Clinical Medicine Research
2021; 10(3): 95-101
http://www.sciencepublishinggroup.com/j/cmr
doi: 10.11648/j.cmr.20211003.15
ISSN: 2326-9049 (Print); ISSN: 2326-9057 (Online)

A 5-year Follow-up of Subjects with Fasting Plasma Glucose Above 5.6 mmol/l Found in a Screening Study of the Bulgarian Population

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To cite this article:

Anna-Maria Borissova, Jordan Vlahov, Alexander Shinkov, Lilia Dakovska, Boyana Trifonova. A 5-year Follow-up of Subjects with Fasting Plasma Glucose Above 5.6 mmol/l Found in a Screening Study of the Bulgarian Population. *Clinical Medicine Research*. Vol. 10, No. 3, 2021, pp. 95-101. doi: 10.11648/j.cmr.20211003.15

Received: May 22, 2021; **Accepted**: June 9, 2021; **Published**: June 16, 2021

Abstract: The WHO and many other diabetes organizations recommend performing OGTT at fasting plasma glucose ≥ 6.1 ÷ 6.9 mmol/L mmol/L, but ADA indicates a lower cut-off for this parameter - ≥ 5.6 ÷ 6.0 mmol/L mmol/L. *Aim:* We decided to evaluate the role of baseline glucose tolerance for the development of Diabetes or Prediabetes over time by a prospective study of the changes in glucose tolerance 5 years after the last nationwide cross-sectional study in Bulgaria. *Material:* The study included 204 subjects from a total of 2033 tested 5 years ago. These 204 individuals were selected among those with a fasting plasma glucose (FPG) 6.1 – 6.9 mmol/L (Group 1) and FPG ≥ 5.6 ÷ 6.0 mmol/L (Group 2) found during the screening in 2012. As a part of the screening in 2017, a standard OGTT was performed (WHO'1999) and HbA1c was determined. *Methods:* Plasma glucose was measured in all the studies by an automated glucose-oxidase analyzer (Glucose Analyzer II, Beckman Coulter, Inc). HbA1c was determined by immunoturbidimetric method after hemolysis of a whole blood sample. *Results:* Half of the subjects with FPG 6.1 - 6.9 mmol/L in 2012 had Diabetes during the follow up, 31% remained in the Prediabetes group and 19% had Normal glucose tolerance (NGT) in 2017. Among the subjects with FPG ≥ 5.6 - 6.0 mmol/L in 2012, 24.7% had Diabetes in 2017, 34.6% - Prediabetes and 40.7% had NGT. The difference in the Diabetes prevalence between the two groups was significant – 50% vs. 24.7% (T=2.443, P < 0.02). In 5 years'time, 29.9% of the Individuals who had FPG ≥ 5.6 - 6.9 mmol/L in 2012, became Diabetics, 33.6% became Prediabetics and only 36.3% had NGT. In 57% (35/61) of the diabetics the disease was newly diagnosed and in about 2/3 of the cases it was decompensated (HbA1c ≥ 7%). During the 5-year period, Diabetes was diagnosed in 26 (42.6%) persons and 34.6% of them were in metabolic decompensation under treatment. *Conclusion:* The most important conclusion from our screening from 2017 is that ¼ people with FPG ≥ 5.6 – 6.0 mmol/L after a few years became diabetics, so systematic efforts should be directed towards this border group.

Keywords: FPG over 6.1 mmol/L, FPG over 5.6 mmol/L, Risk of Diabetes, Risk of Prediabetes

1. Introduction

Two cross-sectional, multicenter population-based studies (2006 and 2012) were conducted in Bulgaria, related to the most common endocrine diseases (diabetes, thyroid diseases) and cardiovascular risk factors (arterial hypertension, obesity, dyslipidemia, chronic kidney disease) [1, 2]. The geographical distribution of the nests, the size and the structure of the sample correspond to the structure of the population in the country after in-depth analysis with biostatistics and calculations based on the actual data from

the respective national census in the country [3, 4]. A comparative analysis of the two studies was performed.

A general change in the prevalence of diabetes (known and newly diagnosed) was found for the study period from 7.9% (190/2396) in 2006 to 9.55% (194/2033) in 2012, P = 0.06. The relative increase was 20.88% or 3.5% per year [5].

