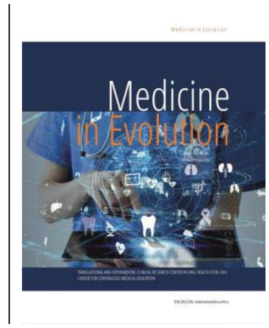
Post covid Follow up on Diabetic Patient



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Abstract

Aim and objectives: This study aimed to explore insulin necessity in hospitalized patients with non-insulin-dependent diabetes mellitus (DM) for the first six months after COVID-19 infection. A pro-inflammatory and pro-coagulative status probably contribute to the risk of worse outcomes in diabetes. Material and Methods: A number of 78 non-insulin necessitate diabetic patients with COVID-19 infection which needed oxygen therapy were included in the research. There were collected parameters routinely assessed to detect the possible predictors of diabetic patient evolution in SARS-CoV-2 infection. Results: The evolution of insulin necessity for 78 patients with non-insulin-dependent DM at admission was towards transformation into insulin-dependent DM at 6 months after discharge in 30 cases (38.5%), while the rest of the patients remained on oral antidiabetic drugs (48 patients, 61.5%). Conclusions: At hospitalized diabetic patient with covid-19 infection under corticotherapy, statistically significant differences were noted in HbA1c and aPTT level at 3 and 6 months after discharge.

Keywords: corticotherapy, COVID-19 infection, diabetes mellitus

INTRODUCTION

Since the initial COVID-19 outbreak in China, much attention has focused on people with diabetes because of poor prognosis in those with infection. Studies have shown that COVID-19 does not affect all population groups equally. In diabetic patients' evolution three important factors are age, race, and ethnicity.

In a study conducted by Yang at all it has been reported that patients infected with SARS-CoV2 suffered from hyperglycemia, which might be caused by SARS-Cov 2 damaging the pancreatic islets though ACE2 [1,2]. ACE2 is known as being a protein that permits the attachment of SARS-Cov2 virus to pancreatic cell. Loss of beta cell identity through the differentiation, degranulation and upregulation of inflammatory stress is potential underlying mechanism of pancreatic insulin secretion dysfunction [3].

Preexisting disease and a pro-inflammatory and pro-coagulative state all probably contribute to the risk of worse outcomes [4]. Data about monitoring post COVID-19 infection at patients with diabetes is limited at present. In a study conducted by C. Yuchen and all. for patients with diabetes and COVID-19, increasing odds of in-hospital death were associated with older age and elevated CRP (C-reactive protein), whereas risk factors for poor prognosis were lower albumin and higher CRP [5]. A better glycemic control among people living with diabetes could reduce the severity of the COVID-19 symptoms and the outcome of patient evolution in post covid. COVID-19 is associated with low-grade inflammation, which in turn, may induce or exacerbate insulin resistance [6]. The management of diabetes in the context of COVID-19 infection, using corticosteroids, is difficult. It must be dynamic because all the variables change from one day to the next [7,8].

Aim and objectives

This study aimed to explore evolution of hospitalized patients with non-insulin-dependent diabetes mellitus (DM) compare to insulin dependent patients for the first six months following COVID-19 infection.

MATERIALS AND METHODS

Data collection

Our clinical retrospective observational study has been conducted in the Medical Department of Pelican Clinical Hospital Oradea between 01.01.2021- 30.06.2021 and we selected a number of 98 diabetic patients who were admitted for SARS-CoV 2 infection.

Inclusion/ exclusion criteria

All patients with SARS-CoV2 infection and diabetes admitted in the Medical Department of Pelican Clinical Hospital Oradea between 01.01.2021-30.06.2021 were screened. Inclusion criteria were diabetic patients with COVID-19 infection which needs oxygen therapy, age above 18 years and the COVID-19 confirmed through real time-polymerase chain reaction (RT-PCR). The exclusion criteria were pregnant women, hospital stay less than 7 days, deceased patients, transferred to intensive care, patients with insulin therapy at admission, diabetic patient with advanced CKD (chronic kidney disease) patient under chemotherapy. Among the patients hospitalized a number of 90 patients met all the inclusion criteria. 12 patients were lost to follow-up because they did not complete all the required assessments. The evolution of the 78 patients with non-insulin-dependent DM at admission was towards transformation into insulin-dependent DM at 6 months after discharge in 30 cases (38.5%), while the rest of the patients remained on oral antidiabetic drugs (48 patients, 61.5%).

