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TITLE: PREVALENCE OF DIABETES MELLITUS IN CROATIA

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ABSTRACT

The aim of this study was to obtain an accurate estimate of diabetes prevalence in Croatia and additional estimates of impaired fasting glucose (IFG), undiagnosed diabetes and insulin resistance.

The study was part of the First Croatian Health Project. Field work included a questionnaire, anthropological measurements and blood sampling. A nationally representative sample of 1,653 subjects aged 18-65 years was analyzed.

A total of 100 participants with diabetes were detected, among them 42 with previously unknown diabetes. The prevalence was 6.1% (95%CI:4.59-7.64), with a significant difference by age. IFG prevalence (WHO-criteria) was 11.3%. The ratio of undiagnosed/diagnosed diabetes was 72/100, unevenly distributed by the regions. HOMA-IR was >1 in 40.4% of the subjects.

This survey revealed a higher prevalence of diabetes than previously estimated, whereas that of IFG was as expected. A significant difference in the proportion of undiagnosed diabetes among the regions warrants attention.

Key words: diabetes mellitus, prevalence, impaired fasting glucose, HOMA-IR

1. INTRODUCTION

Diabetes mellitus (DM) is a major public health problem worldwide [1]. Although its prevalence has been used as one of the parameters in the assessment of the quality of health care by the World Health Organization (WHO) [2], surveys have been conducted in only a limited number of countries [3]. The prevalence of type 2 diabetes increases with that of obesity. This increase in the number of people with diabetes will lead to unforeseen and unsustainable costs in most of the countries of the world [1]. In Croatia, diabetes prevalence has been estimated according to data from questionnaires completed by diabetes centers [4]. However, as these were not survey data, the estimates of diabetes prevalence in Croatia as reported in the International Diabetes Federation (IDF) atlas [5,6] have been made by extrapolating data from similar populations [7,8].

The aim of the present study was to obtain an accurate estimate of diabetes prevalence in Croatia. Its additional aims were to estimate the percentage of impaired fasting glucose (IFG), undiagnosed diabetes, and the prevalence of insulin resistance (IR) in the country. It was the first Croatian survey targeting diabetes prevalence. The study was part of the First Croatian Health Project [9], preliminary data of which had been reported earlier [10].

2. PARTICIPANTS, MATERIALS AND METHODS

The design of the First Croatian Health Project has been described previously [9]. In short, a large field study was performed from 1995 to 1997 in 10,074 participants aged 18-80 years from 30 communities of 4 geographical regions: two continental (Osijek and Zagreb) and two Mediterranean ones (Rijeka and Split). All personnel involved in the field work (physicians, nurses and laboratory technicians) underwent a training program before its onset. The field work consisted of questionnaires completion, blood pressure, weight and height measurements, and venous blood sampling. The questionnaire asked respondents about their personal and family history of chronic noncommunicable diseases including diabetes. Completed questionnaires, respondents' record forms and frozen blood samples were delivered to the Center for Coordination. Samples were stored at -20^0C within 30 minutes. A representative sample of 5,840 randomly selected participants aged 18-65 yrs with age, gender and regional distribution identical to the national population was created for analysis. More than 97% of the Croatian population are white Europeans [11].

2.1 Defining the sample for diabetes prevalence subanalysis. Before performing a subanalysis on diabetes prevalence, sample size was estimated with allowed relative error of 2%, a 99% confidence interval, and an assumed diabetes prevalence lower than 10% [12] . Data from 1635 subjects were analyzed. The representativeness of the sample was confirmed by statistical analyses revealing no differences in age, gender and regional distribution between this sample (N=1635) and the original stratified one from The First Project (n=5840) (ANOVA $p<0.01$). There were 814 female and 821 male participants with mean age of 41.49 years (41.49 ± 12.18) and no difference between women and men (women 42.03±14.44, men 41.35±12.41; $p>0.01$, t-test). The research was performed in small towns with mixed urban and semi-urban population. All participants signed an informed consent and the whole study was approved by the Central Research Ethics Committee.

2.2 Assessment of diabetes. Subjects who reported having diabetes and those taking oral hypoglycemic agents or insulin were considered as persons with previously diagnosed diabetes. Those with no such history but with fasting blood glucose (FBG) of 7 mmol/l or above were considered to have previously unknown diabetes. According to the WHO criteria, the participants without previous history of diabetes and with FBG greater than 6.1 and lower than 7.0 mmol/l were diagnosed as having IFG [13].

