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RELATIONS BETWEEN DIABETES, KIDNEY DISEASE AND METABOLIC SYNDROME: DANGEROUS LIAISONS

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Abstract

Background and aims: *Diabetes mellitus is the disease-challenge of our century, characterized by an increase in serum glycemia, which may lead to the occurrence of micro- and macro-vascular complications with serious consequences on both patient and public health. The Framingham risk score was obtained from a complex study and it estimates the individual risk of each patient to develop a cardiovascular event over the next 10 years depending on certain parameters (age, smoking, total cholesterol, HDL-cholesterol, systolic blood pressure). Our study main aim was to evaluate the cross-associations between the components of the metabolic syndrome, cardiovascular risk, diabetes-related biological parameters and chronic kidney disease in patients hospitalized due to poor metabolic control.* ***Material and methods:*** *In this cross-sectional study, we enrolled 218 patients with type 2 diabetes, admitted in the Diabetes Clinic of the "Pius Brinzeu" Emergency Hospital Timisoara according to a consecutive-case population-based principle.* ***Results:*** *We observed that the quality of the glycemic control is impaired in patients with higher age; the body mass index was positively correlated with HbA1c and hypertension accompanies diabetes in more than half of the cases. Moreover, we observed that high levels of LDL cholesterol are significantly correlated with high levels of HbA1c.* ***Conclusions:*** *There was poor metabolic control in patients with associated complications such as hyperlipidemia, cardiovascular disease or chronic kidney diseases. Also, in most of the cases hypertension was associated with type 2 diabetes mellitus.*

key words: *diabetes mellitus, chronic kidney disease, hypertension, hyperlipidemia, Framingham risk score.*

Background and Aims

Diabetes mellitus (DM) is the disease-challenge of our century, characterized by an increase in serum glycemia. During the course of the disease the occurrence of micro and macro-vascular complications is possible, a fact which represents the cause of increased mortality and morbidity related to DM [1,2].

Gender, age, family history of coronary artery disease, increased serum levels of C reactive protein, fibrinogen, microalbuminuria, decreased glomerular filtration rate are cardiovascular risk factors – uninfluenced by

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patient behavior – contributing to the development of above mentioned pathologies [3,4]. There are also many important cardiovascular risk factors that result from the lifestyle of the patient: hypertension, obesity, dyslipidemia, smoking, sedentariness [5].

Framingham score is an algorithm obtained from a complex study that estimates the individual risk of each patient to develop a cardiovascular event over the next 10 years depending on certain parameters (age, smoking, total cholesterol, HDL-cholesterol, systolic blood pressure) [6,7].

Our study aimed to evaluate the cross-associations between the components of the metabolic syndrome, cardiovascular risk (evaluated by the Framingham risk score), diabetes-related biological parameters and chronic kidney disease in patients hospitalized due to poor metabolic control.

Material and methods

Study design and patients

In this cross-sectional study, we enrolled 218 patients with type 2 diabetes (T2DM), admitted in the Diabetes Clinic of the "Pius Brinzeu" Emergency Hospital Timisoara, according to a consecutive-case population-based principle. All these patients were hospitalized due to the presence of a metabolic imbalance which required hospitalization to be corrected.

Patients enrolled in the study were aged between 30 and 84 years, mean 62±9.5 years. More than a half were males (58.7%), with a mean age of 61.08 (±9.945), 95% CI (59.34; 62.82), while 41.3% were females, mean age of 63.30 (±8.735), 95% CI (59.34; 62.82).

The population was divided into the following age strata, 30-44, 45-59, 60-74 and 75-84 years. Participants of the strata 60-74 represent more than a half of the patients (52.3%), both in men and women (males: 47.7%, females: 58.9%). Patients in the strata 30-44 years represented the lowest proportions in both sexes (males: 4.7%, females: 1.1%).