Study tolos

For all participants, there were registered basic demographic data: age, gender, body mass index (BMI), medical history and the type of treatment followed at home for diabetes mellitus and treatment in hospital. All patients received dexamethasone in the first 10 days after admission in the dosage of 16 mg/day. Other data collected included the HbA1c value at 3 and at 6 months after discharge.

For this study, there were collected parameters routinely assessed to detect the possible predictors of diabetic patient evolution in SARS-CoV-2 infection: complete blood count (leucocyte, lymphocyte, neutrophil), FBG (fasting blood glucose), HbA1c (glycated hemoglobin test), CRP (C-reactive protein), AST (aspartate aminotransferase), ALT (alanin aminotransferase), eGFR(estimated glomerular filtration rate), ferritin, procalcitonin, D-dimer, LDH (lactate dehydrogenase), aPTT (activated partial thromboplastin clotting time), natrium, potassium, INR (International Normalized Ratio), fibrinogen. All analyses were performed using standard clinical chemistry techniques in the clinical laboratory of the hospital where the study was performed. The samples were collected in the morning, a jeun, and we extracted data from the first day of admission, during hospitalization (days 3–7), and upon discharge, at 3 months and 6 months after discharge.

Statistical análisis

After checking the distribution by the Kolmogorov-Smirnoff test, the variables were described by mean and standard deviation, respectively median and interquartile range. The comparison of the variables between the two groups were checked out using the Student's test for independent batches, respectively the Mann-Whitney test, depending on the distribution. Categorical variables were analyzed by the chi-square test and described as percentages of the total number of cases. For variables with a statistically significant difference, a logistic regression model with stepwise entry was built to analyze the independence of the risk factors and determine the odds ratio. In order to verify the linear correlation between independent risk factors and glicated hemoglobin at 6 months after discharge, we used the Pearson correlation coefficient, as these are variables with a normal distribution.

RESULTS

We selected a number of 360 patients admitted for SARS-CoV2 infection. A number of 270 patients were excluded due to not meeting the inclusion criteria or had exclusion criteria, or not consent. Among the patients hospitalized a number of 90 patients met all the inclusion criteria. Of these, 12 patients were lost to follow-up because they did not complete all the required assessments. The evolution of the 78 patients with non-insulin-dependent DM at admission was towards transformation into insulin-dependent DM at 6 months after discharge in 30 cases (38.5%), while the rest of the patients remained on oral antidiabetic drugs (48 patients, 61.5%) (Figure 1).

The difference between the two study groups from a demographic and medical history point of view is shown in the following table (Table 1).

Table 1. Demographic and medical history for the two study groups

Parameter	Group IN	Group NIN	p-Value
Gender (M/F)	20/10	28/20	0,6193*
Age (years) – media (SD)	65,07 (8,43)	64,75 (10,56)	0,8900**
Environment of origin (U/R)	18/12	34/14	0,4590*
BMI (kg/m^2) – media (SD)	28,93 (3,68)	28,29 (3,33)	0,4295**
PMH, N (%)			
HTN	26 (86,67%)	46 (95,83%)	0,2977*
Heart failure	6 (20%)	18 (37,5%)	0,1685*
AF	6 (20%)	2 (4,17%)	0,0631*
CVA	2 (6,67%)	6 (12,5%)	0,6581*
MI	4 (13,33%)	14 (29,17%)	0,1807*
COPD	8 (26,67%)	8 (16,67%)	0,4387*
Asthma	8 (26,67%)	12 (25%)	0,9184*
Cognitive disorders	2 (6,67%)	6 (12,5%)	0,6581*
Dyslipidemia	22 (73,33%)	32 (66,67%)	0,7125*

Group-IN = insulin-necessity at 6 months after discharge, Group-NIN = non-insulin necessity at 6 months after discharge, M=male, F=female, SD=standard deviation, U=urban, R=rural, BMI = body mass index, PMH=personal medical history, N=number, HTN= hypertension, AF= atrial fibrillation, CVA = cerebrovascular accident, MI = previous myocardial infarction, COPD= chronic obstructive pulmonary disease; *chi square test with Yates' correction, **the Student test for independent groups.

Among all preexistent comorbid conditions only atrial fibrillation was prevalent as having a weak statistically significance (p=0,0631) at patients who required insulin treatment at 6 months after admission but did not reach the threshold of statistical significance between groups. The rest of the criteria were similar for the two groups.

