Type 2 Diabetes among Circassians in Israel

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Abstract

Background: The Muslim Circassians in Israel represent a unique ethnic community, distinct from Jews and Arabs. This endogamous group has a limited genetic variability that allows studying risk factors associated with type 2 diabetes.

Objectives: To estimate the prevalence of type 2 diabetes among Israeli Circassians and its correlation to obesity and genetic susceptibility.

Methods: Israeli Circassian women (n=450) and men (n=289) older than 35 were included in the study. They were classified as having or not having diabetes, and their risk factors (including hypertension, body mass index, family history of diabetes) and laboratory tests, were examined retrospectively.

Results: The age-adjusted prevalence of diabetes among the 739 participants was 12% (men 14.6%, women 10.7%). It was higher among those with BMI > 30 than in those with lower BMI and a family history of diabetes without high BMI. But the risk of diabetes with BMI > 30 plus a family history was three times higher than when these factors were missing (odds ratio 2.96, 95% confidence interval 1.30–6.6). Multivariate analysis, however, found familial history of diabetes to be the strongest risk factor, independent of obesity (OR 2.47, 95% CI 1.45–4.20).

Conclusions: The results yielded by this homogeneous Circassian population, sharing the same environmental influences and having an endogamous pattern of marriage, suggest a role of genetic risk factors for diabetes. Israeli Circassians are suitable for additional genetic studies that may lead to the identification of susceptibility genes for type 2 diabetes.

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Extremely high rates of type 2 diabetes in a particular ethnic group suggest genetic susceptibility [1]. In addition, diabetes rates seem to increase in groups that are subject to rapid changes in their way of life, often described as "westernization." Change in lifestyle was demonstrated to be a cause of obesity and type 2 diabetes in several non-white homogenous communities [2]. When obesity and parental diabetes were found together, the incidence of diabetes was increased [3,4]. However, most of the data in these studies had been derived from the general white population and from non-white ethnic groups [5].

The Adyge people, commonly known as Circassians, are the oldest indigenous people of the North Caucasus region of Eastern Europe [6]. Under military pressure, a mass exodus of Circassians to Turkey and other parts of the Ottoman Empire, including the Middle East, occurred between 1825 and 1864 [7], and Circassians settled in Ottoman-occupied Palestine in the late 19th century. Today, Circassian communities are found in the Caucasus, Turkey, Jordan, the United States and Germany. The villages of Rehania and Kfar Kama, founded in the 1870s, are the only surviving Circassian communities in Israel.

The Muslim Circassian community in Israel represents a unique population that is distinct from both Jews and Arabs. There are few medical or genetic reports on this unique population [8]. The Circassians are endogamous and live in relative cultural and geographic isolation in two small villages in northern Israel, preserving their language, culture and tradition. They maintain a homogeneous society, rarely intermarrying with other groups, including other Muslims. The tradition of consanguineous marriage with first- and second-degree relatives, practiced by Muslims, is unacceptable among the Circassians. For many years the Circassians were farmers, but in the last two decades many members of the community, both men and women, have been professionally integrated into Israeli life as industry workers, civil servants and teachers.

This small, genetically and culturally homogeneous population presents an excellent opportunity to discern the risk factors associated with type 2 diabetes with the background of limited genetic variability. The objectives of the present study were to estimate, for the first time, the prevalence of type 2 diabetes among Circassians in Israel and to examine its association with obesity and genetic susceptibility.

Patients and Methods

Of the approximately 3150 Circassians living in two villages in northern Israel, all those aged 35 and older (n=902) were approached. Since all of them have full medical coverage, the recruitment was performed through the local healthcare providers;

BMI = body mass index
OR = odds ratio
CI = confidence interval

82% of the eligible individuals agreed to participate and signed an informed consent. The study group included 450 women and 289 men, reflecting a response rate of 94% and 68%, respectively. Screening of pregnant women was postponed until 3 months after delivery. The Institutional Ethics Committee approved the study.

All participants underwent a physical examination that included measurement of blood pressure and body mass index, and blood samples were drawn for glucose, total cholesterol, high density lipoprotein-cholesterol, low density lipoprotein-cholesterol, and triglycerides. All participants were interviewed by trained interviewers, and their medical records were reviewed.

