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Original Article

Diabetes mellitus: relation between cardiovascular events and pharmacological treatment

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Abstract. *Background and aim*: Cardiovascular diseases are characterized by problems affecting the circulatory system, specifically the heart and blood vessels. This study evaluates the relationship between cardiovascular events and pharmacological treatment for Type II Diabetes Mellitus (T2DM). *Methods:* We recruited 227 individuals, 191 with T2DM (EG) and 36 pre-diabetics (CG), with a mean age of 70.3 years (SD=8.3), and 62 years (SD=10.3) respectively. The individuals were distributed into five groups concerning the following variables: body mass index (BMI), age, diagnosis age of T2DM, glycated hemoglobin value (HbA1c), Homeostatic model that estimates the function of β cells value (HOMA2-B), and Homeostatic model that estimates insulin resistance (HOMA-IR) value. At the time of data collection, there were no individuals with T1DM, so it was decided to use prediabetic individuals (with a high risk of developing T2DM). *Results:* Group 1 had the pre-diabetic patients (15.9%), while diabetic individuals were divided into groups 2 (1.8%), 3 (17.6%), 4 (21.1%) and 5 (43.6%). It was possible to conclude that most of the patients in the different groups had a history of acute myocardial infarction (AMI). Regarding the prevalence of pharmacological treatment, it was possible to conclude that metformin was the most used drug in most of the groups. *Conclusions:* It was possible to create different groups and to observe the existence of dependency relationships between different cardiovascular events and pharmacological treatment. (www.actabiomedica.it)

Key words: Diabetes mellitus; cardiovascular events; pharmacological treatment.

Introduction

Type II Diabetes Mellitus (T2DM) is responsible for about 90–95% of cases of diabetes, being associated with ineffective use or production of insulin by the pancreas (1stroke, peripheral neuropathy, renal disease, blindness and amputation. The best-known predictors of increased diabetes risk are elevated fasting plasma glucose, elevated 1- and 2-hour plasma glucose after an oral glucose tolerance test, obesity and evidence of impaired insulin action. However, the mechanisms by which people with impaired fasting glucose and/or abnormal glucose tolerance 'progress' to overt T2DM are not completely understood. Moreover, T2DM is defined in a 'negative' sense (hyperglycaemia not accounted for by autoimmune destruction of islet cells or other known causes). It is the most common type of DM in adults, appearing more frequently in individuals over 40 years. However, it can appear at younger ages, especially in populations where there is a higher prevalence of this pathology (2).

T2DM complications are responsible for more than 2 million deaths per year (3), being the seventh

leading cause of disability worldwide. As this is a silent pathology, there are several complications that evolve imperceptibly and, when are found, they are already present in the body (4).

Cardiovascular diseases (CVDs) and hypertension (HTA) are related to macrovascular complications as they are due to lesions that occur in larger blood vessels. Microvascular complications correspond to lesions that occur in small blood vessels. The first and most important step in the T2DM treatment implies an adaptation and modification of eating habits together with the practice of daily exercise (5). When diet and exercise are not enough to control plasma glucose levels, pharmacological treatment with oral antidiabetic drugs (OAD) and/or insulin is used. Unlike Type 1 Diabetes Mellitus (T1DM), individuals with T2DM are not dependent on exogenous insulin, but may require it to control hyperglycemia if they do not achieve it through the diet conjugated with OAD (6).

The medication used to treat T2DM can be divided into two main groups: the injectable group, which includes insulins and glucagon-like peptide 1 (GLP-1) analogues and the OAD group, drugs whose route of administration is oral (7). It is essential that there is an approach centered on each individual to be chosen the most appropriate pharmacological treatment in order to prevent and avoid complications, maintaining the quality of life of the person (8-11).

The purpose of this study is to divide the participants in five different groups to identify individuals at high risk of developing DM complications at the time of diagnosis. It will help to choose the treatment to be prescribed to each person, allowing the individualization of the treatment and the identification of people at higher risk of complications at the time of diagnosis.

