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The Importance of Prediabetes Screening in the Prevention of Cardiovascular Disease

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ABSTRACT

Background: Prediabetes is a disordered state of glucose metabolism defined by an elevated blood glucose level that is below the level required for the diagnosis of diabetes. Prediabetes is associated with an increased risk of cardiovascular disease. The onset and progression of macrovascular disease occur during the prediabetes phase. Early diagnosis and screening of prediabetes are essential steps to prevent diabetes and its associated complications. **Objective:** To assess the prevalence of prediabetes and undiagnosed diabetes in patients with cardiovascular disease according to the ADA criteria. **Methods:** This cross-sectional study included 2968 a high cardiovascular risk patients aged 40 to 75 years admitted to the Department of Internal Medicine. Sociodemographic variables and other relevant medical history information were collected by the researchers during the clinical interview. A fasting blood sample was obtained to determine HbA1c levels and other relevant laboratory findings. **Results:** Of the total number of participants, 1496 participants were not diagnosed with diabetes, 485 (32.4%) of them had HbA1c values indicating prediabetes and 158 (10.6%) of them had HbA1c values indicating new diagnosed diabetes. Up to one-third of those with undiagnosed prediabetes had already been diagnosed with cardiovascular complications. **Conclusion:** Routine screening of glycemic metabolism could be valuable in identifying high-risk individuals before a cardiovascular event occurs.

Keywords: prediabetic state, glycated hemoglobin A, cardiovascular diseases, preventive medicine.

1. BACKGROUND

Prediabetes is an impaired state of glucose metabolism defined by elevated blood glucose levels that fall below the level required for a diagnosis of diabetes (1). Prediabetes refers to an intermediate stage of dysglycemia with glycemic variables between normal and diabetes in individuals who are at high risk of developing diabetes (2). It is typically identified by laboratory measurement of fasting blood glucose (FBG) or an oral glucose tolerance test (OGTT) as impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), or based on glycosylated hemoglobin (HbA1C) levels (3).

Prediabetes is defined as one of the two states of an asymptomatic phase along the continuum of hyperglycemia, with an estimated duration of 8.5 to 10.3 years (4). The second phase is preclinical latent diabetes between the biological onset of diabetes and the clinical diagnosis of the disease that lasts 4 to 7 years (5). Individuals with pre-diabetes are at a high risk of developing type 2 diabetes (T2D) and are phenotypically similar to patients with T2D, with a higher body mass index (BMI), higher blood pressure and dyslipidemia (6). The prevalence of abnormal blood glucose metabolism grows worldwide, and estimations are that more than 600 million people will develop prediabetes and diabetes by 2045 (7). Current global prevalence of prediabetes in adults is about 7.3%, with a projection of 5–10% progression to overt type 2 diabetes each year (8). As diabetes progresses, it becomes increasingly difficult to treat and current evidence suggests that diabetes prevention is most effective when implemented early in the disease process (9). The early diagnosis and screening of prediabetes are essential steps towards the prevention of diabetes and associated complications. The American Diabetes Association (ADA) recommends screening adults over 45 years old without known diabetes every 3 years (3). Fasting plasma glucose (FPG) and the 2 h glucose concentration following an oral glucose tolerance test (OGTT) are the traditional meth-

ods of diagnosis (10). ADA definitions for prediabetes include impaired fasting glucose (IFG) = fasting glucose 5.6–6.9 mmol L–1 and impaired glucose tolerance (IGT) = 2 h glucose 7.8–11.0 mmol L–1. ADA has subsequently recommended glycated hemoglobin (HbA1c) levels between 5.7% and 6.4% (39 to 46 mmol/mol) to define prediabetes (3). Haemoglobin A1c concentration serves as a long-term indicator of glucose metabolism regulation because it reflects the average blood glucose concentrations within the erythrocytes' lifespan and testing is especially convenient because there is no need for fasting and blood sampling is not limited to a specific time of the day (11). However, the World Health Organization (WHO) does not include the HbA1c criterion for defining prediabetes (12).