2.3 FBG, fasting plasma insulin (FPI), body mass index (BMI) and IR assessment. Glucose and insulin concentrations were analyzed from frozen samples using standard methods: glucose oxidase was determined [14] (Thermo Trace, Noble Park, Victoria, Australia) on a spectrophotometer (AU 600 Olympus, Tokyo, Japan) and insulin was measured by a solid-phase radioimmunoassay (Diagnostic Products Corporation, Los Angeles, CA, USA), with a reference value of < 22 μU/l. The analyses were made centrally at the Vuk Vrhovac University Clinic laboratory with continuous external quality control [15]. Homeostasis model assessment insulin resistance index (HOMA-IR) was calculated as IR = insulin/ (22.5e -ln BG) to assess insulin resistance [16]. BMI was calculated as weight (kg) divided by the square of height (m).

2.4 Statistical analyses. Variance homogeneity was tested using Lindman's test prior to the analysis of correlation and between-group differences. Normality of distribution was tested using Shapiro-Wilk's W test. Differences between groups of independent variables were analyzed using t test (for two groups), ANOVA (for three or more groups of variables) and Bonferroni post hoc procedure. Differences in the prevalence of individual conditions were compared using chi^2 test.

The level of significance of correlation between variables and the correlation trend were analyzed by Pearson Correlation Test. Statistical significance was defined as a p value of 0.01 or less in all analyses, carried out using STATISTICA version 7.0.

3. RESULTS

Fifty-eight persons with previously known diabetes and 42 with previously unknown diabetes were detected based on the described criteria, yielding an estimated prevalence of 6.1% (95% confidence interval: 4.59-7.64) in the 18-64-year age group. The difference in diabetes prevalence was statistically significant by age, but not by gender and regions (Table 1).

Among the subjects with no history of DM or drug therapy for diabetes there were 2.7% of those with FBG >7 mmol/L. The frequency of previously unknown DM was significantly higher in men compared to women (3.8% vs. 1.5%; chi^2 $p<0.001$), with a significant increase in age (1.5% vs. 1.4% vs. 2.8% vs. 4.6%; chi^2 $p=0.013$) and with an even regional distribution (3% vs. 2.5% vs. 1.8% vs. 2.9%; chi^2 $p=0.755$) (Figure 1).

In total, the calculated number of undiagnosed persons with diabetes to every 100 diagnosed was 72 (31-114 per region). Distribution between different types of diabetes mellitus was not analyzed.

There were 11.3% of subjects with FBG equal to or higher than 6.1 mmol/L and less than 7.0 mmol/L (IFG) among those with no history of DM or receiving drug therapy for diabetes. The frequency was significantly higher in men than in women (14.6% vs. 7.9%), significantly increasing with age, and revealing significant differences among the studied regions (higher in the two continental regions (Osijek and Zagreb) than in the two Mediterranean ones (Rijeka and Split). (Figure 1).

Subjects without a previous history of diabetes who were diagnosed with DM or IFG in this study had significantly higher BMI indices than individuals with normal FPG in both men (29.18 ± 4.68 vs. 28.09 ± 4.06 vs. 26.53 ± 3.27; ANOVA $p<0.001$) and women (28.07 ± 5.21 vs. 28.42 ± 4.50 vs. 25.10 ± 3.95; ANOVA $p<0.001$), whereas the difference in BMI indices between the subjects with DM and those with IFG was not significant.

Mean FPI and FBG, and HOMA-IR index are shown in Table 2. Insulin concentrations were significantly higher in men as compared to women ($p<0.01$, chi^2 test). HOMA-IR greater than 1 was present in as much as 40.4% of the subjects, significantly more frequently in men than in

women ($p<0.01$, chi^2 test) and in higher BMI categories ($p<0.01$, chi^2 test), with an uneven distribution per regions ($p<0.01$, chi^2 test). Correlation between BMI, FBG, IR and age was revealed for the entire sample as well as for women and men separately (Pearson's, $p<0.01$).

ANOVA revealed significant differences in FBG by age, gender and region ($p<0.01$), and the interaction of age and region ($p<0.01$). A significant difference in FPI was revealed by age ($p<0.01$) and the interaction between age and region ($p<0.01$), but not by gender ($p=0.06$) or region ($p=0.04$). For HOMA-IR the difference was significant by age, gender and region as well as by the interaction of age and region ($p<0.01$).

