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Detection of Dysglycemia, a Pre-Risk Factor for Cardiovascular Events, During World Diabetes Day 2018 and 2019 in An Urban Population Sample

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Abstract It is well established that hypertension, hypercholesterolemia and type 2 diabetes (T2DM) are the main modifiable risk factors. The aim of this study was to identify the prevalence of dysglycemia in the general population screened during world diabetes day 2018 and 2019. In the context of the World Diabetes Day 2018 and 2019, promoted by the Department of Internal Medicine and Therapeutics, University of Pavia and IRCCS Policlinico San Matteo Foundation Hospital, Pavia, Italy, a total of 666 subjects aged ⩾ 18 years, of either sex, agreed to participate in the screening for detection of pre-risk and risk cardiovascular factors. Exclusion criteria was prandial state. Participants included 274 men (41.14%) and 392 women (58.86%) with an average age of 55 (SD 13) years. There were 13 underweight subjects (1.95%), 317 subjects with normal weight (47.60%), 267 overweight subjects (40.09%) [body mass index (BMI), between 25.0 and 29.9 kg/m2] and 69 obese subjects (10.36%) (BMI ⩾ 30 kg/m2). The prevalence of normo-glycemia was 61% (95% CI 57-65); of dysglycemia 28% (95% CI 24-31) and diabetes 11% (95% CI 9-14). In conclusions, in the context of the World Diabetes Day 2018 and 2019, we identified a prevalence of diabetes lower than the National reported value. Our main finding was the identification of a high prevalence of dysglycemic subjects, which should be taken into account in any primary or secondary prevention strategies.

Keywords: *Dysglycemia, dyslipidemia, pre-hypertension, hypertension, pre-risk*

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1. Introduction

It is well established that hypertension, hypercholesterolemia and type 2 diabetes (T2DM) are the main modifiable risk factors contributing considerably to the onset of cardiovascular events. In addition to them, it is of remarkable importance to consider the cardiovascular pre-risk factors represented by pre-hypertension, prediabetes (dysglycemia) and hypercholesterolemia in primary prevention. These asymptomatic states indicate the earlier phase of hypertension, hypercholesterolemia and T2DM, and their proper recognition and treatment can help to prevent or, in any case, delay the development of the disease. [1]

According to National Italian Statistical Institute (ISTAT), in 2016 more than 3 million 200 thousand people in Italy were reported to suffer from diabetes, 5.3% of the total population (16.5% among people aged 65 and over). The prevalence of self-reported diabetes has almost doubled in the last thirty years (it was 2.9% in 1980). In a more recent perspective, the number of people with diabetes has increased by 1 million and over comparing to the year 2000. The prevalence has increased from 3.8% to 5.3%, but comparing standardized prevalence (controlling aging effect of the population), the increase is significantly smaller (from 4.1% to 4.9% in 2016). This increase is therefore due to the aging of the population and other factors, such as early diagnoses and increased survival of patients with diabetes. Mortality due to diabetes has decreased more than 20% in all age groups in the last decade. [2]

Prediabetes is defined by fasting plasma glucose (FPG) levels between 100 and 125 mg/dL and/or glycated hemoglobin (HbA_{1c}) levels between 5.7 and 6.4%. [3] It is also possible to make a further distinction in dysglycemia, considering glucose value at the second hour after an oral glucose tolerance test (OGTT). On the basis of the results recorded 2 hours after the OGTT, we can diagnose patients as being affected by impaired fasting glucose (IFG), impaired glucose tolerance (IGT) or type 2 diabetes mellitus. In particular:

- IFG: was defined by glycemia at 120 minutes from OGTT < 140 mg/dL;
- IGT: was defined by glycemia at 120 minutes from OGTT between 140 mg/dl and 199 mg/dL;
- type 2 diabetes mellitus: was defined by glycemia at 120 minutes from OGTT ≥ 200 mg/dL.