Prediabetes is associated with an increased risk of cardiovascular diseases (13), suggesting the pathogenic effects of dysregulated glucose metabolism on micro- and macro-vascular disease development even before diabetes is manifest (14). The initiation and progression of macrovascular disorders such as CVD, stroke, and peripheral vascular disease occur during the prediabetes stage (15), which can be explained by high prevalence of the traditional CVD risk factors (dyslipidemia, obesity, hypertension) among individuals with prediabetes (16). Prediabetes is associated with a nearly 3-fold higher prevalence of unrecognized myocardial infarction (17) and an increased risk of cerebrovascular diseases, including transient ischemic attack, stroke, and recurrent stroke (18). Recent studies show a twofold increased risk of recurrent stroke in patients with impaired glucose tolerance (19) as well as an increased risk of recurrent cardiovascular disease in patients with prediabetes and a myocardial infarction (20), which was confirmed by meta-analysis that reported the association between prediabetes, atherosclerosis, coronary artery disease (CAD), myocardial infarction and congestive heart failure (21).

2. OBJECTIVE

There is an undeniable need for prediabetes screening which will help to stop the progression rate to diabetes, improve the effectiveness of interventions for diabetes prevention, and associated macrovascular and microvascular complications. Therefore, the primary aim of this study was to assess the prevalence of prediabetes and undiagnosed diabetes in patients with cardiovascular disease according to the ADA criteria.

3. MATERIAL AND METHODS

Participants and Study Design

This study was conducted as a cross-sectional study. The study was approved by the Ethics Committee of the General Hospital "Dr. Josip Benčevic" Slavonski Brod (approval no. 04000000/21-36). The study protocol was conducted in accordance with the principles of the Declaration of Helsinki. All participants signed an informed consent form. The study included 2968 patients aged 40 to 75 years who were admitted to the Department of Internal Medicine

Methods

Sociodemographic variables and other relevant medical history information were collected by the researchers during the clinical interview. Participants were considered dyslipidemic if they were taking lipid-lowering agents or had LDL levels above normal. Data on acute myocardial infarction, stroke, and peripheral arterial disease were collected during the clinical interview and from the medical history. A fasting blood sample was obtained to measure complete blood count with differential, lipid, liver and renal panel, glucose, and HbA1c level.

The HbA1c results obtained were interpreted according to the diagnostic criteria of ADA: Normoglycemia was defined by HbA1c values < 5.7%; prediabetes was defined by HbA1c values between 5.7 and 6.4%, and diabetes was defined as newly diagnosed diabetes (HbA1c ≥6.5%) or known diabetes. Prevalence was calculated as the number of patients with HbA1c concentrations within the defined categories divided by the total number of patients included. In addition, glycemic control in diabetic patients was defined as poor if HbA1c was ≥7.5%, moderate if HbA1c was between 7.1 and 7.4%, and good if HbA1c was < 7.0%.

Statistical Analysis

Descriptive statistical methods were used to describe the frequency distribution of the investigated variables. Numerical variables were expressed as means and standard deviations. T-test was used to determine differences between tested groups. Chi squared test was used to determine the association between categorical variables. A value of $p < 0.05$ was taken as the statistical significance level. The statistical analyses were carried out using the statistical package IBM SPSS 25 (Chicago, USA, in 2017)..

4. RESULTS

Table 1 shows that 2,968 subjects participated in the study, of whom 1,728 (58.2%) were female and 1,450 (48.9%) were diagnosed with diabetes. The arithmetic mean age was 63 years (SD = 19,596) and the mean HbA1c was 6.74 & (SD = 1,901) (Table 1).

		N (%)
Gender	Male	1240 (41.88)
	Female	1728 (58.2)
Diabetes	Yes	1450 (48.9)
	No	1496 (50.4)
	Unknown	22 (0.7)
	Mean (min – max)	SD
Age	58.01 (3 – 100)	19.596
HbA1c	6.74 (3.6 – 16.5)	1.901

Table 1. The characteristics of the respondents

		N (%)
Hba1c values	< 5.7 % (good control)	598 (41.2)
	5.7 %–6.4 %	163 (11.2)
	> 6.5 % (poor control)	689 (47.5)