The changes we noticed, were similar to those in other countries. Data on the regional prevalence of Diabetes mellitus and Impaired Glucose Tolerance (IGT) were published in 2003 in the Second edition of the International Diabetes Federation (IDF) Diabetes Atlas - in Europe there were 48 million patients with Diabetes (prevalence 7.8%) and 63 million patients with Prediabetes (prevalence 10.2%) [6]. Data from the IDF Diabetes Atlas, published in 2011, show that at the time there were 55 million diabetics in Europe, ie. the prevalence increased to 8.4%. The number of undiagnosed patients with Diabetes in Europe is 21 million or 38% of all patients with the disease [7, 8]. In the United States, there is also a 39% increase in the prevalence of known diabetes in the two periods 1988-1994 compared to 2005-2006 (from 5.1% to 7.1%) [9].

We found a direct link between an increase in the incidence of diabetes for this 6-year period and two main factors - age and gender. An increase in diabetes prevalence was found in both genders, but was more prominent in males, in whom it was marginally significant (by 2.3% or a relative increase of 25%: 9.2% in 2006 vs. 11.5% in 2012, P = 0.06). In the female subgroup, the increase was minimal, from 6.9% in 2006 to 7.8% in 2012, a relative increase of 13% (NS). We found a strong relationship between age and the increase in diabetes prevalence between 2006 and 2012. Moreover, the age group 50–59 years seemed critical with an increase in the disease prevalence from 9.4% (49/523) in 2006 to 15.7% (53/338) in 2012, P < 0.01. A logistic regression model including the age was created and the statistical analysis showed that age is a significant factor, particularly among people who were over 45, associated with an OR 7.3 (4.4 - 11.9). [5]. The role of baseline glucose tolerance in the development of Prediabetes or Diabetes was a new problem for us, which we decided to explore over time. The American Diabetes Association (ADA, 2013) cites fasting plasma glucose (FPG) range of 5.6 - 6.9 mmol/L as a risk factor for diabetes and cardiovascular disorders [10]. On the other hand, the IDF recommends additional FPG measurement or HbA1c or oral glucose tolerance test (OGTT), when a random blood glucose is detected between 5.6 mmol/L and < 11.0 mmol/L [11]. For many years, the World Health Organization (WHO, 1999) reported a cut off of FPG for Prediabetes 6.1 - 6.9 mmol/L [12]. Prediabetes is defined as an intermediate metabolic state between Normoglycemia and Diabetes and includes those with IGT and Impaired Fasting Glucose (IFG) [13].

Although IGT is systematically defined as a two-hour plasma glucose concentration of 7.8 - 11.0 mmol/L during the OGTT, the cut-off point for the diagnosis of IFG remains controversial. The WHO defines Impaired Plasma Glucose (IPG) as fasting plasma glucose of 6.1 - 6.9 mmol/L [11], while the ADA Recommendations for Diabetes in 2003 and 2013 give a cut-off point of 5.6 - 6.9 mmol/L [10, 14]. This ADA proposal for such a low cut-off point for Fasting blood glucose is controversial and has not been accepted by other international diabetes organizations [15, 16].

The aim of the present study is to compare individuals with defined Prediabetes according to IFG-ADA (fasting glucose 5.6 - 6.9 mmol/L) or IFG-WHO (fasting glucose 6.1 - 6.9 mmol/L), and/or with impaired glucose tolerance 2-hour plasma glucose concentration 7.8 - 11.0 mmol/L during an OGTT), and during a 5-year period to follow prospectively the two groups of already studied population in 2012, as well as assessing the role of baseline glycemia in the manifestation of Diabetes and Prediabetes after this period of time.