4. DISCUSSION

The results of this study revealed a higher diabetes prevalence in Croatia than estimated by the IDF atlas from 2000 [6], comparable to the IDF atlas estimates from 2006 [3]. The present results would be expected to be comparable to the 2000 estimate, as the survey was conducted in the period from 1995 to 97. It is possible that the study [17] used for the 2006 estimate was carried out in a population more similar to the Croatian one and using a more appropriate methodology. The achieved prevalence of diabetes in Croatia was shown to be higher than estimates for Croatia and the neighbouring countries (Bosnia and Herzegovina 3.4 % and Slovenia 4.3 % for the 20-65-year age groups) published by King et al. [1] The more recent prevalence estimates have been higher in the older age group as well (Bosnia and Herzegovina 9.6%, Slovenia 9.6 % for the 20-79-year age groups) [3]. The difference could also be explained by the different method used (OGTT compared to fasting plasma glucose in our study).

The real prevalence of diabetes can be presumed to be somewhat higher, as OGTT was not performed in our study, and so persons with diagnostically significant 2-hour post-load glucose values remained undiagnosed. Two-hour value is less reproducible than FBG [18], which is why the methodology used (a questionnaire and FBG) is considered sufficient for epidemiological purposes [13]. It has been shown that FPG alone underestimates the prevalence of diabetes in women and elderly men of European descent [19,20,21]. Hence, without data obtained by OGTT, the obtained prevalence can be hypothesized to be somewhat underestimated [22]. The prevalence in women in this study did not significantly differ from that in men.

The high prevalence of diabetes in Europe might be associated with relative poverty, as suggested by the results of a study in a British inner city [23]. The average annual household income in

Croatia was less than 15,000 US$ in the observed period [24], which is comparable to the low-income households in the developed European countries [23]. This might in part account for a seemingly higher diabetes prevalence in Croatia, and would be interesting to examine across comparable transitional economies. On a global level, a huge increase in diabetes prevalence is expected [25], for which reason further periodic surveys should be carried out in Croatia on a regular basis.

Although a small country, Croatia has natural regional differences: a part of the country is Mediterranean, while the other part is continental. Diabetes prevalence was not different among the regions although there were significant differences in FBG by age, gender and region.

There were 11.3% of participants with IFG, which was more frequent in men than in women (14.6% vs. 7.9%), significantly increasing with age. The overall prevalence of IFG was lower than that reported for the US [26] and higher than the prevalence from an Indian study [27], being in range with recent studies on the population of Iran [28].

However, it is interesting to note that the prevalence of IFG showed an uneven regional distribution, being lower in the Mediterranean regions than in the continental ones, although the same pattern was not observed for the prevalence of diabetes.

The high proportion of undiagnosed persons with diabetes is comparable to the average of 0.7 obtained from thirteen European studies from the DECODE Study [20] and the one from Denmark [29]. The proportion of undiagnosed persons was higher in men and lower in older and obese individuals, as reported in most studies [18,20,29,30]. As these data depend on various factors, there might even be as many as 150 undiagnosed patients with DM to every 100 diagnosed individuals with diabetes [31].

A significant difference in the proportion of undiagnosed diabetes within Croatian regions warrants attention. It might reflect an uneven awareness of diabetes in the country, pointing to the need for regional educational programs for health care professionals.

As expected from the previously published data on the impact of overweight on the development of diabetes [32] and on BMI in diabetic patients [33], BMI indices were found to be higher in the subjects with newly diagnosed DM and IFG than in those with normal FPG.

HOMA-IR > 1 was found in as much as 40.4% of the respondents, significantly more frequently in men than in women and in higher BMI categories, the correlation between BMI, FBG, IR and age being as expected.

The prevalence of persons with HOMA-IR index greater than 1 was unevenly distributed: it was higher in one continental and one Mediterranean region (Osijek region: 61.6% and Rijeka region: 59.6%) and lower in the other pair (Zagreb region: 28.0% and Split region: 27.6%). In spite of the 40.4 percent prevalence, HOMA-IR index was lower than that in the previously published studies [34].