Table 2. Glycemic control in diabetic participants

		N (%)
Hba1c values	< 5.7 %	853 (57)
	5.7 %–6.4 % (prediabetes)	485 (32.4)
	> 6.5 % (diabetes	158 (10.6)

Table 3. HbA1c values in non-diabetic participants

		N (%)
Acute myocardial infarction	No	1168 (80.6)
	Yes	281 (19.4)
	Missing	1 (0.1)
Cerebrovascular insult	No	1230 (84.8)
	Yes	219 (15.1)
	Missing	1 (0.1)
Peripheral arterial disease	No	1268 (87.4)
	Yes	180 (12.4)
	Missing	2 (0.1)
Hyperlipoproteinemia	No	578 (39.9)
	Yes	870 (60)
	Missing	2 (0.1)

Table 4. Comorbidities in diabetic participants

		N (%)
Acute myocardial infarction	No	1320 (88.2)
	Yes	174 (11.6)
	Missing	2 (0.1)
Cerebrovascular insult	No	1313 (87.8)
	Yes	181 (12.1)
	Missing	2 (0.1)
Peripheral arterial disease	No	1426 (95.3)
	Yes	68 (4.5)
	Missing	2 (0.1)
Hyperlipoproteinemia	No	1002 (67)
	Yes	491 (32.8)
	Missing	3 (0.2)

Table 5. Comorbidities in non-diabetic participants

Of the total number of subjects diagnosed with diabetes (N = 1450), 744 (51.3%) of them were male. The mean age was 64.23 years (SD = 16.393) and the mean Hba1c value was 7.88 % (SD =2.065). Of the total number of respondents not diagnosed with diabetes (N = 1496), 1014 (67.8%) were female. The mean age was 61.55 years (SD = 17.568) and the mean Hba1c value was 7.045 % (SD = 1.689). In the group of respondents diagnosed with diabetes, 598 (41.2%) of them had HbA1c levels under 5.7 % indicating good glycemic control (Table 2).

In the group of respondents who were not diagnosed with diabetes, 485 (32.4%) of them had HbA1c values indicating prediabetes, and 158 (10.6%) of them had HbA1c values indicating diabetes (Table 3). Of the total number of subjects diagnosed with diabetes, 281 (19.4%) had an acute myocardial infarction, 219 (15.1%) had a cerebrovascular insult, 180 (12.4%) were diagnosed with peripheral arterial disease, and 870 (60%) were diagnosed with hyperlipoproteinemia (Table 4).

Of the total number of respondents not diagnosed with diabetes, 174 (11.6%) had acute myocardial infarction, 181 (12.1%) had cerebrovascular insult, 68 (4.5%) were diagnosed with peripheral arterial disease, and 491 (32.8%) were diagnosed with hyperlipoproteinemia (Table 5). To determine whether there was a difference in HbA1c values regarding comorbidities in diabetic subjects, the T-test was used. It was found that the Hba1c level was significantly higher in subjects who had survived acute myocardial infarction (T=-2.167; P=0.03) and who were diagnosed with hyperlipoproteinemia (T=-2.177; P=0.03) (Table 6).

		M (min – max)	SD	T	P
Acute myocardial infarction	No	7.821 (4 – 16.5)	2.050	-2.167	0.03
	Yes	8.117 (4.1 – 16.5)	2.04		
Cerebrovascular insult	No	7.879 (4 – 46.5)	2.037	0.060	0.95
	Yes	7.879 (4.1 – 16.5)	2.192		
Peripheral arterial disease	No	7.851 (4 – 16.5)	2.059	-1.382	0.16
	Yes	8.078 (4.8 -15.1)	2.068		
Hyperlipopr-oteinemia	No	7.736 (4 – 15.6)	2.210	-2.177	0.03
	Yes	7.976 (4.1 – 16.5)	1.949		