Materials and methods

This study was developed at one Clinical Research Unit in Cardiology (UICC). The UICC corresponds to a national and international center of excellence in the area of clinical research, being inserted in the CHUC which is a highly prestigious hospital. The assent of the Health Ethics Committee and the Board of Directors of CHUC (ref[a] 230/CES) and CHUC (084/19), respectively, was obtained before any procedure. All participants were informed regarding the objectives of the study and anonymity, confidentiality, voluntary nature of their participation and the freedom to refuse or withdraw their consent, were guaranteed at any time without any consequences. This gave them the opportunity to clarify any doubts that might arise about their participation. Thus, free and informed consent was obtained in writing by all participants.

Participants

The population consisted of individuals with T2DM and pre-diabetics, all included in active clinical trials at UICC. The following requirements were defined for the inclusion of individuals in the study. Inclusion Criteria: individuals with T2DM or pre-diabetes, individuals participating in clinical trials at UICC, individuals without cognitive difficulties and individuals with 18 years and older. Exclusion Criteria: individuals without T2DM or pre-diabetes, individuals not participating in clinical trials at UICC, individuals with cognitive difficulties, pregnant females and individuals under the age of 18 years. We requested the participation of 206 individuals with T2DM, however, 12 gave up face-to-face visits, so it was not possible to collect the anthropometric and analytical parameters, 2 refused to participate and 1 presented controversial analytical values because it was not fasting at the time of performing the respective analyses. So, 191 diabetics were included, in the Experimental Group (EG). Regarding prediabetic individuals, 40 were requested to participate and 4 refused. Thus, 36 prediabetic individuals were included in the control group (CG). The final sample consisted of 227 individuals, 191 of them with T2DM and 36 were pre-diabetic. Of the 191 individuals (EG), 78.5% (150) were male, and 21.5% (41) female. Of the 36 individuals (CG), 86.1% (31) were male, and 13.9% (5) were female. In regard to the distribution of these by age and group, it was found that the individuals of the EG had a minimum age of 50 years and a maximum of 90 years, corresponding to an average of 70.3 years (with a standard deviation (SD) of 8.3) and a median of 71 years. Regarding the CG, the individuals presented an age range between

45 and 81 years, with an average of 62 years (SD of 10.3) and a median of 60.5 years.

Procedures

The individuals were distributed in groups with different characteristics. For this division, the following variables were used: BMI, age of each individual, diagnosis age of T2DM, HbA1c value, HOMA2-B value and HOMA-IR value. The group division proposed by a recent study was adopted, except for the use of the variable presence/absence of GADA (11). The presence of GADA is used to identify and classify individuals with Type 1 Diabetes Mellitus (T1DM) (11). Given that at UICC, at the time of data collection, there were no individuals with T1DM, it was decided to use prediabetic individuals (with high risk of developing T2DM). Thus, the following groups with distinct characteristics were defined: Group 1 – Prediabetic individuals (CG); Group 2 – Individuals with low HOMA2-B (equal to or less than 86), high HbA1c (equal to or greater than 7%), early diagnosis of T2DM (equal to or less than 45 years) and relatively low BMI (equal to or less than 25 kg/m^2); Group 3 – Individuals with high HOMA-IR (equal to or greater than 2.35) and high BMI (equal to or greater than 30 kg/m^2); Group 4 – Individuals with low HOMA-IR (less than 2.35) and high BMI (equal to or greater than 30 kg/m^2); Group 5 – Older Individuals (65 years of age or older).

Statistical analysis

The collected data were entered, processed, and analyzed in the R-studio Software, version 1.2.5033 for Windows, with a descriptive and inferential analysis of the sample. Initially, the sample was described in terms of the following parameters: Sociodemographic elements; Clinical profile; Routine laboratory parameters; Health behaviors; Previous cardiovascular events; Microvascular complications associated with T2DM; Pharmacological treatment. Inferential analysis was made considering the characteristics of the sample and the essence of this investigation, it tried to verify the existence or not of association between two or more variables. Chi-square test ($\chi 2$) were applied to measure the probability that the differences found are due to chance, assuming that there are no differences between two variables. Fisher's exact test were applied to assess the independence between two variables when the comparison groups are independent and uncorrelated samples, used especially when more than 20% of the expected frequencies under the independence hypothesis are less than 5.