2. Study Design Based on Available Data

Last cross-sectional epidemiological study on diabetes in our country was carried out in January–February 2012. Thirty-six nests were selected in 12 regions, and 3450 adult subjects were selected randomly from the national population registry. A total of 2032 subjects (58.8%) agreed to participate, signed an informed consent approved by the local Ethics Committee at the University Hospital of Endocrinology in Sofia and were included in the study. The research was conducted in accordance with the Declaration of Helsinki-1964 [17]. The females were 1076 (52.9%) and 957 were males (47.1%) and the mean age of the participants was 49.3 ± 14.7 years (20–80). The age structure of the samples in all Bulgarian studies was planned according to the IDF methodology for diabetes prevalence assessment in adults [18]. The studied population was adjusted for gender, age, and type of place of living according to the reports of the National Statistical Institute [4]. The sample size was calculated with the expectation of at least 6% prevalence of the studied variable among the target population, confidence level 95%, and an absolute precision 5%. The Diabetic status has been defined according to the criteria of the WHO since 1999 [12]. In the case of FPG ≤ 6.1 mmol/L the person is qualified as healthy, between 6.1 - 6.9 mmol/L an OGTT was performed to examine the glycemia at 120 minutes, and in the case of fasting glucose > 7.0 mmol/L the person is defined as diabetic. In fasting blood glucose = 7.0 mmol/L, OGTT was also performed to prove a second pathological point. Two persons (over 60 years old, a man and a woman living in a village) refused to conduct an OGTT - 2.02%. The remaining 97 screened persons (4.77%, 97/2032) underwent standard OGTT - 39 (40.2%) women, 58 (59.8%) men. By age categories, the surveyed 97 persons were distributed as follows: 20-44 y - 16 (16.5%); 45-59 y - 34 (35%); over 60 y - 47 (48.5%). Diabetes was detected in 23 (23.7%) participants and in the remaining 74 (76.3%) persons - Prediabetes (n-32, 33% with IGT and n-42, 43.3% with IFG).

We decided to follow the dynamics of glucose tolerance 5 years later in 2017, inviting all these 74 people with proven Prediabetes in 2012.

3. Material

All 74 participants with proven Prediabetes (FPG 6.1 ÷ 6.9 mmol/L) or/and 2-hour plasma glucose concentration of 7.8 - 11.0 mmol/L formed Group 1. Additionally, Group 2 of all subjects (n=268) with FPG ≥ 5.6 ÷ 6.0 mmol/L was formed, in which no OGTT was performed in 2012. Thus, a total 342 subjects were invited for a follow up five years later in 2017. Seven of these subjects (2%) had died, 204 (59.64%) accepted the invitation and 131 (38.3%) refused or could not be reached. The whole group of 204 participants was of average age - 57.36 ± 16.50 years (29-80 years). A distribution was made by sex and age as follows: men - 118 (57.8%) resp. women - 86 (42.2%); 20-44 years- 48 (23.5%), 45-59 years - 31 (15.2%), ≥60 years- 125 (61.3%). The two groups which had already been formed based on the results of the initial screening in 2012, were changed in 2017: Group 1 - subjects with improved Prediabetes (n-42) and Group 2 subjects with IFG ≥ 5.6 ÷ 6.0 mmol/L (n-162).

4. Methods

4.1. Methodology

The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (1997) defined Impaired Fasting Glucose (IFG) as Fasting Plasma Glucose (FPG) levels between 5.6 and 6.9 mmol/L and Impaired Glucose Tolerance (IGT) as 2-h Plasma Glucose (PG) levels after 75 g Oral Glucose Tolerance Test (OGTT) between 7.8 and 11.0 mmol/L [19], which is confirmed in the report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (2003) and is reflected in the Standards of Medical Care in Diabetes-2017 by the American Diabetes Association [20, 21].

It should be noted that the WHO and many other diabetes organizations set the IFG cut-off at 6.1 mmol/L, which we also used in our screenings in 2006 and 2012 [12], [22, 23, 24]. In the present screening, we also adhered to the same cut-off for IFG, using the same laboratory, apparatus and team (nurse, laboratory assistant) in the tests.

In 2009, the International Diabetes Committee of the ADA, the IDF and the European Association for the Study of Diabetes (EASD) recommended the use of HbA1c to diagnose Diabetes at a threshold of ≥ 6.5% [25].

In a cross-sectional study of Tankova T. (2012) among 2231 Bulgarians with an increased risk of developing Diabetes mellitus, an average level of HbA1c of 5.5% was found as a limit for normal glucose tolerance. The authors recommend screening of individuals with HbA1c ≥ 5.5% to detect undiagnosed Prediabetes, and of individuals with HbA1c ≥ 6.1%, the indicator (with high specificity and sensitivity) can be used to diagnose Diabetes mellitus [11, 26].