Table 6. HbA1c values regarding comorbidities in non-diabetic patients

		M (min – max)	SD	T	P
Acute myocardial infarction	No	5.619 (3.6 – 11.8)	0.746	-4.249	<0.001*
	Yes	5.869 (4.2 – 10.6)	0.601		
Cerebrovascular insult	No	5.627 (3.6 – 11.8)	0.734	-2.982	0.003*
	Yes	5.800 (4.7 – 10.9)	0.723		
Peripheral arterial disease	No	5.638 (3.6 – 11.8)	0.743	-2.354	0.01*
	Yes	5.852 (4.9 – 6.9)	0.479		
Hyperlipo-pr-oteinemia	No	5.527 (3.6 – 11.8)	5.895	-9.347	<0.001*
	Yes	5.895 (4.2 – 11.4)	0.703		

Table 7. HbA1c values regarding comorbidities in non-diabetic patients

To determine whether there was a difference in Hba1c levels regarding comorbidities in non-diabetic subjects, the T-test was used. It showed that the Hba1c level was significantly higher in subjects who had acute myocardial infarction (T=-4.249; P < 0.001), cerebrovascular insult (T=-2.982; P=0.003) and who were diagnosed with peripheral arterial disease (T=-2.354; P=0.01) and hyperlipoproteinemia (T=-9.347; P < 0.001) (Table 7).

To determine if there was an association between the comorbidities and diabetes, the chi-square test was used. It showed that of the total number of respondents, significantly more of those who did not suffer from acute myocardial infarction, 1320 (53.1%) of them, were not diagnosed with diabetes, whereas significantly more respondents, 281 (61 %) who suffered from acute myocardial infarction, have been diagnosed with diabetes

			Diabetes		Total	x^2	p
			No (n = 1496)	Yes (n = 1450)			
Acute myocardial infarction	No	N	1320	1168	2488	33.769	<0.001*
		%	53.1	46.9	100		
	Yes	N	174	281	455		
		%	38.2	61.8	100		
Cerebro-vascular insult	No	N	1313	1230	2543	5.632	0.01*
		%	51.6	48.4	100		
	Yes	N	181	219	400		
		%	45.3	54.8	100		
Peripheral arterial disease	No	N	1426	1268	2694	59.142	<0.001*
		%	95.4	87.6	100		
	Yes	N	68	180	248		
		%	4.6	12.4	100		
Hyperlipo-proteinemia	No	N	1002	578	1580	218.686	<0.001*
		%	63.4	36.6	100		
	Yes	N	491	870	1361		
		%	36.1	36.9	100		

Table 8. The association between diabetes and comorbidities. * P < 0.05

($\chi2$ = 33.769; P < 0.001). Of the total number of respondents, significantly more, 1320 (53.1%), who did not suffer from a cerebrovascular insult were not diagnosed with diabetes, whereas significantly more respondents who suffered from a cerebrovascular insult, 219 (54.8%), were diagnosed with diabetes ($\chi2$ = 5.632; P = 0.01). Of the total number of subjects, significantly more subjects, 1426 (52.9%) who were not diagnosed with peripheral arterial disease did not have diabetes, whereas significantly more subjects who were diagnosed with peripheral arterial disease, 248 (72.6%), had diabetes ($\chi2$ = 59.142; P < 0.001). Of the total number of respondents, significantly more subjects, 1002 (63.4%) who were not diagnosed with hyperlipoproteinemia did not have diabetes, whereas significantly more respondents who were diagnosed with hyperlipoproteinemia, 870 (63.9%), had diabetes ($\chi2$ = 218.686; P < 0.001) (Table 8).

To determine whether there was an association between diseases and HbA1c levels in subjects who were not diagnosed with diabetes, the chi-square test was used. Among subjects not diagnosed with diabetes, in terms of HbA1c levels, significantly more subjects, 786 (59.5%), who did not have acute myocardial infarction had normal HbA1c levels, whereas significantly more subjects, 86 (49.4%), who had acute myocardial infarction had HbA1c levels suggestive of prediabetes ($\chi2$ = 32.043; P < 0.001). Significantly more subjects who were not diagnosed with peripheral arterial disease, 825 of them (59.9%), had normal HbA1c values, whereas significantly more subjects who were diagnosed with peripheral arterial disease, 30 of them (44.1%), had HbA1c values suggestive of prediabetes ($\chi2$ = 10.735; P = 0.005). Significantly more subjects who were not diagnosed with hyperlipoproteinemia, 655 of them (65.4%), have normal HbA1c values, whereas significantly more subjects who were diagnosed with hyperlipoproteinemia, 221 of them (45%), have HbA1c values suggestive of prediabetes and 75 of them (15.3 %) have HbA1c values suggestive of diabetes ($\chi2$ = 88.646; P < 0.001) (Table 9).

