97 mm Hg) blood pressure levels in the residents of high-altitude compared with the low-altitude ($p<0.05$); then smoking (62% and 52.4%) and obesity (53% and 44.91%) (33.6±5.02 kg/m^2 vs 28.1±3.18 kg/m^2, $p <0.05$).

Systematic coronary risk evaluation (SCORE) allows to determine 10-year risk of fatal cardiovascular events in adult population (28, 29). Total CV risk assessment is recommended in presence of risk factors, including diabetes (29). Several studies described value of SCORE in prediction of 10-year CV events in different populations (30, 31).

In Kyrgyzstan at various mountain levels, where mainly native population lives and works, the course of diabetes and the development of CV complications can be modified.

However, there are no studies on total CV risk assessment using SCORE in populations of low and high altitudes with DM type 2 and IGT.

Thus, there is a need to study the total CV risk among the native population of Kyrgyzstan, depending on the altitude of the region of residence and gender to control the 10-year risk of death from CV disease in patients with DM type 2.

We aimed to study the total CV risk of the indigenous people of Kyrgyzstan with impaired carbohydrate metabolism (DM type 2 and IGT), depending on the

altitude (high and low altitude) of the region of residence, and to develop targeted preventive measures.

Methods

A total of 248 families (992 people) in the high-altitude Naryn (study group) and 260 families (1041 people) in the low-altitude Chui region (control group) were examined. Of these, 363 people with DM type 2 and IGT were identified, of them: 138 people in the study group, 10 people with diabetes, 128 people with IGT, and 225 people in the control group, 54 people with diabetes and with IGT - 171 people. We also divided participants by age groups: 18-45 years old, 46-65 years old and over 65 years old.

The study was approved by the bioethics committee of the Kyrgyz State Medical Academy. Before the survey, we obtained personal informed consent from each participant. The study was conducted in compliance with Helsinki declaration 2013.

The altitude of 1500 - 3500 m (International Society for Mountain Medicine) is attributed to the high-altitude. The high-altitude Naryn region, where the native population was surveyed is located at an altitude of 2040-3500 m, the low-mountain Chui region is located at an altitude of 500-1500 m above sea level (32-34).

Randomization was performed according to the number of families and the number of patients examined.

The smokers were people who smoked at least one cigarette per day, with gradations: never smoked, smoked in the past, smoke now.

Overweight and obesity were defined by the formula of body mass index (BMI) = weight (kg) / height (m^2), according to BMI: overweight—BMI: 25–29.9kg/m^2, and obesity—BMI: ≥30kg/m^2. A diagnosis of abdominal or central obesity was established if waist circumference was >94cm in men and >80cm in women (35).

Blood pressure was measured by a standard method, and hypertension was established if blood pressure of ≥140/90 mm Hg (36).

The total cholesterol (mmol/l) level in serum was determined by photocalorimetric method and the level of glucose concentration in capillary blood was determined by the express method using a glucometer (Fine test).

Diagnostic criteria for diabetes: whole capillary blood: fasting glucose ≥6.1 mmol/L , two-hour blood glucose ≥11.1 mmol/L following a 75g oral glucose load; impaired glucose tolerance (IGT) diagnostic criteria, whole capillary blood : fasting glucose < 6.1 mmol/L; two-hour blood glucose ≥ 7.8 and <11.1 mmol/L following a 75g oral glucose load (10, 18).

The total CV risk was determined using the SCORE (Systematic Coronary Risk Evaluation) scale, the European model which determines the 10-year total CV risk of all events. The degree of total CV risk : very high risk –≥10%, high risk -> 5% and <10%, moderate risk -> 1% and <5%, low risk -< 1% (28, 29).

Statistical analysis was performed by using Medstatistic and Graphpad softwares. We used descriptive statistics to present categorical variables, Fisher exact and Chi-square tests to compare proportions, and Spearman ρho correlation analysis to estimate the association of score components with altitude, age, and sex. Odds ratios with 95% confidence intervals were also calculated.

Results

Of the 992 native-population of the high-altitude Naryn region of Kyrgyzstan, 14.91% and of 1041 people of the low-altitude Chui region, 26.8% had diabetes or IGT. Among risk factors of CV risk in the native population of Kyrgyzstan with DM type 2 or IGT, in the high-altitude group in men, BMI prevails>25 kg/m^2, in women hypercholesterolemia varies from 4.1 to 4.5 mmol/l; in the low-altitude group in men, high blood pressure predominates, in women, BMI>25 kg/m^2 (see Table 1). Comparison of high and low altitude groups showed higher blood pressure levels and cholesterol levels (4.1-4.5 mmol/l) in men and women of low altitudes as compared to men and women of high altitudes (p<0.001 and p<0.001).