Our study shows a significant correlation between plasma glycemic level at 120 minutes of OGTT and value of HbA1c (Y = 0.0866x + 5.3366, R2 = 0.2896) [27].

It should be emphasized that the diagnostic test must be performed with a certified method from the National Program for Standardization of Glycated Hemoglobin (NGSP) and standardized according to the Diabetes Control and Complications Trial (DCCT) [30].

Currently, according to the IDF Recommendations for accidental glycemia ≥ 5.6 mmol/L and < 11.0 mmol/L, Fasting glycemia must be measured or OGTT performed or HbA1c determined with a certified method. Four ways to diagnose diabetes are officially accepted [28, 29].

4.2. Laboratory Tests

Plasma glucose: Blood was drawn between 7 and 9 a.m. after an overnight fast. Plasma glucose was measured in all of the studies by an automated glucose-oxidase analyzer (Glucose Analyzer II, Beckman Coulter, Inc), and all samples were processed by a single laboratory technician.

Daily calibration and quality control were performed according to the manufacturer recommendations with a standard Presinorm (Roche) – glucose 4.9 ± 0.3 mmol/L and Presipath (Roche) – glucose 12.6 ± 0.5 mmol/L.

HbA1c: Venous blood was taken separately in a special tube with the anticoagulant EDTA for the determination of HbA1c by immunoturbidimetric method after hemolysis of a whole blood sample. The method was certified following the National Program for Standardization of Glycated Hemoglobin (NGSP) and standardized according to the Diabetes Control and Complications Trial (DCCT) [30].

4.3. Statistical Processing

The data were analyzed with SPSS for Windows v.13.0. A descriptive analysis and a diagnostic analysis were performed to assess the presence of statistically significant effects by conducting statistical hypothesis tests for certain relationships, including variables measured at nominal or ordinal scales. Suitable assumptions about the variable distribution were made to measure the significance levels of the analyzed empirical characteristics. Unless otherwise stated, the reference point for significance was 95% (risk of I type error 5%).

5. Results

The 204 participants, who responded to the invitation, were divided into two groups: 1. Group 1 - 42 (20.6%) people with FPG 6.1 - 6.9 mmol/L and conducted OGTT, classified as Prediabetics in 2012 and further divided into: IGT - 14 (33.3%) and IFG only - 28 (66.7%). 2. Group 2 – 162 (79.4%) people with FPG ≥ 5.6 ÷ 6.0 mmol/L and without conducted OGTT in 2012.

It was found that 26 of the participants had already been diagnosed with Diabetes, which appeared in the period between the two screenings in 2012 and 2017, so OGTT was conducted only among the rest of them.

Fasting plasma glucose was above 7.00 mmol/L in 35 of the tested people. According to the results obtained in 2017 from FPG and at 120 minutes from OGTT, participants were divided into four categories: 0 – Normal glucose tolerance, 1 – IFG, 2 – IGT (at 120 minute of OGTT), 3 – Diabetes, table 1.

Table 1. *Distribution of the studied subjects based on the OGTT in 2017.*

categories	Category in 2017	Number of patients	%
0	Normal glucose tolerance	74	36.3%
1	IFG	33	16.2%
2	IGT (at 120 minutes of OGTT)	36	17.6%
3	Diabetes	61	29.9%
	Total	204	100%

The same distribution was made for each of the two groups specified in 2017: Group 1 (n-42) with proven Prediabetes (FPG 6.1 – 6.9 mmol/L) and Group 2 (n-162) with FPG ≥ 5.6 - 6.0 mmol/L. Table 2 shows changes that occurred in each of the groups in 2017 compared to 2012 year.