To determine whether there is a relationship between the comorbidities in subjects diagnosed with diabetes and the regulation of diabetes, the chi-square test was used. In terms of glycemic control, significantly more respondents, 503 (43.1%), who did not have acute myocardial infarction had well-regulated diabetes, whereas significantly more respondents, 152 (54.1%), who had acute myocardial infarction had poorly regulated diabetes ($\chi2$ = 8.137; P = 0.01). Significantly more subjects who were not diagnosed with hyperlipoproteinemia, 272 of them (47.1%), had well-regulated diabetes, whereas significantly more subjects who were diagnosed with hyperlipoproteinemia, 442 of them (50.8%), have poorly regulated diabetes ($\chi2$ = 13.553; P = 0.001) (Table 10).

			HbA1c values			Total	x^2	p
			< 5.7 %	5.7 – 6.4 %	> 6.4%			
Acute myocardial infarction	No	N	786	399	135	1320	32.043	<0.001*
		%	59.5	57.9	10.2	100		
	Yes	N	65	86	23	174		
		%	37.4	57.9	13.2	100		
Cerebro-vascular insult	No	N	762	419	132	1313	6.005	0.05
		%	58	31.9	10.1	100		
	Yes	N	89	66	26	181		
		%	49.2	36.5	14.4	100		
Peripheral arterial disease	No	N	825	455	146	1426	10.735	0.005*
		%	57.9	31.9	10.2	100		
	Yes	N	26	30	12	68		
		%	38.2	44.1	17.6	100		
Hyperlipo-proteinemia	No	N	655	264	83	1002	88.646	<0.001*
		%	65.4	26.3	8.3	100		
	Yes	N	195	221	75	491		
		%	39.7	45	15.3	100		

Table 9. The association between HbA1c values and comorbidities * P < 0.05

5. DISCUSSION

Diabetes mellitus and its associated complications are a major public health threat with an expected prevalence of 5.4% by 2025 (22). Being asymptomatic in the early stages, it may remain undiagnosed for several years, leaving half of diabetic patients unaware of their condition (23). Therefore, early detection and diagnosis of diabetes through timely screening have recently become increasingly important (24). Although the two

			Glycemic control				
			Good	Moderate	Poor	x^2	p
Acute myocardial infarction	No	N	503	129	536	8.137	0.01*
		%	43.1	11	45.9		
	Yes	N	95	34	152		
		%	33.8	12.1	54.1		
Cerebro-vascular insult	No	N	510	136	584	0.341	0.84
		%	41.5	11.1	47.5		
	Yes	N	88	27	104		
		%	40.2	12.3	47.5		
Peripheral arterial disease	No	N	530	146	592	2.865	0.23
		%	41.8	11.5	46.7		
	Yes	N	67	17	96		
		%	37.2	9.4	53.3		
Hyperlipo-proteinemia	No	N	272	60	246	13.553	0.001*
		%	47.1	10.4	42.6		
	Yes	N	325	103	442		
		%	37.4	11.8	50.8		

Table 10. The association between glycemic control and comorbidities. * P < 0.05

most widely used diagnostic tests for diabetes are the FPG test and the OGTT, the HbA1c level has also been shown to be sensitive and specific for detecting undiagnosed diabetes (25). Elevated HbA1c levels have been shown to be a better predictor of disease progression to diabetes than the FPG or OGTT, making it of great value in identifying patients in early stages of the disease (26). In addition, HbA1c results are less prone to preanalytical errors and are not affected by acute illness and acute stress reactions (27). According to data from the Croatian Registry, the prevalence of diabetes in the adult Croatian population is 6.8%, whereas estimates of the prevalence of prediabetes are lacking (11). However, it is estimated that only 60% of diabetic patients are correctly diagnosed and registered, which indicates the important role of HbA1c method in the accurate identification of adults with prediabetes and undiagnosed diabetes. In our study, we used HbA1c level as a screening tool for prediabetes and undiagnosed diabetes in the adult population examined in the General Hospital "Dr. Josip Benčevic" Slavonski Brod.