Obesity was defined as BMI > 30; hypertension was defined as blood pressure > 140/90 mmHg on two occasions for individuals not on antihypertensive therapy or when such therapy was already being administered [9]. The criteria of the American Diabetes Association [10] were applied for the diagnosis of type 2 diabetes: namely, if individuals were already receiving insulin or oral anti-diabetes medication, or if they had a fasting glucose concentration > 7.0 mmol/L (126 mg/dl) on two occasions or a 2 hour glucose concentration > 11.1 mmol/L (200 mg/dl) after a 75 g oral glucose tolerance test.

Laboratory tests were performed by the same laboratory at the Sieff Medical Center in Safed on samples drawn after an overnight 12 hour fast. Values indicative of hypercholesterolemia were total cholesterol > 5.17 mmol/L (200 mg/dl), or LDL-cholesterol > 3.36 mmol/L (130 mg/dl), HDL-cholesterol < 1.03 mmol/L (40 mg/dl for men and < 50 mg/dl for women). Hypertriglyceridemia was indicated by triglycerides > 1.68 mmol/L (150 mg/dl). The cholesterol content of lipoprotein fractions and serum triglycerides was measured enzymatically [11,12].

The structured interview included questions related to socioeconomic factors, family health history, medical history, and lifestyle including smoking and physical activity [13]. Parental or sibling history of diabetes was assessed from self-reports. Information on anti-hypertension or anti-diabetes medication was extracted from the medical records in the local clinics.

Statistical analysis was performed, separately for men and women, with the SPSS-PC software (Version 9; SPSS, Chicago). To enable comparison with national data, prevalence was adjusted for age and gender using standard epidemiologic methods.

For discrete variables, the chi-square test was applied to calculate the odds ratios and their 95% confidence interval. Mean values of the risk factors of men and women with diabetes were compared using the Student two-tailed *t*-test for independent samples. Logistic regression was applied for the exploration of the independent relationships of potential risk factors for type 2 diabetes. The more defined effects of obesity and family history were examined by separate logistic regression models that included the interaction terms of these two factors.

LDL = low density lipoprotein
HDL = high density lipoprotein
ADA = American Diabetes Association

Results

Table 1 presents the characteristics of the study population. The prevalence of type 2 diabetes, as defined by the ADA guidelines, in the Circassian population above the age of 35 was 12%: 14.6% in men and 10.7% in women. In both genders the prevalence of the disease increased progressively with age [Table 2]. In the two extreme age groups diabetes was more prevalent in men, but was similar in men and women aged 45–64.

Men with type 2 diabetes, compared with afflicted women, had a higher prevalence of chronic heart disease (26.2% vs. 10.4%, $P < 0.05$), and were currently smoking (33.3% vs. 8.3%, $P < 0.01$) [Table 3]. However, fewer men than women were obese (38.1% vs. 56.3%, $P < 0.01$) or had hypertriglyceridemia (64.3% vs. 78.7%, $P < 0.005$). The differences between diabetic men and women in age distribution, prevalence of hypertension or family history of diabetes were statistically insignificant.

Among non-diabetic subjects, the prevalence of impaired fasting glucose was 5% in women and 2.4% in men [Table 1]. Subjects with impaired fasting glucose compared with subjects

Table 1. Demographic and clinical characteristics of the study group

	Women (n=450)	Men (n=289)	*P*
Age, mean (SD)	52.04 (12.08)	53.16 (11.78)	0.217
BMI, mean (SD)	29.35 (5.05)	27.54 (4.08)	0.0001
Glucose mmol/L, mean (SD)	4.69 (1.46)	4.62 (1.99)	0.806
Obesity (BMI > 30) (%)	40.6	24.9	0.0001
Current smoker (%)	10.0	33.3	0.0001
Total cholesterol > 5.17 mmol/L (%)	54.5	40	0.004
LDL > 3.36 mmol/L (%)	37.8	29.2	0.022
HDL < 40 mg /dl (male) < 50 mg/dl (female)	62	57	0.341
Triglycerides > 1.68 mmol/L (%)	58.5	59.4	0.445
Physical inactivity (%)	81.4	52.7	0.0001
Hypertension* (%)	44.3	40	0.224
Chronic heart disease (%)	4.6	11.7	0.0001
Family history of diabetes (%)	30.2	27.3	0.209
Type 2 diabetes (%)	10.7	14.6	0.134
Impaired fasting glucose (glucose 5.55–7 mmol/L)**	5.0%	2.4%	0.148

* Blood pressure > 140/90 mmHg on two occasions.
** Among non-diabetics.