Anthropometric, clinical and biological data

During the hospitalization, objective data such as: height, weight, BMI calculation were collected. Blood pressure values were measured initially and during hospitalization. A complete set of biochemical explorations (HbA1c, albumin-to-creatinin ratio, total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, serum creatinine) was performed for each patient.

Statistical analysis

Data was analyzed and collected using SPSS v.17 (SPPS Inc, Chicago, IL, USA) and is presented as mean and standard deviation (continuous variables having Gaussian distribution), median and interquartile range (IQR – in case of continuous variables without Gaussian Distribution) respectively percentages and absolute frequency for categorical variables. The variable's distribution type was evaluated using the Shapiro-Wilk test and for homoscedasticity using Levene's test.

The statistical tests used were: the Student's t-test (differences in means, variables with Gaussian distribution), Mann-Whitney U test (medians, non-Gaussian populations) respectively Pearson's Chi-Square and Fisher's exact test for proportions.

The correlation between studied variables was evaluated using Spearman's rank sum correlation coefficient (non-Gaussian distributed variables), its statistical significance being assessed using the *t*-distribution score test.

A *p*-value of 0.05 was considered as the threshold for statistical significance, and a confidence level of 0.95 was considered for estimating intervals.

Results

As a result of the evaluation of the baseline clinical and biochemical characteristics of the patients included in the study, we have obtained the results presented in Table 1.

Table 1. Baseline characteristics of the patients.

Number of patients	Men 128 (58.7%)	Women 90 (41.3%)	*p-value*
Age [years][(a)]	61.08 (9.945)	63.30 (8.735)	0.089[(d)]
DM duration [years][(b)]	13.00 (7.50-17.00)	10.00 (5.00-15.00)	0.014[(e)]
BMI [kg/m^2][(b)]	31.00 (27.25-35.00)	30.00 (27.00-34.20)	0.662[(e)]
HbA1c [%][(b)]	8.80 (7.60-10.10)	8.85 (7.30-10.20)	0.924[(e)]
High SBP[(c)]	57 (44.5%)	42 (46.7%)	0.755[(f)]
High DBP[c]	51 (40.2%)	36 (40.4%)	0.966[(f)]
HDLc [mg/dL][b]	42.00 (34.00-49.00)	39.00 (31.00-45.00)	0.010[(e)]
LDLc [mg/dL][b]	98.00 (74.50-126.50)	98.00 (71.00-122.00)	0.612[(e)]
VLDLc [mg/dL][b]	29.00 (18.00-46.00)	31.50 (19.00-46.00)	0.488[(e)]
Triglycerides [mg/dL][b]	144.00 (99.50-215.00)	161.00 (108.00-230.00)	0.399[(e)]
GFR [ml/min][a]	71.48 (24.07)	73.71 (26.84)	0.597[(d)]
ACR [mg/g][b]	46.00 (21.00-153.00)	42.50 (17.00-89.00)	0.426[(e)]

[(a)]Continuous variables (with Gaussian distribution)
[(b)]Continuous variables (with non-Gaussian distribution)
[(c)]Nominal variables
[(d)]t-test for equality of means
[(e)]Independent samples Mann-Whitney U test
[(f)]Pearson Chi-square test or Fisher's Exact Test
Abbreviations: DM – Diabetes Mellitus; BMI – Body Mass Index; SBP – Systolic Blood Pressure; DBP – Diastolic Blood Pressure; HDLc – High-density lipoprotein cholesterol; LDLc – Low-density lipoprotein cholesterol; VLDLc – Very low density protein; GFR – Glomerular Filtration Rate; ACR - Albumin/creatinine ratio.

Diabetes Duration

The study sample included both patients with newly diagnosed diabetes as well as patients with diabetes duration longer than 30 years (Table 2).

Table 2. Diabetes duration in the study group.