Table 1. Prevalence rates of cardiovascular risk factors among native population of Kyrgyzstan with impaired carbohydrate metabolism (DM or IGT), depending on the region of residence (high and low-altitude regions) and gender (%)

	Men, n(%)				Women, n(%)			
	High-altitude	Low-altitude	p		High-altitude	Low-altitude	p	
BMI>25 kg/m^2	19 (43.6)	47 (51.62)	>0.05		41 (43.6)	94 (70.12)	>0.05	
BP≥140/90 mmHg	10 (22.72)	49 (53.83)	systolic	<0.02	16 (17.01)	59 (44.02)	systolic	>0.05
			diastolic	<0.001			diastolic	<0.001
Cholesterol 4.1-4.5 mmol/l	18 (40.2)	42 (46.14)	<0.001		49 (52.12)	69 (51.48)	<0.001	
Cholesterol >4.5 mmol/l	7 (15.9)	30 (32.95)	>0.05		8 (8.5)	22 (16.41)	>0.05	

Table 2. Age- and sex-dependent distribution of demographic, anthropometric data and risk factors in native population of high and low altitudes

Parameters	Men, n (%)	Women, n (%)		p
	Low-altitude	High-altitude	Low-altitude	High-altitude
Age				
18-45	11 (12.08)	34(77.27)	22 (16.41)	36 (38.30)
46-65	71 (78.03)	10(22.72)	104 (77.61)	57 (60.64)
> 65 years	9(9.89)		8(5.98)	1(1.06)
BMI, kg/m² <25 kg/m²			a	b
18-45	9 (9.89)	20(45.45)	14 (10.44)	33(35.11)
46-65	32 (35.16)	5(11.36)	22(16.41)	20(21.27)
> 65 years	3 (3.29)		4 (2.98)	
25-29.9, kg/m²	c	d		<0.001
18-45	2(2.19)	10(22.72)	6 (4.47)	3(3.19)
46-65	23(25.27)	2(4.54)	32 (23.88)	17(18.08)
> 65 years	3(3.29)		3 (2.23)	
>30 kg/m²				
18-45		4(9.09)	2 (1.49)	
46-65	16 (17.58)	3(6.81)	50 (37.31)	20(21.27)
> 65 years	3(3.29)		1 (0.74)	1(1.06)
Blood pressure <140/90, mmHg				
18-45	9(9.89)	28(63.63)	21 (15.67)	35(37.23)
46-65	28 (30.76)	6(13.63)	52 (38.81)	43(45.74)
> 65 years	5(5.49)		2 (1.49)	
≥140/90,mmHg				
18-45	2 (2.19)e	6(13.63)	1 (0.74)	1(1.06)h
46-65	43 (47.25) f	4(9.09)	52 (38.81)	14(14.89)i
> 65 years	4 (4.39)g		6 (4.47)	1(1.06) j
Smokers				
18-45	1 (1.09)	10(22.72)		17(18.08)
46-65	32 (35.16)	3(6.81)	1(0.74)	1(1.06)
>65 years	4 (4.39)			
Non-smokers				
18-45	10 (10.98)	24(54.54)	22 (16.41)	19(20.21)
46-65	39 (42.85)	7(15.91)	103 (76.86)	56(59.57)
> 65 years	5(5.49)		8 (5.97)	1(1.06)
DM type 2				
18-45		4(9.09)		1(1.06)
46-65	19(20.87)	1(2.27)	26(19.41)	4(4.25)
> 65 years	6(6.59)		3(2.23)	
IGT				
18-45	11(12,08)	30(68.18)	22(16.41)	35(37.23)
46-65	52(57.14)	9(20.45)	78(58.21)	53(56.38)
>65 years	3(3.29)		5(3.73)	1(1.06)
Cholesterol<4 mmol/l				
18-45	1(1.09)	18(40.91)	10(7.46)	19(20.21)
46-65	18(19.78)	1(2.27)	32(23.88)	18(19.15)
> 65 years			1(0.74)	