The most important finding of our study is that of the participants who were not diagnosed with diabetes, 32.4% had HbA1c levels equivalent to prediabetes. Of participants with diabetes, only 41.2% had HbA1c values under 5.7% indicating good glycemic control. The overall prevalence of prediabetes was 17.3% in a previous study in the Croatian population. A possible explanation for the higher prevalence in our study is that we examined participants in the continental part of Croatia, who also had a higher prevalence of prediabetes compared with participants on the Mediterranean coast in the aforementioned study. No significant difference prevalence of diabetes in the continental part of Croatia and prevalence of prediabetes compared with participants on the Mediterranean coast in the aforementioned study. The finding that 32.4% of our patients with previously unknown diabetes had HbA1c values corresponding to prediabetes supports the assumption that between one-half and one-third of people with diabetes are undiagnosed (11).

The prevalence of prediabetes in our study was within the ranges found in other population studies. The overall prevalence of impaired glucose regulation in developed European countries was 22.3% (28), whereas the worldwide prevalence was 7.3%, with the highest prevalence in North America (15.4%) (29). The prevalence of prediabetes in a semi-rural population in Catalonia was 39.3% (6), whereas a large national Chinese study showed a prevalence of prediabetes of 35.7% (30). In a study of Caribbean populations and England, the corresponding figures were 44.1% and 35.5%, respectively, with higher prevalence in older, overweight, and obese participants (31,32). Similar characteristics of prediabetes were found in a study of patients with three-vessel coronary artery disease who were also older, had higher body mass index, total cholesterol, low-density lipoprotein cholesterol, and triglycerides, and were more likely to have peripheral artery disease, acute coronary syndrome (ACS), and previous stroke (33).

Prediabetes is associated with an increased risk of macrovascular and microvascular complications, cancer, and dementia (34). Hyperglycemia-related tissue damage is often present even at the asymptomatic diabetes stage. Approximately 50% of people with diabetes already have macrovascular or microvascular complications, meaning that tissue damage is already present at the asymptomatic diabetes stage (35). Increased oxidative stress, inflammation, and dyslipidemia contribute to microvascular and macrovascular complications in prediabetes and diabetes. Vascular dysfunction results from the effects of hyperglycemia and vascular insulin resistance. In addition, proinflammatory and metabolic consequences of obesity, including abnormal insulin signalling and abnormal tissue responses to insulin, signalling to vascular endothelial dysfunction (34).

It is important to highlight the relationship between HbA1c levels and vascular complications. In both diabetic and non-diabetic participants, higher HbA1c levels were associated with a higher incidence of acute myocardial infarction, cerebrovascular insults, and peripheral arterial disease.

Although the mortality rate and the rate of vascular complications have decreased significantly worldwide, patients with diabetes still have a relatively doubled risk of death (36). Diabetes has long been recognized as an independent risk factor for the development of CAD (37), and prediabetes is common in patients with peripheral vascular disease and serves as a strong predictor of CVD (38). The 2011-2014 NHANES survey found a high prevalence of hypertension (36.6%), dyslipidemia (51.2%), albuminuria (7.7%), and decreased estimated glomerular filtration rate (4.6%) in adults with prediabetes (2).