The results of this survey revealed a higher prevalence of diabetes in Croatia than previously estimated, whereas that of impaired fasting glucose was as expected. A significant difference in the proportion of undiagnosed persons with diabetes among the geographic regions warrants further attention.

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TABLES AND FIGURES

FIGURE LEGENDS

Figure 1: Diabetes and impaired fasting glucose in persons with no previous history of diabetes as percentage of participants.

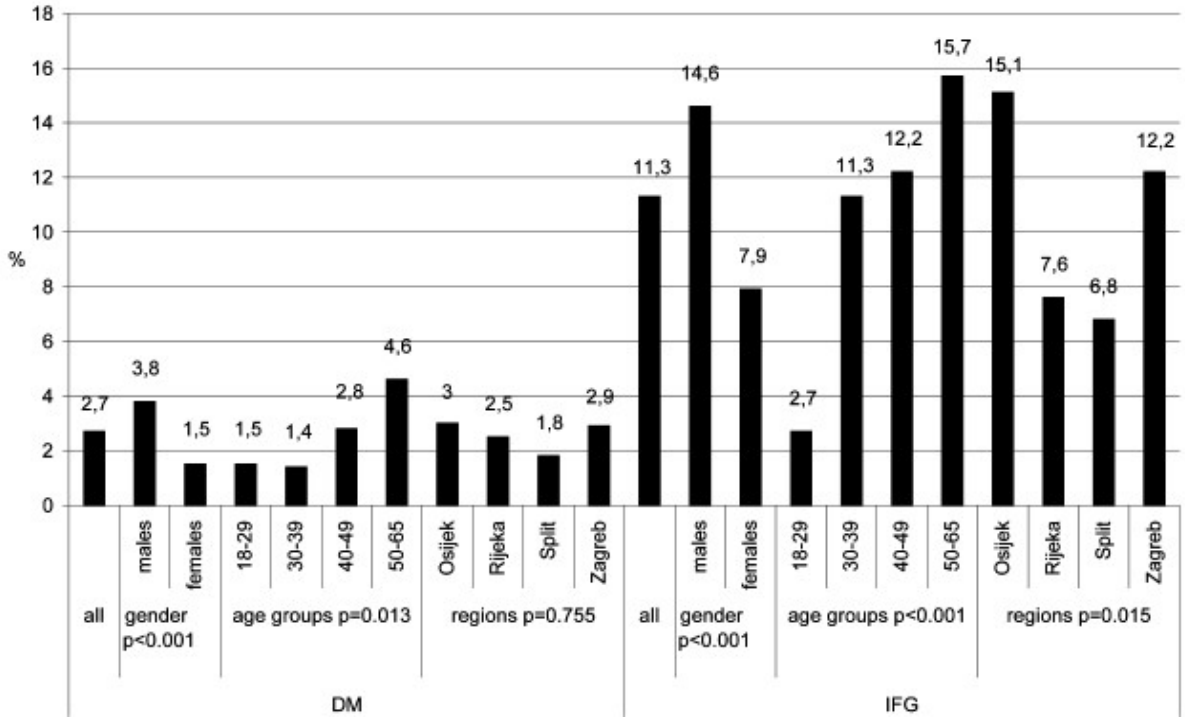

Table 1: Diabetes prevalence and differences in prevalence according to gender, age and region

	prevalence (%)	99% CI	p value
overall	6.1	4.59-7.64	-
gender			0.122
men	7.1	4.76-9.37	
women	5.2	3.16-7.16	
age			p<0.01
18-29	1.9	0.37-5.75	
30-39	2.0	0.38-3.63	
40-49	6.9	3.68-10.21	
50-65	12.1	8.25-16.01	
region			0.690
Osijek	6.7	3.73-9.58	
Rijeka	5.9	2.51-10.18	
Split	7.1	3.24-10.9	
Zagreb	5.3	2.85-7.66	

Table 2: Mean fasting plasma insulin (FPI) and glucose (FPG) concentrations, and mean HOMA insulin resistance indexes (HOMA-IR), with standard deviation (SD)

	TOTAL N=1635		men N =821		women N =814	
	mean	SD	mean	SD	mean	SD
FPI	6.72	8.55	7.12	8.92	6.32	8.14
FBG	5.03	1.40	5.18	1.51	4.83	1.25
HOMA-IR	1.45	2.38	1.58	2.53	1.31	2.22