It has been estimated that, globally, subjects with dysglycemia are around 200 million which expected to reach 420 million in 2025. [4]

Most of prediabetic patients present insulin-resistance and altered pancreatic β-cell function long before the onset of diabetes [5] and since insulin-resistance can cause an increase of blood pressure and triglycerides (Tg) with a reduction of high-density lipoprotein-cholesterol (HDL-C), prediabetes is also considered a risk factor for macrovascular dysfunction. Therefore, it is critical to treat appropriately dysglycemia in order to delay diabetes development and prevent cardiovascular complications.

Based on data above, the purpose of the study was to identify the prevalence of dysglycemia in the general population screened during world diabetes day 2018 and 2019. Secondary objective was to evaluate if there is association between dysglycemia and other risk factors such as dyslipidemia and pre-hypertension or hypertension.

2. Materials and Methods

2.1. Patients and Setting

In the context of the World Diabetes Day 2018 and 2019, promoted by the Department of Internal Medicine and Therapeutics, University of Pavia and IRCCS Policlinico San Matteo Foundation Hospital, Pavia, Italy, a total of 666 subjects aged ≥ 18 years, of either sex, agreed to participate in the screening for detection of pre-risk and risk cardiovascular factors. Exclusion criteria was prandial state.

Written informed consent was provided from all participants before starting the screening.

In order to meet an unselected general population sample, the World Diabetes Day took place in Pavia at four different locations: municipal hall, Piazza della Vittoria, IRCCS Policlinico San Matteo Foundation Hospital and a large shopping center.

2.2. Assessments

All participants were requested: gender, age, anthropometric parameters (weight, height and BMI), and a medical history (smoking habit, presence of diabetes, hypertension and dyslipidemia). All subjects were evaluated for blood pressure (BP), FPG, total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C) and triglycerides (Tg).

Body mass index was calculated by the investigators as weight in kilograms divided by the square of height in meters.

Blood pressure measurements were obtained from each participant (using the right arm) in the seated position, using a standard mercury sphygmomanometer. [6] The use of antihypertensive drugs was also requested.

Fasting plasma glucose was measured from capillary blood samples, by pricking the fingertip, using changing reagent strips based on an amperometric system with a portable point-of-care testing (POCT) device (LUX METER, Biochemical System International, Arezzo, Italy). The intra-assay coefficient of variation (CV) was 3.79% and 2.88% with glucose levels between 88.00 and 320.00 mg/dL; inter-assay CV was between 3.44% and 2.37% with glucose concentrations comprised from 144.40 mg/dL to 338.80 mg/dL. [7] FPG was categorized as <100 mg/dL (normo-glycemic), 100-125 mg/dL (dysglycemic), FPG >125 mg/dL (diabetes).

Total cholesterol and Tg levels were determined from a finger-prick capillary blood samples, by using changing reagent strips based on a reflectometric system with a portable POCT instrument (HPS MultiCare-In, Biochemical System International, Arezzo, Italy). For TC, the intra-assay CV was between 4.72% and 10.17% and the inter-assay one was 4.51% with TC values ranging from 132.00 to 368.00 mg/dL. For Tg, the intra-assay CV ranged from 4.72% to 10.17% and the inter-assay one was 3.29% with Tg concentrations between 79.00 and 323.00 mg/dL. [8]

High-density lipoprotein-cholesterol values were assessed from capillary blood samples, by pricking the fingertip, using changing reagent strips based on a reflectometric system with a portable POCT instrument (LUX METER, Biochemical System International, Arezzo, Italy). The intra-assay CV was 3.30% and 3.40% with HDL-C levels of 54.05 and 69.50 mg/dL, respectively; inter-assay CV was 3.70% and 4.80% for HDL-C values between 45.50 and 70.10 mg/dL. [7] Hypolipidemic medications assumption was also evaluated.