Results

Group 1 had 36 individuals (15.9%), group 2, due to specificity, presented only 4 individuals (1.8%), group 3, 40 (17.6%), group 4, 48 (21.1%) and, group 5, 99 (43.6%). To better characterize the different groups, we chose to present the prevalence values of previous cardiovascular events and micro and macrovascular complications associated with T2DM. Regarding stroke, the vast majority had no antecedents: group 1 with 86.1%, group 2 with 75%, group 3 with 90%, group with 4 with 89.6% and group 5 with 88.9%, contrasting with the minority who had a previous history of stroke: 13.9% in group 1, 25% in group 2, 10% in group 3, 10.4% in group 4 and 11.1% in group 5.

Regarding AMI, 94.4% of the individuals in group 1 revealed antecedents of this event. In group 2, only 25% had a history of AMS while 75% did not. Regarding group 3, there was a history of this cardiovascular event in 45% of the individuals, and the same was not the same in the remaining 55%. In group 4 and group 5, it was observed that the majority from these two groups, 60.4% and 65.7%, respectively, had a history of AMI.

Regarding heart failure (HF), it was found that in all groups, the majority had no previous antecedents: 72.2% in group 1, 75% in group 2, 57.5% in group 3, 58.3% in group 4 and 65.7% in group 5. In terms of HTA, it was found that the majority of individuals in all groups had antecedents: 91.7% in group 1, 100% in group 2, 100% in group 3, 100% in group 4 and 99% in group 5. Regarding auricular fibrillation (AF), most individuals in all groups did not reveal antecedents: 86.1% in group 1, 100% in group 2, 77.5% in group 3, 87.5% in group 4 and 78.8% in group 5. Regarding angina (ANG), the vast majority of individuals in all groups did not present a history of this cardiovascular event: 91.7% in group 1, 100% in group 2, 85% in

group 3, 83.3% in group 4 and 85.9% in group 5. Finally, regarding dyslipidemia (DYSL), it was found that 100% of the individuals in all groups presented antecedents of this event (Table 1).

Regarding the prevalence of pharmacological treatment for T2DM, since individuals in group 1 (pre-diabetics) did not do any kind of pharmacological treatment, we chose to verify the prevalence in the remaining 4 groups (2, 3, 4 and 5). Regarding metformin, 50% of individuals in group 2, 35% of group 3, 75% of group 4 and 68.7% of group 5 were treated with this drug.

Treatment with sulphonylureas was nonexistent among individuals in group 2, and only 2.5% in group 3, 8.3% in group 4 and 7.1% in group 5 did so. It should also be noted that treatment with thiazolidinediones was nonexistent among individuals of all groups.

Regarding alpha-glucosidase inhibitors (α-glucosidase), only 25% of individuals in group 2 and 2.1% of group 4 used these drugs and it was found that in groups 3 and 5 the use of this drugs was nonexistent. Regarding dipeptidyl peptidase-4 (DPP-4) inhibitors, it was found that 50% of group 2, 45% of group 3, 37.5% of group 4 and 39.4% of group 5 resorted to this treatment.

Regarding GLP-1 agonists, it was observed that most individuals in all groups did not do them: 100% in group 2, 82.5% in group 3, 93.9% in group 4 and 98% in group 5. The same was visible about sodium-glucose co-transporter-2 (SGLT2) inhibitors which were used only by 20% of group 3, 18.8% of group 4 and 24.2% of group 5.

Regarding human insulin (HI) it was found that most individuals did not use it: 75% in group 2, 85% in group 3, 93.8% in group 4 and 90.9% in group 5. Finally, insulin analogues (IA) were used by 75% of group 2, 70% of group 3, 14.6% of group 4 and 33.3% of group 5 (Table 2).

Fisher's exact test was used to verify the existence of a relationship between the occurrence of previous cardiovascular events and the occurrence of microvascular complications per group. After performing this

Table 1. Prevalence of previous cardiovascular events in the different 5 groups.