Table 2. *Distribution of the participants in Group 1 and Group 2 based on the results of the OGTT in 2017.*

Groups according status in 2012 y	Category in 2017 y	Number	%
	3	21	50%*
Group 1 proven Prediabetes (n=42)	2	9	21.5%
FPG 6.1÷6.9 mmol/l) and after OGTT	1	4	9.5%
	0	8	19%
	3	40	24.7%*
Group 2 (n=162)	2	27	16.7%
FPG ≥ 5.6÷6.0 mmol/l and without OGTT	1	29	17.9%
	0	66	40.7%

Additional studies of HbA1c showed that the mean level of HbA1c for the whole group (n-204) was 5.51%, in diabetics (n-61) - 6.65%, in participants with Prediabetes (n-69) - 5.72% and in persons with Normal glucose tolerance (n-74) - 5.21%. The following Table 3 presents the frequency at the different HbA1c levels for each of these groups.

Table 3. *Distribution of participants - with Diabetes (known, newly diagnosed), with Prediabetes and Healthy persons according to the level of HbA1c.*

Level of HвA1c (%)	26 known diabetics, number (%)	35 newly diagnosed diabetics, number (%)	69 persons with Prediabetes, number (%)	74 Healthy persons, number (%)
5.00-6.00		8 (23.0)	67 (97.1)	74 (100)
6.00-7.00	17 (65.4)	22 (63.0)	2 (2.89)	
7.00-8.00	3 (11.5)	5 (14.0)		
8.00-9.00	4 (15.4)			
>9.00	2 (7.7)			
Total	26 (100)	35 (100)		

6. Discussion

In 2012, a screening for diabetes was conducted in Bulgaria among 2032 people from 12 regions. The screening established 9.55% prevalence of Diabetes in Bulgaria. In ¼ of the cases it was newly diagnosed Diabetes. According to the WHO 1999 criteria, as well as the current Bulgarian recommendations for Diabetes, OGTT was performed in 4.77% (97/2032) of all participants with FPG 6.1 ÷ 6.9 mmol/L [12, 22, 23, 24]. Thus, three groups of individuals with Impaired Glucose Tolerance were identified:

1) Impaired Fasting Glucose (IFG): 120 minutes glucose <7.8 mmol/L
2) Impaired Glucose Tolerance (IGT): 120 minutes glucose 7.8–11.0 mmol/L
3) Diabetes mellitus: 120 minutes glucose ≥ 11.1 mmol/L

Newly diagnosed Diabetes had 24.2% (n=23), 29.5% (n=28) had IGT, and 46.3% (n=46) - IFG. These 74 people with proven Prediabetes in 2012 were invited for re-examinations after 5 years. Forty-two (56.8%) people of them responded. From 268 people invited for re-examinations with FPG of ≥ 5.6 - 6.0 mmol/L in 2012, for whom no OGTT was performed at that time, 162 (60.4%) people responded or a total of 204 people - Group 1 (subjects with improved Prediabetes, n-42) and Group 2 (with IFG ≥ 5.6 ÷ 6.0 mmol/L, n-162).

The results of the repeated studies 5 years later showed that half of the prediabetic participants (FPG 6.1 ÷ 6.9 mmol/L) in 2012 had Diabetes at follow up, 31% remained in the Prediabetes group and 19% had Normal glucose tolerance (NGT) in 2017. Among those with FPG ≥ 5.6 - 6.0 mmol/L in 2012, 24.7% had Diabetes in 2017, 34.6% - Prediabetes and 40.7% had NGT. The difference in Diabetes prevalence between the two groups reached statistical significance – 50% vs. 24.7% ($T = 2.443$, $P < 0.02$). Although no statistical significances were found among the other categories, the difference between the two groups with NGT was quite impressive - 19% in Group 1 (the initial Prediabetes in 2012) vs. 40.7% in Group 2 (the subjects with FPG ≥ 5.6 - 6.0 mmol/L in 2012), $T = 1.288$, NS. The difference increased twice. It should be emphasized that the recommendation for regular screening in proven Prediabetes is extremely important for early detection of Diabetes [24, 31, 32]. Moreover, timely and adequate therapeutic intervention is

another important factor in the development of the disease.

In 2017, 29.9% (61/204) of the people tested in 2012 had Diabetes. Diabetes was found in 57.4% (n-35) during the follow-up in 2017. Diabetes was diagnosed during the 5-year period between the two studies in 42.6% (n-26). Therefore, we must conclude that in 57.4% of the cases (35/61) Diabetes was newly diagnosed, i.e. it had existed for years and was diagnosed only after our active intervention.