Cholesterol 4.1-4.5 mmol/l				
18-45	10(10.98)	12(27.27)	11(8.21)	16(17.02)k
46-65	25(27.47)	6(13.63)	54(40.29)	32(34.04)l
> 65 years	7(7.69)		4(2.98)	1(1.06)m
Cholesterol >4.5mmol/l				
18-46		4(9.09)	1(0.74)	1(1.06)
46-65	28(30.76)	3(6.81)	18(13.43)	7(7.44)
> 65 years	2(2.19)		3(2.24)	
Cardiovascular risk Low <1%				
18-45	11(12.08)	30(68.18)	22 (16.41)	36(38.29)
46-65	30 (32.96)	5(11.36)	96 (71.64)	55(58.51)
> 65 years	2 (2.19)		5(3.73)	1(1.06)
Moderate risk >1-<5%				
18-45		4(9.09)		
46-65	17 (18.68)	2(5.49)	5 (3.73)	1(1.06)
> 65 years	5(5.49)		1 (0.74)	
High risk >5-<10%				
18-45				
46-65	13 (14.28)		2 (1.49)	1(1.06)
> 65 years			1 (0.74)	
Very high risk>10%				
18-45				
46-65	11 (12.08)	3(6.81)	1 (0.74)	
> 65 years	2(2.19)		1(0.74)	

1) p<0.05 BMI<25 kg /m^2 in women of low-altitude and high-altitude, a, b OR is equal to 3.038 (CI95% 1.752-5.268).
2) p<0.05 BMI>25 kg/m^2 in men of low-altitude and high-altitude, c, d OR is 0.711 (CI 95% 0.345-1.468).
3) p<0.001 BP above 140/90 in low-altitude men aged 46–65 years compared with other ages e,g, OR is 0.093 (CI 95% 0.020-0.428).
4) p<0.001 above 140/90 mm Hg in low-altitude women aged 46–65 years with other ages h, j, OR is equal to 3.286 (CI 95% 1,297-8,322).
5) p<0.001 cholesterol>4.1 mmol/l in women of high-altitude aged 46-65 years with other ages k, m, OR is equal to 2.287 (CI 95% 0.975-5.367).

Anthropometric indicators, depending on sex, age and region of residence (Table 2), show a BMI of <25kg/m^2 detected more often in population of high-altitude (for women, p<0.05). Overweight / obesity (BMI> 25kg/m2) is more common in low-altitude men (51.62%) than in high-altitude men (43.16%) (p<0.05).

In the high-altitude, BP ≥140/90 mm Hg prevails in women aged 46–65 years (14.89%) (p<0.001), and in low-altitude in men aged 46–65 years (47.25%) (p<0.001).

In the high-altitude, mostly men aged 18–45 years (22.72%) smoke, and in the low-altitude, mostly men aged 46–65 years (35.16%) are smokers. In the high-altitude, diabetes was first detected only in 11.36% of men and in 5.31% of women aged 18–65 years, and in the low-altitude DM type 2 prevails between the ages of 46-65 years in 20.87% of men and in 19.41% of women. IGT prevails in 68.18% of men aged 18–45 years in the high-altitude, and in 58.21% of women aged 46–65 years in the low-altitude. Cholesterol >4.1-4.5 mmol /l prevails in women (p <0.001) in the age group 46-65 years in both altitudes, however being significantly lower in women residing in high altitudes as compared to low altitudes (p<0.05).

A moderate risk of CV complications was detected in low mountains in 17 (18.68%) men (p<0.01) aged 46–65 years, the leading risk factors are: BMI> 25 kg/m^2 in 58.82%, HT in 52.94% and smoking in 47.05%, and 3 of them have a combination of 3 risk factors and 7 men have 2 risk factors; in high-altitude men, in 2 (5.49%) aged 46–65 years, the leading risk factors are: BMI>25 kg/m^2 in 100%, HT in 50% and hypercholesterolemia in 50%, and all of them have a combination of 2 risk factors. A moderate risk of CV complications was found in low mountains in 5 (3.73%) women aged 46–65 years, the leading risk factors are: hypercholesterolemia in 20%, and smoking in 20%, and 1 of them has a combination of 2 risk factors; in high-altitude — only 1 (1.06%) woman aged 46–65 years has a moderate risk due to a combination of 3 risk factors.

High risk of CV complications was detected in low-altitude in 13 (14.28%) men aged 46-65 years old, the leading risk factors are: HT and hypercholesterolemia in 84.61% and BMI>25 kg/m^2 in 46.15%, and in 7 of them there is a combination of 3 risk factors and in 4 men -2 risk factors.

A high risk of CV complications was found in low-altitude in 2 (1.49%) women aged 46-65 years old, the leading risk factors are: BMI> 25 kg/m2, hypercholesterolemia in 100% and HT in 50%, and 1 of them has a combination of 3 risk factors and 1 woman -2 risk factors; in the high-altitude, only 1 (1.06%) woman aged 46–65 years has high risk , and there is a combination of -3 risk factors. Very high risk of CV complications was found in low-altitude in 11 (12.08%) men aged 46–65 years, in high-altitude in 3 (6.81%) and in women in low-altitude in 1 (0.74%) women aged 46 -65 years, and there is no very high risk in the high-altitude women (p> 0.05).