Table 2. Prevalence of type 2 diabetes among Israeli Circassians, stratified by age

Age (yrs)	Women N (%)	Men N (%)	Total N (%)	OR (95%CI)
35–44	4 (2.8)	5 (6.0)	9 (3.9)	2.23 (0.58–8.54)
45–54	13 (9.5)	7 (9.2)	20 (9.4)	0.96 (0.36–2.53)
55–64	12 (15.2)	11 (16.7)	23 (16.0)	1.11 (0.45–2.72)
≥ 65	19 (24.4)	16 (30.2)	35 (26.7)	1.34 (0.61–2.93)
Total	48 (10.7)	42 (14.6)	87 (12.1)	1.42 (0.99–2.20)

Table 3. Clinical characteristics of women and men, with and without diabetes in the Circassian study group (%)

	Females			Males		
	No diabetes (n=403)	Diabetes (n=48)	OR (95% CI)	No diabetes (n= 246)	Diabetes (n= 43)	OR (95% CI)
HDL < 1.03 mmol/L (M), 1.29 (F) mmol/L	61	61.7	0.9 (0.5–1.8)	56.5	59.5	1.1 (0.5–2.2)
Triglycerides > 1.68 mmol/L	56	78.7	2.8 (1.3–5.9)	58.5	64.3	1.2 (0.6–2.5)
Hypertension*	42.5	62.5	2.3 (1.2–4.2)	36.6	59.5	2.5 (1.3–4.9)
Chronic heart disease**	4.0	10.4	2.8 (1.0–8.0)	8.9	26.2	3.6 (1.6–8.1)
BMI > 30**	38.9	56.3	2.0 (1.1–3.7)	22.8	38.1	2.1 (1.0–4.2)
Diabetes in family	28.9	39.6	1.60 (0.9–3.0)	26.0	33.3	1.4 (0.8–2.9)
LDL > 3. 36 mmol/L	37.7	39	1.0 (0. 5–2.0)	28.6	32.5	1.2 (0.5–2.4)
Total cholesterol > 5.17 mmol/L	52	76.6	3.07 (1.5–6.1)	38.6	47.6	1.1 (0.7–2.8)
Physical inactivity	81.3	81.6	1.0 (0.4–2.3)	53.5	50.0	1.1 (0.6–2.6)
Currently smoking**	10.3	8.3	0.8 (0.3–2.3)	33.2	33.3	1.0 (0.5–2.0)

* Blood pressure > 140/90 mmHg on two occasions.

** $P < 0.05$ for the difference between men and women with diabetes

Table 4. Logistic regression analysis of risk factors for type 2 diabetes

Risk factors	B	P	OR (95% CI)
Model 1			
Familial history of diabetes *	0.90	<0.001	2.5(1.5–4.2)
Gender (male)	0.55	0.05	1.7 (1.0–2.9)
Hypertension	0.37	0.17	1.5 (0.9–2.5)
Age	0.07	<0.001	1.07 (1.0–1.09)
BMI	0.05	0.05	1.06 (1.00–1.08)
HDL	0.01	0.31	1.0 (0.98–1.03)
Triglycerides	0.04	0.001	1.0 (1.00–1.01)
Model 2			
Gender (male)	0.29	0.24	1.4 (0.9–2.2)
Age	0.06	<0.001	1.07 (1.0—1.09)
Family history × BMI (interaction)	0.03	<0.001	1.03 (1.01–1.05)
Triglycerides	1.00	<0.001	1.00 (1.00 –1.04)

* Parents or siblings with type 2 diabetes

with lower levels of glucose (< 5.5 mmol/L) had a higher prevalence of obesity (BMI > 30) (57.7% vs. 32%, $P = 0.009$); however, there were no differences in prevalence of family history of diabetes.

Table 3 also lists the risk factors for diabetes. Obesity (BMI > 30) was much more likely to be present among diabetic men (OR 2.0, 95% CI 1.04–4.16) and women (OR 2.0, 95% CI 1.1–3.7), compared with their non-afflicted counterparts. Increased prevalence of chronic heart disease, hypertension, and family history of diabetes (namely, siblings or parents with the disease) was found in both men and women with diabetes. In addition, increased prevalence of hypertriglyceridemia (OR 2.8, 95% CI 1.32–5.90) and total cholesterol (OR 3.07, 95% CI 1.5–6.1) was present in the diabetic women. Smoking and physical inactivity were similar in members of the same gender with or without diabetes.