Diabetes duration	Male	Female
	Percentage	
>20 years	4.1 %	11 %
15-20 years	21.9 %	11 %
10-15 years	25.0 %	25.6 %
5-10 years	18.8 %	25.6 %
<5 years	20.3%	26.8 %

In the age stratum of 60-74 years, most of the patients (29.8%) had a diabetes duration in the interval between 10 and 15 years, while in the other diabetes duration categories, namely, less than 5 years, 5-10 years and 15-20 years were equally distributed proportions, 20.0%.

Considering the BMI, we observed that half of the patients (49.1%) were obese and 31.7% of patients were overweight, while 7.8% presented extreme obesity (BMI >40 kg/m^2). Moreover, most of the overweight (84.1%), obese (87.9%), and extreme obese (88.2%) patients had suboptimal values of HbA1c.

Hypertension

The proportion of patients with high blood pressure was almost 50% for both males (systolic: 44.5%, diastolic: 46.7%) and females (systolic: 46.7%, diastolic: 40.4%). Most of the patients with hypertension were in the age group 60-74 years (systolic: 56.6%, diastolic: 54.0%). For males, the highest proportions of patients found to be hypertensive were in the age group, 45-59 years (systolic: 43.9%, diastolic: 45.1%) and 60-74 years (systolic: 45.6%, diastolic: 45.1%), while for females, most of the

hypertensive patients were in the age group 60-74 years (systolic: 71.4%, diastolic: 66.7%).

Hyperlipidemia

We observed that 13.8% of patients presented high and very high LDL cholesterol levels (160-189 mg/dL and more than 189 mg/dL), while 32.2% of patients had borderline high LDL cholesterol levels (130-159 mg/dL) as shown in Table 3. The proportions of patients included in the five LDL cholesterol levels were equally distributed between males and females. In the diabetes duration interval of 10-15 years were most of the patients in the borderline high and high LDL cholesterol levels (130-150 mg/dL and 160-189 mg/dL), 17.5% and 10.5%, respectively. We observed that all the patients with very high LDL cholesterol levels (more than 189 mg/dL) presented a suboptimal diabetes control. At the same time, almost all the patients (95.7%) with high LDL cholesterol levels (160-189 mg/dL) had HbA1c below 7%. Moreover, we observed that high levels of LDL cholesterol are significantly correlated with high levels of HbA1c ($r = 0.141$, $p < 0.05$). Most of the female patients (90%) presented low levels of HDLc (<50 mg/dl), being exposed to an increased risk of CHD. Moreover, most of them (85.2%) had suboptimal HbA1c levels. We observed that high levels of HbA1c are significantly correlated with low levels of HDL cholesterol ($r = 0.134$, $p < 0.05$).

We observed that 32.6% of patients had high and very high triglycerides levels (200-499 mg/dL and 500 mg/dL or above), while 16.5% presented borderline high triglycerides levels (150 to 199 mg/dL). Most of the patients with high and very high triglycerides levels were in the age stratum of 60-74 years, 54.0% and 75.0%, respectively. We observed that all the patients with very high triglycerides levels (500 mg/dL or above) presented a suboptimal diabetes control. At the same time, most of the patients (79.4%) with high triglycerides levels (200-499 mg/dL) and almost all the patients (91.7%) with borderline high triglycerides levels (150 to 199 mg/dL) had HbA1c below 7%. Moreover, we observed that high levels of triglycerides are significantly correlated with high levels of HbA1c ($r =. 0.193$, $p < 0.01$). Also, we observed that high levels of HbA1c are significantly correlated with high levels of VLDL cholesterol ($r = 0.160$, $p < 0.05$).

Table 3. Description of the lipid parameters.