With the stratification of the total CV risk, low risk is more pronounced in the high- altitude and moderate risk prevails in low-altitude men and women (Table 3).

Table 3. Stratification of total cardiovascular risk depending on the region of residence and gender

Low risk				Moderate risk				High risk				Very high risk			
High-altitude		Low-altitude		High-altitude		Low-altitude		High-altitude		Low-altitude		High-altitude		Low-altitude	
M, %	W, %	M, %	W, %	M, %	W, %	M, %	W, %	M, %	W, %	M, %	W, %	M, %	W, %	M, %	W, %
79.55	97.86	47.23	91.78	14.58	0.06	24.17	4.47	-	1.06	14.28	2.23	6.81	-	14.27	1.48

Discussion

Despite the fact that patients with DM type 2 are categorized as high/very high total CV risk, hyperglycemia is an independent risk factor of CV complications and their risk stratification is justified because their timely detection contributes to a significant reduction in overall and CV mortality.

Previously, we studied the significance of the risk factors and the stratification of the 10-year risk of developing DM type 2 in native population of the Chui and Naryn regions of Kyrgyzstan. The following features were identified: low risk prevails in both women and men, high risk in 4.6% of women and 2.1% of men in the Chui region and in 1.4% of women and 1% of men in the Naryn region, regardless of gender, and a very high risk does not occur (21). Different mountain levels of Kyrgyzstan, where mostly native population live and work, can modify the course of DM type 2 and the development of the CV complications. Of the 992 native population of the high-altitude Naryn region of Kyrgyzstan, 14.91% and of 1041 people of the low-altitude Chui region, 26.8% revealed impairment of carbohydrate metabolism in form of DM type 2 and IGT.

For the first time in Kyrgyzstan, we identified the components of the total CV risk in these patients: BMI <25kg /m2 was detected more often in native women of high-altitude than low-altitude (OR 3.038, CI 95% 1.752-5.268), BMI>25kg/m2 was more characteristic for low-altitude men than the high-altitude men (OR 0.711, CI 95% 0.345-1.468), in the high-altitude the HT prevails in women (OR 3.286, CI 95% 1,297-8,322), and in the low-altitudes in men aged 46-65 years (OR 0.093, CI 95% 0.020-0.428); in the high-altitude, there is a tendency of cholesterol >4.1 mmol/l prevailing in women in the 46–65 age group, though insignificantly (OR 2.287, CI 95% 0.975-5.367).

Both in the high-altitude and in the low-altitude, low and moderate CV risk are predominantly expressed, and high and very high CV risks are rare. The comparative frequency of CV risk is higher in the low-altitude, in men aged 46–65 years than in the high-altitude.

Moderate CV risk was found in low-altitude and high-altitude in men aged 46–65 years; the leading risk factor was BMI>25kg/m^2. When studying the linear relationship between risk ratios and leading risk factors (ρ), there is a close relationship between very high CV risk in men in the low-altitude at the age of 46–65 years old with HT ($\rho = 0.673$, $p < 0.05$) and in men in the high-altitude age 46-65 years old with a BMI>25 kg/m^2 ($\rho = 0.500$, $p < 0.05$).

Moderate CV risk was found in the low-altitude and high-altitude women aged 46-65 years, the leading risk factors are: hypertension and hypercholesterolemia. A high risk of CV complications was detected only in the low-altitude in men aged 46–65 years, the leading risk factor is HT. High and very high risks of CV complications are rarely found both in the low-altitude and high-altitude.

Conclusion

In the Kyrgyz population, when studying the 10-year total CV risk in patients with impaired carbohydrate metabolism (DM type 2 and IGT), the leading risk factors-components of the total CV risk were revealed: overweight (BMI> 25 kg/m^2) in men of low-altitude and high-altitude, HT and hypercholesterolemia in women of high-altitude, and in men of low-altitude only HT. Both in the high-altitude and in the low-altitude, low and moderate CV risk are predominantly expressed, and high and very high CV risk are rare. First of all, men of both high-altitude and low-altitude need to be targeted for fighting BMI, then with HT, and for women with HT and hypercholesterolemia, it is necessary to monitor adherence to CV risk prophylaxis measures, first of all, adherence to diet and antihypertensive therapy.

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