Regarding people with newly diagnosed Diabetes during the screening in 2017, 14% (5/35) of them not only had diabetes but also metabolic decompensation (HbA1c > 7%). Thus, it can be assumed that in more than 2/3 of the participants in this subgroup, the disease had been present for a long time. 63% had HbA1c between 6.5% and 7%, and 14% - over 7%. It turned out that only 23% of the people with newly diagnosed Diabetes were diagnosed on time (with HbA1c between 5.0 and 6.0%).

Twenty-six diabetics diagnosed during this 5-year period had the following treatment: Metformin - 19 (73%), SU - 2 (7.7%), DPP4i - 1 (3.8%), GLP-1RA - 1 (3.8%), SGLT2i - 1 (3.8%), Insulin - 2 (7.7%). As can be seen from Table 3, in the group with known Diabetes 65.4% had HbA1c below 7%, 34.6% had HbA1c over 7% despite the treatment, i.e. they were decompensated. These data showed that timely diagnosis of Diabetes as well as regular therapeutic monitoring are important.

7. Conclusion

Our task in this study was to illustrate with our material in a prospective study, the benefit of screening of both groups of participants – Group 1 with proven Prediabetes (FPG 6.1 ÷ 6.9 mmol/L) and Group 2 with FPG ≥ 5.6 - 6.0 mmol/L. Although, in the second group, newly diagnosed Diabetes was only half of that found in individuals with proven Prediabetes, screening of the group with FPG ≥ 5.6 - 6.0 mmol/L would help detect more diabetics. Our specific data illustrate that. Approximately 24.7% of the people with FPG over ≥ 5.6 - 6.0 mmol/L became diabetics. The risk of Diabetes was doubled among those with Prediabetes (FPG 6.1 ÷ 6.9 mmol/L) as compared to that with FPG ≥ 5.6 - 6.0 mmol/L [50% vs 24.7% ($T = 2.443$, $P < 0.02$)]. The screening for Diabetes of the population with Prediabetes or elevated FPG between ≥ 5.6 - 6.0 mmol/L should be obligatory, as to reduce the proportion of late-diagnosed diabetics.

Of the 61 participants with Diabetes occurring after 2012, 57.4% or more than half (n=35) were found during the survey in 2017, hence Diabetes might have existed undiagnosed and untreated for several years. The reason for this assumption is that at diagnosis 63% of this group had HbA1c between 6.5% and 7%, and 14% - over 7%. This decompensation needs time to occur. The other main conclusion from the data of the present study is that in addition to timely diagnosis, adequate treatment is also needed. When treating diabetics who have already been diagnosed, their compensation should be monitored regularly to reduce the incidence of decompensated Diabetes. The proportion of treated diabetics in metabolic decompensation turned out to be too high - 34.6% in our material.

The most important thing in the end is that in our screening from 2017, it was found that ¼ of people with FPG ≥ 5.6 - 6.0 mmol/L after a few years become diabetics and this should be well remembered in order to direct systematic efforts to this controversial border group of people.

We consider it necessary to introduce a mandatory standard of diagnostic behavior and people with Impaired Fasting Glucose and especially those with Impaired Glucose Tolerance to be under annual glycemic control, so as not to miss the moment of its transformation into Diabetes.

Conflicts of Interests

All the authors do not have any possible conflicts of interest.

Acknowledgements

The authors thank the endocrinologists who provided *local support:* E. Dimitrova (Vidin), J. Stoyanova (Montana), V. Jotova (Troyan), R. Bobeva, A. Momtcheva, V. Sabev (Sliven), J. Gerenova (Stara Zagora), P. Velkova, D. Jekova (Dobritch), B. Savova, A. Kisselova (Russe), V. Margaritov (Byala), T. Kotselova (Blagoevgrad), and K. Anastassov (Sandansky); *Technical support:* A. Popov, G. Michaylov, K. Pantcheva, G. Antalavitcheva, T. Kornilova, S. Michaylova, B. Petrovska, E. Blajeva, and A. Palmarev.

This work was supported by grants from the Bulgarian Society of Endocrinology (Project Number 5/2012) as part of the National Epidemiological Program for Endocrine diseases in Bulgaria, 2012-2017.

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