Existence Event	Group 1		Group 2		Group 3		Group 4		Group 5	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Stroke	13.9	86.1	25.0	75.0	10.0	90.0	10.4	89.6	11.1	88.9
AMI	94.4	5.6	25.0	75.0	45.0	55.0	60.4	39.6	65.7	34.3
HF	27.8	72.2	25.0	75.0	42.5	57.5	41.7	58.3	34.3	65.7
HTA	91.7	8.3	100.0	0.0	100.0	0.0	100.0	0.0	99.0	1.0
AF	13.9	86.1	0.0	100.0	22.5	77.5	12.5	87.5	21.2	78.8
ANG	8.3	91.7	0.0	100.0	15.0	85.0	16.7	83.3	14.1	85.9
DYSL	100.0	0.0	100.0	0.0	100.0	0.0	100.0	0.0	100.0	0.0

Table 2. Prevalence of pharmacological treatment for T2DM in groups 2, 3, 4 and 5.

Existence Treatment	Group 2		Group 3		Group 4		Group 5	
	Yes	No	Yes	No	Yes	No	Yes	No
Metformin	50.0	50.0	35.0	65.0	75.0	25.0	68.7	31.3
Sulphonylureas	0.0	100.0	2.5	97.5	8.3	91.7	7.1	92.9
Thiazolidinediones	0.0	100.0	0.0	100.0	0.0	100.0	0.0	100.0
χglucosidase inhibitors	25.0	75.0	0.0	100.0	2.1	97.0	0.0	100.0
DPP-4 inhibitors	50.0	50.0	45.0	55.0	37.5	62.5	39.4	60.6
GLP-1 agonists	0.0	100.0	17.5	82.5	6.2	93.9	2.0	98.0
SGLT2 inhibitors	0.0	100.0	20.0	80.0	18.8	81.2	24.2	75.8
HI	25.0	75.0	15.0	85.0	6.2	93.8	9.1	90.9
IA	75.0	25.0	70.0	30.0	14.6	85.4	33.3	66.7

test, for a significance level of 0.05, it was observed that, in the values represented in bold, the p-value < 0.05, so the hypothesis of independence was rejected. Thus, in these cases, there was a dependence between a certain previous cardiovascular event and pharmacological treatment in the respective group.

In group 1, it was not possible to perform fisher's exact test and, therefore, to establish any type of relationship, because the individuals belonging to it did not perform any pharmacological treatment for T2DM. In group 2, due to the low number of patients, it was not possible to perform the teste and this group was not included in the analysis. Regarding group 3, it was found that there was a dependency relationship between previous AMI occurrence and the administration of metformin (p=0.0027; p<0.05) and SGLT2 inhibitors (p=0.0006; p<0.05), and between the occurrence of previous ANG and the administration of DPP-4 inhibitors (p=0.0048; p<0.05).

In group 4, it was found that there was a relationship of dependence between previous AMI occurrence and administration of DPP-4 inhibitors (p=0.0319; p<0.05) and between previous ANG occurrence and administration of SGLT2 inhibitors (p=0.0307; p<0.05). Regarding group 5, there was a relationship of dependence between previous AMI occurrence and the administration of metformin (p=0.0059; p<0.05), sulphonylureas (p=0.0451; p<0.05), DPP-4 inhibitors (p=0.0013; p<0.05) and IA (p=0.0142; p<0.05), between previous HF and the administration of metformin (p=0.0059; p<0.05) and HI (p=0.0072; p<0.05) and between the occurrence of previous ANG and the administration of DPP-4 inhibitors (p=0,0429; p<0,05). In the remaining cases, the p-value > 0.05, so was no dependence between the microvascular complication concerned and the pharmacological treatment (Table 3).

Discussions

Regarding the distribution of individuals by groups, it was expected that group 5 presented a greater number of individuals (99) since it contained those with older age and who did not fit in the other groups. Group 2, due to its specificity (individuals would have to present at the same time an early onset of T2DD, high value of HOMA2-B and HbA1c and low BMI value), presented only 4 individuals.