Among the obese, the prevalence of type 2 diabetes was doubled in individuals who also had a family history of diabetes (parents or siblings, n=182; both parent and sibling, n=33) compared with those without it (n=215) (OR 1.86, 95% CI 0.85–4.0). Among the obese with a familial history of diabetes the likelihood of diabetes was significantly increased (OR 2.96, 95% CI 1.30–6.6).

Multivariate logistic regression of the risk factors indicated that increased BMI and triglycerides, age, and family history of type 2 diabetes were all positively and significantly associated with the occurrence of diabetes [Table 4]. Of these factors, family history of diabetes was the most important risk factor (OR 2.47, 95% CI 1.45–4.20). Smoking, hypertension, HDL and total cholesterol were not associated with diabetes; nonetheless, there was a weak but statistically significant effect modification of the interaction between family history and obesity (OR 1.03, 95% CI 1.01–1.05).

Discussion

This study provides the first reported estimates of diabetes prevalence among the Circassian population. The findings of the present study indicate that the age-adjusted prevalence of type 2 diabetes in adults older than 35 was higher among the Circassians as compared with the corresponding Israeli general population. Because a central registry for diabetes does not exist in Israel, comparisons were made with data in selected populations and in surveys [14-17]. The prevalence rates in those studies ranged from 4.4% to 7.1% for women and 5.5% to 6.8% for men. An overall prevalence of 4.3% was calculated in a study by Clalit Health Services, the largest health management organization in Israel [18]. The high prevalence of type 2 diabetes among Circassians could reflect the increased prevalence of diabetes in the general population, especially considering that the Israeli studies had been conducted 5 to 10 years earlier and their diagnosis was based on a draft of the American Diabetes Association guidelines. Moreover, in contrast to such estimates of prevalence, which were based on stratified random samples, our data defined an entire unique population, and screening of diabetes was based on both administrative and clinical data (reviewing medical files and questionnaires, physical measurements and fasting blood samples).

The prevalence of diabetes among Circassians was even higher than in the Arab population in Israel (5.5% in men and 8.6% in women) [19], although in the Arab community studied (an Arab

village in northern Israel) obesity (BMI > 30) was more prevalent among diabetic subjects (men 42% and women 77.5%) compared with diabetic Circassians (men 38% and women 56.3%).

In the Circassian community, the high prevalence of type 2 diabetes could also support a mechanism of specific genetic susceptibility because this ethnic group's way of life has altered considerably with the increasing prosperity and westernization, as reflected by the change of diet, reduced physical activity and the consequential development of obesity. The age, gender, occupation and other demographic characteristics of the Circassians were not different from those of the general population in Israel, and therefore the higher prevalence of diabetes among the endogamous Circassians community is most likely related to an inherent genetic susceptibility. This is consistent with the metabolic syndrome hypothesis, according to which modern life impacts populations with particular genetic susceptibilities, as was found in several distinctive populations in various countries [20]. The increasing prevalence of diabetes with age among both men and women concurs with findings in epidemiologic studies of other groups [21]. The National Health and Nutrition Examination Survey in the United States found that the prevalence of type 2 diabetes was 8–10% among older (> 65 years) white adults [22], 16–19% among old African-American men, and 20–24% in old African-American women [23]. In Israel, the prevalence of type 2 diabetes in this age group is higher than in the U.S. (16% vs. 9.8%, respectively), and still, among the older Circassians the prevalence reached 26.7%, much higher than the Israeli surveys' finding of 16% [15-18] and closer to that of the American minorities.

Circassian men had a higher prevalence of diabetes than women of almost all ages, particularly the younger ages (35–45 years), disagreeing with most studies that found females, especially postmenopausal women, to have a higher prevalence of the disease. Our findings are consistent with type 2 diabetes prevalence in some populations, with evidence of male preponderance in early middle age [24]. In our study group, diabetes type 2 was characterized by obesity and by diabetes among first-degree relatives. Indeed, by multivariate analysis, such a familial history was the strongest risk factor and was independent of obesity. Other studies that compared the effect of obesity and family history of diabetes found that the likelihood of the disease increased when both conditions were met [25]. We therefore conclude that a family history of diabetes, independent of obesity, is strongly associated with type 2 diabetes in the Circassian community of Israel.

In conclusion, this homogeneous Caucasian population, sharing the same environment and having an endogamous pattern of marriage, provides information on the predictive role of genetic factors on the risk of developing diabetes. It could, therefore, be a candidate for further genetic studies to enable the identification of genes of susceptibility to type 2 diabetes.

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