HDLc	Men	Women
60 mg/dL or higher	31 (24.2%)	3 (3.3%)
40-50 mg/dL for men, 50-59 for woman	45 (35.2%)	6 (6.7%)
<40 mg/dL for men, <50 mg/dL for women	52 (40.6%)	81 (90%)
LDLc		
<100 mg/dL	68 (53.1%)	50 (55.6%)
100-129 mg/dL	28 (21.9%)	20 (22.2%)
130-159 mg/dL	11 (8.6%)	11 (12.2%)
160-189 mg/dL	16 (12.5%)	7 (7.8%)
>189 mg/dL	5 (3.9%)	2 (2.2%)
Triglycerides		
<150 mg/dL	69 (53.9%)	42 (46.7%)
150-199 mg/dL	22 (17.2%)	14 (15.6%)
200-499 mg/dL	34 (26.6%)	29 (32.2%)
500 mg/dL or above	3 (2.3%)	5 (5.6%)
Total cholesterol		
<200 mg/dL	85 (67.5%)	66 (74.2%)
200-239 mg/dL	20 (15.9%)	11 (12.4%)
240 mg/dL or above	21 (16.7%)	12 (13.5%)

Abbreviations: CHD – Cardiac heart disease; HDLc – High-density lipoprotein cholesterol; LDLc – Low-density lipoprotein cholesterol;

Chronic kidney disease (CKD)

Considering the measured glomerular filtration rate (GFR), we observed that 12.4% of patients were placed in CKD stage G3b (30-44 ml/min and 15-29 ml/min), while 0.9% of patients were included in the G5 stage (<15 ml/min) (KDIGO2012 classification). We observed that all the patients with kidney failure presented a suboptimal diabetes management. At the same time, most of the patients with G3b

kidney failure (30-44 ml/min), i.e. 84.3%, and G4 stage (15-29 ml/min), i.e., 94.4% had HbA1c below 7%.

When considering albumin-to-creatinin ratio (ACR), we observed that almost half of the patients presented microalbuminuria (30-300 mg/g), so a moderate CKD stage (A2). Additionally, a percent of 13.8% presented a severely increased risk of developing CKD. We observed that most of the patients at moderately increased and severely increased risk of CKD presented a suboptimal diabetes management, 85.3% and 80.0%, respectively. Additionally, computing the prognosis of CKD based on GFR and Albuminuria categories (KDIGO2012), we observed that a percent of 20.0% were at high risk of CKD, while 13.3% were at very high risk of CKD. Figure 1 presents the CKD risk groups based on both GFR and ACR values.

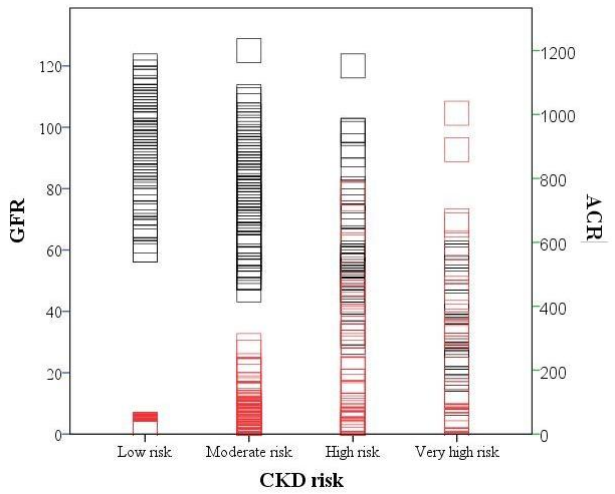

Figure 1. *Prognosis of CKD risk level based on GFR and ACR values (KDIGO2012). CKD – Chronic Kidney Disease; GFR – Glomerular Filtration Rate; ACR - Albumin/creatinine ratio.*

Treatment

Diabetes treatment included metformin (76.1% of patients), sulfonylurea (23.1% of patients), DPP-4 inhibitors (16.1% of patients), GLP-1receptor agonists (6.9% of patients), and two types of insulin, basal (50.5% of patients) and rapid (25.7% of patients). In addition, more than a half of the patients followed a treatment including hypertension medications: ACE inhibitors/ARBs (58.7%), beta-blockers (61.9%), and diuretics (57.6%), while calcium channel blockers were administrated to 11.5% of patients. Moreover, 67.9% of patients followed a treatment including cholesterol-lowering drugs, such as statins (Table 4).