Regarding the relationship between the occurrence of previous cardiovascular events and pharmacological treatment for T2DM per group, there was a dependence between previous AMI and metformin administration in groups 3 (p=0.0027; p<0.05) and 5 (p=0.059; p<0.05). The cardioprotective potential of this drug is well established in preclinical studies (12). The use of metformin at the time of the first AMI is associated with an increased cardiovascular risk and mortality in individuals with T2DM, while its continued use after AMI may be beneficial in reducing mortality (13), supporting the results obtained in the present study.

In group 5, there was a dependency relationship between previous AMI and administration of sulphonylureas (p=0.0451; p<0.05). In newly diagnosed individuals with T2DM, the use of sulphonylureas as the first line of treatment is not associated with an increased risk of developing AMI (14). Still, these drugs are related to a higher risk of stroke development, death from CVDs and increased mortality from other causes, so the administration should be well considered (15-17).

Regarding the dependency relationship between previous AMI and administration of DPP-4 inhibitors, it was observed in groups 4 (p=0.0319; p<0.05) and 5 (p=0.013; p<0.05). In individuals with T2DM and prior history of AMI, administration of DPP-4 inhibitors increases the likelihood of long-term survival, regardless of gender (18), which may help to corroborate the relationship obtained in the present study. There was also a dependency relationship between previous AMI and administration of SGLT2 inhibitors in group 3 (p=0.0006; p<0.05. It was demonstrated in the EMPA-REG OUTCOME study that empaglifozin (SGLT2 inhibitor), in addition to providing safety, has beneficial effects in reducing cardiovascular risk, namely by reducing the risk of AMI and stroke in patients with T2DM and established CVD (19), supporting the results obtained.

Regarding the dependency relationship and between previous AMI and IA administration, it was found in group 5 (p=0.0142; p<0.05). In general, in-

Table 3. Relationship between the occurrence of previous cardiovascular events and the pharmacological treatment for T2DM by group.

Treatment		Stroke	AMI	HF	Event HTA	AF	ANG	DYSL
Metformin	Group 1	NA	NA	NA	NA	NA	NA	NA
	Group 3	0.6017	**0.0027**	0.7385	NA	0.6935	0.6456	NA
	Group 4	0.5872	0.1764	0.1977	NA	0.6313	0.0939	NA
	Group 5	1	**0.0059**	**0.0059**	1	1	0.5389	NA
Sulphonylureas	Group 1	NA	NA	NA	NA	NA	NA	NA
	Group 3	1	1	1	NA	1	0.1500	NA
	Group 4	1	1	0.6309	NA	1	1	NA
	Group 5	0.5736	**0.0451**	0.4166	1	0.1624	0.5887	NA
Thiazolidinediones	Group 1	NA	NA	NA	NA	NA	NA	NA
	Group 3	NA	NA	NA	NA	NA	NA	NA
	Group 4	1	1	0.6309	NA	1	1	NA
	Group 5	NA	NA	NA	NA	NA	NA	NA
χglucosidase	Group 1	NA	NA	NA	NA	NA	NA	NA
ihnibitors	Group 3	NA	NA	NA	NA	NA	NA	NA
	Group 4	0.1042	0.3958	1	NA	0.1250	1	NA
	Group 5	NA	NA	NA	NA	NA	NA	NA
DPP-4	Group 1	NA	NA	NA	NA	NA	NA	NA
inhibitors	Group 3	0.3100	0.0619	0.3476	NA	0.4761	**0.0048**	NA
	Group 4	0.0586	**0.0319**	0.0681	NA	0.6583	1	NA
	Group 5	0.1055	**0.0013**	0.8308	1	1	**0.0429**	NA
GLP-1	Group 1	NA	NA	NA	NA	NA	NA	NA
agonists	Group 3	1	0.4271	0.6770	NA	0.6446	0.5672	NA
	Group 4	0.2865	0.0560	1	NA	0.3363	1	NA
	Group 5	0.2109	0.1156	0.5444	1	1	0.2641	NA
SGLT2	Group 1	NA	NA	NA	NA	NA	NA	NA
inhibitors	Group 3	1	**0.0006**	1	NA	0.6553	0.5803	NA
	Group 4	0.5677	0.0682	0.7161	NA	0.5777	**0.0307**	NA
	Group 5	1	0.6265	0.3289	1	0.7747	0.7391	NA
HI	Group 1	NA	NA	NA	NA	NA	NA	NA
	Group 3	0.4925	0.6726	0.3725	NA	1	0.5650	NA
	Group 4	1	1	0.5629	NA	1	0.4288	NA
	Group 5	0.5915	0.7145	**0.0072**	1	0.6795	0.6108	NA
IA	Group 1	NA	NA	NA	NA	NA	NA	NA
	Group 3	1	0.3154	0.2960	NA	0.0968	0.3407	NA
	Group 4	0.5623	0.4116	0.4294	NA	1	1	NA
	Group 5	1	**0.0142**	0.5046	1	0.7950	0.3742	NA