The characteristics of sensitivity, specificity and diagnostic accuracy of used device had been assessed by using an analyzer of a central laboratory as comparison method on venous blood sample. [8]

Low-density lipoprotein-cholesterol level was calculated using the Friedewald formula. [9]

2.3. Statistical Analysis

We analyzed data using the Stata software (release 16, StataCorp, College Station, TX; USA). A 2-sided p-value < 0.05 was considered statistically significant. A p-value < 0.017 was retained for post-hoc comparisons (Bonferroni correction). We described continuous data with the mean and standard deviation (SD) and categorical data as counts and percent. We compared the latter between glycemic categories with the Fisher exact test. We estimated the prevalence of each glycemic category with their 95% exact binomial confidence interval (95% CI). We used generalized ordered logistic regression to model the association with glycemic categories of age, gender, BMI, TC, Tg and blood pressure, all categorized based on

clinical meaningful cut-offs (Table 3). Non collinear variables with a p-value < 0.2 were included in a multivariable model. We report odds ratios (OR) and 95% CI, to express the odds of a more compromised condition (either normo-glycemic vs hyperglycemic or diabetic or hyperglycemic vs diabetic).

3. Results

Participants included 274 men (41.14%) and 392 women (58.86%) with an average age of 55 (SD 13) years. There were 13 underweight subjects (1.95%), 317 subjects with normal weight (47.60%), 267 overweight subjects (40.09%) [body mass index (BMI), between 25.0 and 29.9 kg/m^2] and 69 obese subjects (10.36%) (BMI ≥ 30 kg/m^2) (Table 1).

The prevalence of normo-glycemia was 61% (95% CI 57-65); of dysglycemia 28% (95% CI 24-31) and diabetes 11% (95% CI 9-14).

The main demographic and clinical features of study population are shown in Table 1. Diabetes, hypertension and dyslipidemia were reported by 13, 27 and 30% of subjects, respectively. Half of patients were overweight or obese.

The characteristics of patients, by glycemic level categories are described in Table 2. The proportion of older, hypertensive and dyslipidemic subjects increases across the glycemic categories.

At the univariable analysis, age, TC, Tg and blood pressure were associated with the odds of a more compromised condition (hyperglycemic or diabetic) (Table 3). At the multivariable analysis, the same variables were identified as independent correlates of gravity, though TC, was borderline non-significant at the overall assessment (Table 4). Age of ≥ 65 years increased by more than two the odds of being dysglycemic or diabetic in subjects who were normo-glycemic, and by two the risk of being diabetic of those who were in a lower category at the time of assessment. Total cholesterol was independently associated with the decrease in odds of a worse glycemic condition in both cases. Conversely, high Tg were associated in an almost three-fold increased odds of diabetes in patients who were hyper- or normo-glycemic, while they did not increase the probability of being hyperglycemic or diabetics in normo-glycemic subjects. Similarly, hypertension increased the odds of diabetes by two for normo-hyperglycemic patients, while it did not affect the odds of being hyperglycemic or diabetic for normo-glycemic subjects. Body mass index was not shown to increase the odds of having higher glycemia levels than the current ones.

Table 1. Demographic and clinical characteristics of the study population

Variable	Description
N	666
Age (years)	55 ± 13
Gender (M/F)	274/392 (F: 59%)
Smoke (y)	109 (16%)
Diabetes (y)	84 (13%)
Hypertension (y)	181(27%)
Dyslipidemia (y)	202 (30%)
BMI (kg/m^2)	25 ± 4
<18.5	13 (2%)
18.5-24.9	317 (48%)
25.0-29.9	267 (40%)
≥30.0	69 (10%)
SBP (mmHg)	132 ± 16
DBP (mmHg)	81 ± 10
SPB<140/DBP<90	210 (32%)
SPB 130-139/DBP 85-89	197 (30%)
SPB≥140/DBP≥90	259 (39%)
FPG (mg/dL)	100 ± 22
<100	405 (61%)
100-125	185 (28%)
>125	76 (11%)
TC (mg/dL)	199 ± 38
<200	293 (44%)
200-249	342 (51%)
>249	31 (5%)
LDL-C (mg/dL)	123± 38
<100	169 (25%)
100-130	165 (25%)
130-160	243 (36%)
160-190	76 (11%)
≥190	13 (2%)
HDL-C (mg/dL)	48 ± 10
<40	117 (18%)
40-60	473 (71%)
>60	76 (11%)
Tg (mg/dL)	134 ± 60
<150	490 (74%)
≥150	176 (26%)