Table 4. Frequences of the used medication.

Metformin	166 (76.1%)
Sulfonylurea	51 (23.4%)
DPP-4 inhibitors	35 (16.1%)
GLP-1receptor agonists	15 (6.9%)
Insulin	
Basal	110 (50.5%)
Rapid	56 (25.7%)
Statin	149 (67.9%)
Antiplatelet drug	148 (67.9)
ACE inhibitors/ARB	128 (58.7%)
BB	135 (61.9%)
CCB	25 (11.5%)
Diuretics	125 (57.6%)

Abbreviations: ACE - Angiotensin-converting enzyme; ARB - angiotensin receptor blockers; BB - Beta blockers; CCB - Calcium channel blockers.

Risk of cardiovascular disease (CVD)

We assessed the risk score of developing heart disease or having a heart attack by computing the Framingham 10-year risk estimation. For male patients, the Framingham scores ranged between 6 and 24, mean 18.88±3.275, while the scores for female patients were slightly lower, ranging from 10 to 23, mean 18.47±32.581.

We observed that the Framingham scores highly correlated with GFR for both men and women, $r = -419$, $p < 0.0001$, and $r = -0.391$, $p < 0.0001$, respectively. At the same time, we observed significant differences between the score values of patients with and without systolic and diastolic hypertension, for both male, systolic: Mann-Whitney U test ($U = 7.662$, $p < 0.001$), diastolic: Mann-Whitney U test ($U = 6.999$, $p < 0.01$), and female patients, systolic: Mann-Whitney U test ($U = 8.169$, $p < 0.001$),

diastolic: Mann-Whitney U test (U = 7.396, p < 0.001), respectively.

Median Framingham risk scores (IQR) in *female* patients with low (FRS<10%), moderate (FRS 10-19%), high (≥20%) and very high CVD risk scores were 18.51 (13.7–24.8), 21.5 (18.51–27.5) , 24.8 (21.5–27.5) and 24.8 (20.75-30), respectively, showing a significant increase as the CVD risk increases (Kruskal-Wallis test, $X^2(3) = 15.41$, p = 0.001) (Figure 2, left).

Median Framingham risk scores (IQR) in *male* patients with low, moderate, high and very high CKD risk scores were 18.00 (16.00–20.00), 19.00 (18.00–21.00) , 21.00 (19.00–23.00) and 20.5 (19.00-23.00), respectively, showing a significant increase as the CVD risk increases (Kruskal-Wallis test, $X^2(3) = 16.721$, p = 0.001) (Figure 2, right).