NA: One of the categories (Yes or No) in Event or Complication does not present observations.

dividuals with T2DM treated with IA have more comorbidities, cardiovascular or other, than those without T2DM or with T2DM treated with OAD (20), which can help corroborate the relationship found in this investigation. Also, in group 5, a dependency relationship was observed between previous HF and

metformin administration (p=0.0059; p<0.05). The use of this drug in individuals with moderate CKD, congestive HF or liver failure may be associated with an improvement in clinical results (21), which may help to substantiate the result obtained in the present study.

Regarding the dependency relationship between previous HF and HI administration, this occurred in group 5 (p=0.0072; p<0.05). The prescription of HI is associated with a higher risk of death and re-hospitalization for HF (22). In individuals with T2DM and a history of HF, this risk is higher when compared to individuals with the same characteristics but not treated with HI (22-23).

In groups 3 (p=0.0048; p<0.05) and 5 (p=0.0429; p<0.05) there was a dependency relationship between previous ANG and administration of DPP-4 inhibitors. The risk of hypoglycaemia, the absence of association with weight gain and the fact that they are not associated with increased cardiovascular risk and other side effects are rare, reason why PPD-4 inhibitors are generally well tolerated (24-27) and may help to sustain the relationship of dependence.

Regarding the dependency relationship between previous ANG and administration of SGLT2 inhibitors, this occurred in group 4 (p=0.0307; p<0.05). The use of a SGLT2 inhibitor is recommended in patients who have established CVD or high risk of developing it (28), which is the reasons that support the result obtained.

Conclusions

Although it was possible to create different groups and to observe the existence of dependency relationships between different cardiovascular events and pharmacological treatment, some limitations were identified. The reduced number of individuals in group 2, due to their specificity, made it, at some point, to opt for the study of dependency relationships only with groups 1, 3, 4 and 5. Another limitation was due to the small number of individuals in the total sample (227) compared to other studies. The low number of individuals was related to this investigation being conducted only at UICC, which only allowed the use of individuals with prediabetes and T2DM from that unit. Nevertheless, an effort was made so that all individuals with these particularities and without any of the exclusion criteria presented during the work were included, something that was very close to the desired. The lack of individuals with T1DM represented another weakness, so it was decided to use prediabetic individuals to establish comparations. The small number of studies and the fact that they are longitudinal and prospective, unlike the present one that is cross-sectional in nature, presented itself as another limitation. T2DM represents a high complex pathology that affects mostly individuals of an older age. Thus, it would be relevant to extend the study to a larger number of individuals to optimize their division by groups so that they can, in the future, present validity and applicability. Accordingly, it is necessary to extend the study to a larger number of individuals. It would also be interesting to conduct further studies with the use of other markers that, hypothetically, may help in the division of individuals with T2DM into different groups.

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Conflicts of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Author contributions: CS, SBC, PM: conceptualization, methodology; CS: investigation; CS, SBC, LM: formal analysis, data curation; CS, SBC: original draft preparation; SBC: review, and editing.

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