Data are expressed as n and (%).
M: male; F: female; y: yes; BMI: body mass index; BMI <18.5 kg/m^2: underweight; BMI of 18.5-24.9 kg/m^2: normal weight; BMI of 25.0-29.9 kg/m^2: overweight; BMI ≥30.0 kg/m^2: obese; SBP: systolic blood pressure; DBP: diastolic blood pressure; SPB <140 mmHg/DBP <90 mmHg: normotension; SPB of 130-139 mmHg/DBP of 85-89 mmHg: pre-hypertension; SPB ≥140 mmHg/DBP ≥90 mmHg: hypertension; FPG: fasting plasma glucose; TC: total cholesterol; LDL-C: low density lipoprotein-cholesterol; HDL-C: high density lipoprotein-cholesterol; Tg: triglycerides.

Table 2. Distribution of patient characteristics by glycemic level categories

	Normo-glycemic FPG <100 mg/dL	**Dysglycemic FPG 100-125 mg/dL**	**Diabetes FPG >125 mg/dL**	**Overall p-value**	***p-value (<100 vs 100-125)***	***p-value (<100 vs >125)***	***p-value (100-125 vs >125)***
Age (years)				<0.001	<0.001	<0.001	*0.149*
≥ 65	71 (17.5%)	57 (30.8%)	31 (40.8%)				
Gender				0.382	-	-	-
Female	244 (60.2%)	101 (54.6%)	47 (61.8%)				
BMI (kg/m^2)				0.135	-	-	-
≥25	193 (47.7%)	98 (53.0%)	45 (59.2%)				
SBP/DBP (mmHg)				0.005	*0.718*	*0.001*	*0.008*

	Normo-glycemic FPG <100 mg/dL	Dysglycemic FPG 100-125 mg/dL	Diabetes FPG >125 mg/dL	Overall p-value	*p-value (<100 vs 100-125)*	*p-value (<100 vs >125)*	*p-value (100-125 vs >125)*
SPB<140/DBP<90	132 (32.6%)	62 (33.5%)	16 (21.1%)				
SPB 130-139/DBP 85-89	129 (31.9%)	53 (28.7%)	15 (19.7%)				
SPB≥140/DBP≥90	144 (35.6%)	70 (37.8%)	45 (59.2%)				
TC (mg/dL)				0.004	*0.361*	*0.001*	*0.030*
<200	161 (39.8%)	84 (45.4%)	48 (63.2%)				
200-249	221 (54.6%)	94 (50.8%)	27 (35.5%)				
>249	23 (5.7%)	7 (3.8%)	1 (1.3%)				
Tg (mg/dL)				<0.001	*0.462*	*<0.001*	*<0.001*
≥150	98 (24.2%)	39 (21.1%)	39 (51.3%)				

Data are expressed as n and (%).
FPG: fasting plasma glucose; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; SPB <140 mmHg/DBP <90 mmHg: normotension; SPB of 130-139 mmHg/DBP of 85-89 mmHg: pre-hypertension; SPB ≥140 mmHg/DBP ≥90 mmHg: hypertension; TC: total cholesterol; Tg: triglycerides.

Table 3. Crude association of clinical and laboratory parameters with glycemia status from univariable generalized ordered logit models

	Odds to be Dysglycemic or Diabetic			Odds to be Diabetic			
	OR	*95%CI*	*p-value*	*OR*	*95%CI*	*p-value*	*Overall p-value*
Age (years)							<0.001
≥65 vs <65	2.39	1.67-3.44	<0.001	2.49	1.51-4.09	<0.001	
Gender							0.377
Females vs Males	0.86	0.63-1.18	0.365	1.15	0.70-1.88	0.575	
BMI (kg/m^2)							0.131
≥25 vs <25	1.33	0.97-1.82	0.072	1.49	0.92-2.42	0.106	
BP			0.078			<0.001	0.005
Pre-hypertension vs Normal	0.89	0.59-1.34	0.581	1.00	0.48-2.08	>0.900	
Hypertension vs Normal	1.35	0.93-1.96	0.113	2.55	1.40-4.66	0.002	
TC (mg/dL)			0.014			0.002	0.004
200-249 vs <200	0.67	0.49-0.92	0.013	0.44	0.27-0.72	0.001	
>249 vs <200	0.42	0.18-0.98	0.045	0.17	0.02-1.28	0.085	
Tg (mg/dL)							<0.001
≥150 vs <150	1.34	0.94-1.89	0.105	3.49	2.14-5.68	<0.001	

BMI: body mass index; BP: blood pressure; TC: total cholesterol; Tg: triglycerides.