Worldwide, more than 30% of patients with CAD have known diabetes and 10-20% of them have previously undiagnosed diabetes (20). According to the results of the EUROASPIRE survey, 29% of patients with CAD had undiagnosed diabetes (39). In a study of coronary artery bypass graft (CABG) patients, the prevalence of known diabetes in patients requiring cardiac surgery was 32.5% (22), similar to previous studies in which the prevalence of CAD in patients with diabetes ranged from 13% to 43% (37) and the prevalence of diabetes in patients undergoing CABG was 20% to 30% (40). The prevalence of prediabetes in a study of CAD patients undergoing percutaneous coronary intervention (PCI) was 33.5%, and in addition, according to PCI, these patients had a worse prognosis than patients with normoglycemia at admission (41). This confirms the findings of early but severe coronary lesions in prediabetes patients and the presence of lipid-rich coronary plaques resulting from the smaller coronary size and diffuse coronary narrowing together with vascular dysfunction mediated by insulin resistance (42). In a study among AMI patients, 43.3% of patients had HbA1c values above 5.7%, indicating that impaired which demonstrates widespread undetected disturbed glucose tolerance and prediabetes among AMI patients (43). In addition, previous studies following patients with diabetes after admission for ACS have found them to be at increased risk for subsequent cardiac events (44,45). Several reasons have been proposed for these findings: multiple comorbidities and later hospitalization after the onset of ACS symptoms (46), as well as decreased endothelium-dependent vasodilation and increased platelet reactivity, which may also contribute to complications after ACS because of a decreased response to antithrombotic therapy (47). In a study among NSTEMI patients, previously undiagnosed diabetes mellitus was found in 12.2% and prediabetes in 10.8% of these patients after hospital admission. They also had worse early outcomes and a significantly higher 30-day mortality risk (48).

Prediabetes is also considered a risk factor for the development of ischemic stroke and is associated with unfavorable functional outcome and increased mortality after stroke (49). Recently, two meta-analyzes found a slightly increased risk of future stroke in patients with impaired fasting glucose and/or impaired glucose tolerance (50). The risk of stroke increases across the spectrum of dysglycemia, being highest in diabetes, suggesting that hyperglycemia is a continuous risk factor for stroke (51). A similar pathogenesis of insulin resistance, which promotes atherogenesis and inflammation, together with the main effect of dyslipidemia characterized by small, dense, atherogenic low-density lipoprotein particles and accelerated atherogenesis, may explain the increased risk of stroke in diabetic patients (52). In a study by Vermeer, patients with dysglycemia in the range of impaired glucose tolerance had a nearly twofold increased risk of recurrent stroke compared with patients with normal glucose levels, whereas patients with dysglycemia in the range of diabetes had a nearly threefold increased risk (19). This increased risk is observed against a background of poststroke hyperglycemia or stress hyperglycemia, which is associated with mortality and unfavorable functional outcome 3 months after the event (53). It is also important to highlight the impact of hyperglycemia and the presence of diabetes on treatment with intravenous tissue-type plasminogen activator (54).

Given the remarkably high cardiovascular risk in patients with diabetes and the high risk of prediabetes progressing to diabetes, early detection and intervention in prediabetes patients are of paramount importance. The potential consequences of undetected diabetes include prolonged hyperglycemia and failure to initiate preventive measures because individuals with possible cardiovascular disease are not included in a group of high-risk patients (22). Early lifestyle measures and pharmacologic interventions delay the onset of diabetes and improve long-term clinical outcomes (33, 55, 56).

The present study had several shortcomings. First, it was a population-based study of a small cohort that included a sample from a previously unstudied population in eastern Croatia. Therefore, further studies are needed in the future to confirm the present results. Second, we used only HbA1c levels to estimate the prevalence of prediabetes and undiagnosed DM, and the optimal approach would be a combination of FPG and HbA1c. However, considering the design of our study, this was the only feasible method because it does not require any special preparation of the patients and can be performed from the routine hematologic samples available.

6. CONCLUSION

In this study, we showed that up to one third of individuals with undiagnosed prediabetes had already been diagnosed with cardiovascular complications. Routine screening of glycemic metabolism based on HbA1c and FPG could be valuable in identifying such high-risk individuals before an actual cardiovascular event occurs. Early identification and referral of individuals with prediabetes to appropriate prevention programs offers the greatest long-term benefit.

- **Patient Consent Form**: The authors certify that they have obtained all appropriate patient consent forms.
- **Author Contributions:** BM, JJ gave a substantial contribution to the conception and design of the work. BM gave a substantial contribution of data. JJ, MKP, BM gave a substantial contribution to the acquisition, analysis, or interpretation of data for the work. JJ, MKP, BM had a part in article preparing for drafting or revising it critically for important intellectual content. All authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
- **Conflict of interest**: None declared.
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