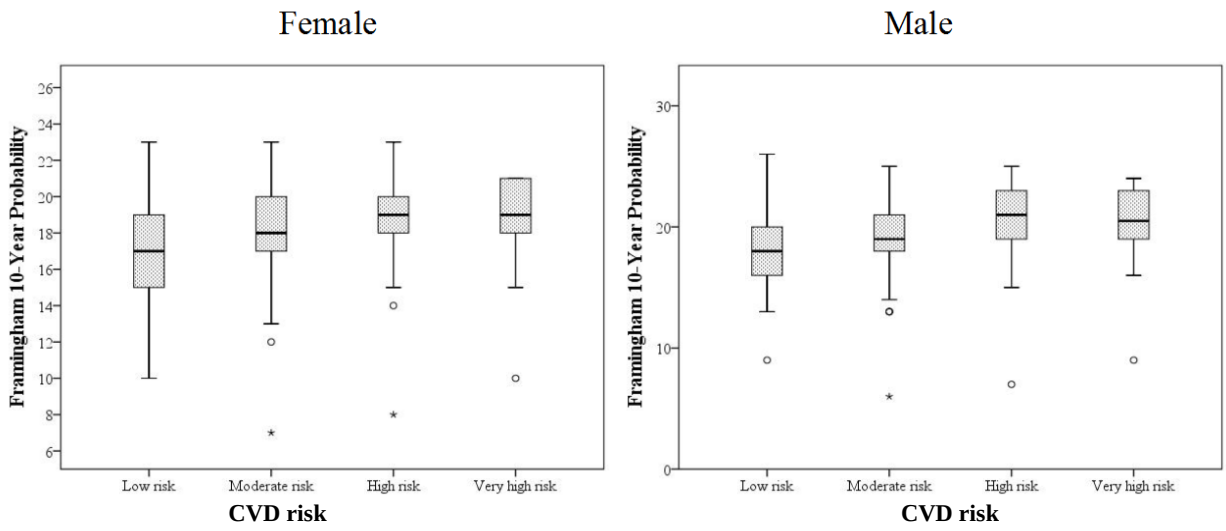

Figure 2. *Calculated Framingham probability of developing CHD within 10 years, stratified by CVD risk group, CVD – cardiovascular disease.*

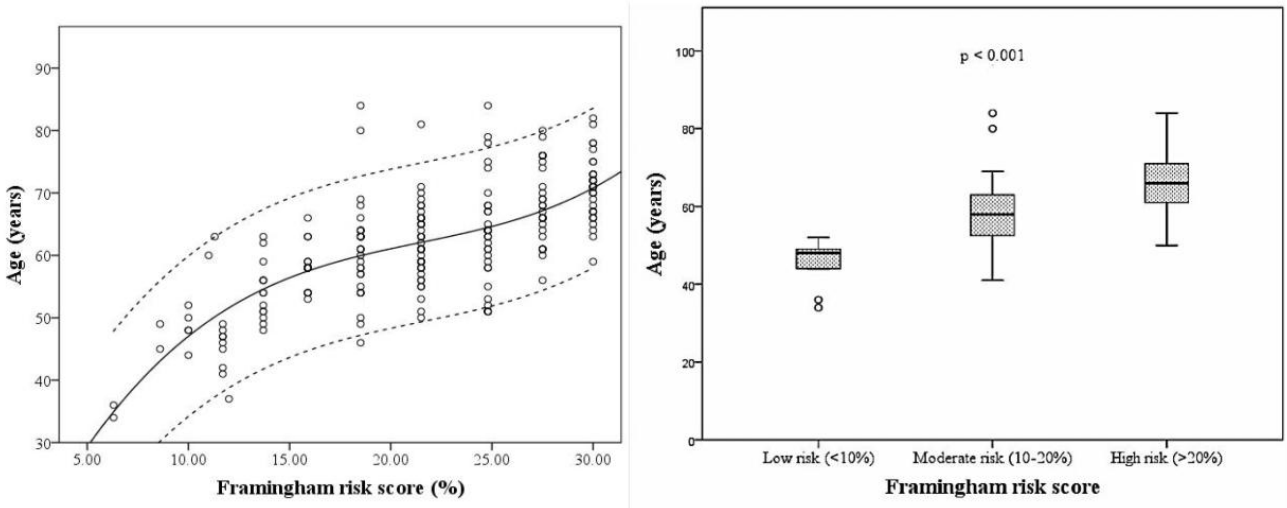

Figure 3. *Correlation of Framingham risk score with age in female patients with diabetes. Left: Scatter plot of Framingham risk score and age. Right: Box plots of patients' age according to their Framingham risk score group, R^2 cubic = 0.523. The p value indicates the statistical significance of comparison of ages between the three score groups (Kruskal-Wallis test, $X^2(2) = 68.98$, p < 0.001).*