Table 4. Mutually adjusted association of clinical and laboratory parameters with glycemia status from multivariable generalized ordered logit model

	Odds to be Dysglycemic or Diabetic			Odds to be Diabetic			
	OR	*95%CI*	*p-value*	*OR*	*95%CI*	*p-value*	*Overall p-value*
Age (years)							<0.001
≥65 vs <65	2.35	1.60-3.43	<0.001	1.91	1.14-3.20	0.014	
BMI (kg/m^2)							0.183
≥25 vs <25	1.35	0.97-1.88	0.075	1.36	0.82-2.25	0.228	
BP			0.082			0.013	0.027
Pre-hypertension vs Normal	0.70	0.46-1.08	0.107	0.82	0.39-1.73	0.601	
Hypertension vs Normal	1.09	0.74-1.61	0.668	1.89	1.01-3.52	0.046	
TC (mg/dL)			0.049			0.035	0.051
200-249 vs <200	0.75	0.54-1.04	0.083	0.62	0.37-1.06	0.079	
>249 vs <200	0.41	0.17-0.97	0.043	0.12	0.02-0.91	0.040	
Tg (mg/dL)							<0.001
≥150 vs <150	1.11	0.77-1.62	0.570	2.84	1.70-4.77	<0.001	

BMI: body mass index; BP: blood pressure; TC: total cholesterol; Tg: triglycerides.

4. Discussion

In this cross-sectional study we were able to classify about 30% of the screened population as dysglycemic and little more than 10% of diabetic subjects (less than the 13% prevalence reported by the subjects). Moreover, we show that simple and easy to measure cardiovascular risk factors can classify subject into one of the three glycemic categories, as defined above. Specifically older age and higher TC levels identify subjects to be more likely dysglycemic or diabetic rather than normo-glycemic; moreover, the same risk factors together with hypertension and higher triglycerides levels

identify subjects more likely to be diabetics, rather than normo- or dysglycemic.

Compared to ISTAT data, [2] we reported a lower prevalence of diabetes in our cohort, probably because they were younger, with mean age of 55 years. In our data, high Tg were associated in an almost three-fold increased odds of diabetes in patients who were hyper- or normo-glycemic, while they did not increase the probability of being hyperglycemic or diabetic in normo-glycemic subjects. This is in line with data reported in literature, Tg and diabetes are very intimately related. Previous studies reported a correlation between glycated hemoglobin (HbA_{1c}) and Tg level. [10] This may in turn help in predicting the Tg status of type 2 diabetics from the degree of glycemic control and therefore identifying patients at increased risk from cardiovascular events. Lebovitz suggested that there is a lipotoxic mechanism by Tg which interferes with gastric or neural pathway which regulates glycemic control. [11] In most of the studies, there is a correlation found between glycemic control and dyslipidemia. [11] In a recent study, [12] it was evident that there was a positive correlation between HbA_{1c} and high Tg and HbA_{1c} can be used as a potent marker for dyslipidemia and mitigate the macro- and micro-vascular complication.

Of course, our study has several limitations: first of all, glycemia was assessed by capillary and not venous sample, this could have missed some cases of diabetes, given that capillary glycemia is lower than venous one, even if the used device has been validated. Moreover, we enrolled a quite younger population, this could have an impact on diabetes incidence. Possibly our results might be influenced by a self-referral bias; however, different data collection was performed at four different locations to increase an unselected attendance.

5. Conclusion

In the context of the World Diabetes Day 2018 and 2019, we identified a prevalence of diabetes lower than the National reported value. Our main finding was the identification of a high prevalence of dysglycemic subjects, which should be taken into account in any primary or secondary prevention strategies.

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