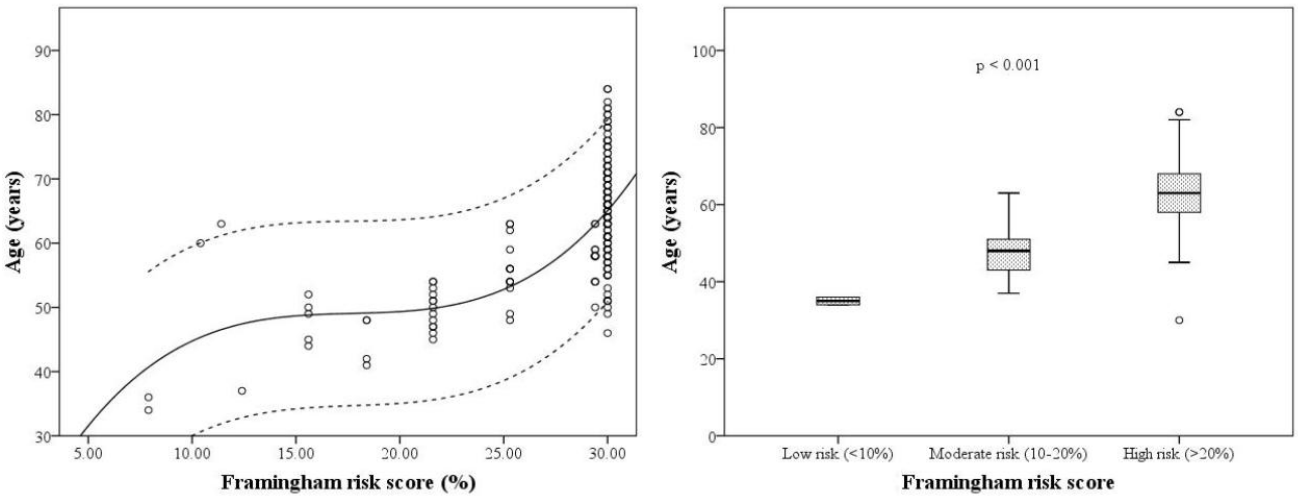

Figure 4. *Correlation of Framingham risk score with age in male patients with diabetes. Left: Scatter plot of Framingham risk score and age. Right: Box plots of patients' age according to their Framingham risk score group, R^2 cubic = 0.410. The p value indicates the statistical significance of comparison of ages between the three score groups (Kruskal-Wallis test, $X^2(2) = 27.54$, $p < 0.001$).*

Figures 3 and 4 include the graphical representation of the correlation of the Framingham risk score and age, and Framingham risk score level stratified by age for female and male patients, respectively. We observed that CVD risk increases as age increases, when considering both the risk score and risk level for both men and women.

Discussion

The increase in the number of diabetic patients highlights the importance for developing new strategies for prevention, early diagnosis and management of disease complications. This is a global problem that concerns both the patient and the medical staff, as well as the general population, given the exorbitant costs generated by DM [8,9].

Screening of the disease is deficient, although there are concrete tests that can be carried out in this regard. This is why at the time of the diagnosis one third of the diabetic patients already have associated complications [10].

Over the course of the last decade, many scores have been proposed to accurately determine the risk of patients developing the disease and its complications, in particular cardiovascular events [11,12].

Framingham risk score provides the individual probability of each patient to develop a cardiovascular event over the next 10 years depending on certain parameters (age, smoking, total cholesterol, HDL-cholesterol, systolic blood pressure) [9]. The initial version thought in calculating this score was upgraded and uses more specific parameters (age range, hypertension treatment, smoking, total cholesterol, and diabetes) [13].

Conclusions

The value of body mass index was positively correlated with an increased level of HbA1c, a significant percentage of the patients being overweight or obese. Half of our study cohort had associated hypertension, the proportion between male and female being equal.

Suboptimal values of HbA1c were correlated with increased LDL-cholesterol levels, high triglycerides and with the presence of low to severe CKD.

As a final conclusion, Framingham risk score revealed that CVD risk increases as age increases in patients with DM, when considering

both the risk score and risk level for both men and women. For female patients Framingham risk score is slightly lower (ranged between 10 to 23) than for male patients (ranged between 6 and 24).

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