Comparing paraclinical investigations, at the time of admission, the results for the two groups are described in the Table 2.

Table 2. Paraclinical investigations at the time of hospitalization for the two study groups

Parameter – median (IQR)	Group IN	Group NIN	p-Value
FBG (mg/dl)	162 (150-220)	186 (131-204)	0,7267*
HbA1c (%)	7,8 (6,9-8,1)	7,75 (6,65-8,2)	0,9344*
CRP (mg/dl)	69,3 (30-102,1)	67,45 (36,65-118,75)	0,6366*
AST (U/L)	31 (22,3-41)	33,25 (26,15-39,5)	0,5377*
ALT (U/L)	39 (23,5-117,6)	38 (23,6-50,6)	0,2255*
eGFR (ml/min/1,73m^2)	98,4 (93,2-100,2)	95,7 (89,75-100,55)	0,4595*
Procalcitonin (ng/ml) <0,5 / 0,5-2 / 2-10 / >10	30/0/0/0	`48/0/0/0	1,0000*
D-dimer (μg/ml)	0,34 (0,26-0,71)	0,38 (0,22-0,54)	0,3880*
Natrium (mmol/L)	133,1 (132,1-134)	133,2 (131,65-135,3)	0,7421*
INR	1 (1,00-1,02)	1 (1,00-1,11)	0,1583*
Lung damage (%)	65 (52-66)	61 (54,5-67)	0,7892*
Leucocytes (10^3/μl)	9,40 (1,76)	7,34 (2,49)	0,0002**
Lymphocytes (10^3/μl)	0,88 (0,42)	0,99 (0,32)	0,1896**
Neutrophil (%)	76,27 (11,90)	73,52 (12,19)	0,3307**
Ferritin (ng/ml)	1176,27 (635,12)	943,97 (473,04)	0,0688**
Parameter − medie (DS)			
LDH (U/L)	429,40 (158,82)	373,75 (156,22)	0,1299**
Potassium (mmol/L)	3,93 (0,44)	3,79 (0,41)	0,0893**
aPTT (second)	19,14 (1,55)	21,7 (3,47)	0,0003**
Fibrinogen (mg/dL)	575,8 (150,4)	543,6 (160,1)	0,3791**

Group IN=insulin-necessity at 6 months after discharge, NIN=non-insulin necessity at 6 months after discharge, IQR=interquartile range, DS=standard deviation, FBG=fasting blood glucose, HbA1c=glycated hemoglobin test, CRP=C-reactive protein, AST=aspartate aminotransferase, ALT=alanine aminotransferase, eGFR=estimated glomerular filtration rate, LDH=lactate dehydrogenase, aPTT=activated partial thromboplastin clotting time, INR=International Normalized Ratio, *Mann-Whitney test; ** the Student test for independent groups.

A higher leukocyte level and a shorter aPTT, at the time of admission, were associated with a higher probability of introducing insulin in the treatment of DM (Figure 1).

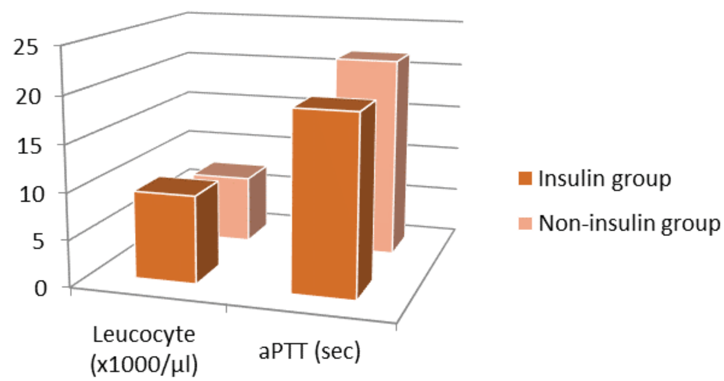

Figure 1. WBC count and aPTT level at the time of admission for the two study groups (IN at 6 months after discharge, NIN at 6 months after discharge, aPTT)

Higher plasma potassium levels and ferritin levels were also observed in these patients, but without reaching statistically significant differences.

The evolution of paraclinical determinations were evaluated as a possible risk factor for the outcomes of diabetes. Results are presented in the following table 3.

Table 3. Evolution of paraclinical investigations during hospitalization for the two study groups

Parameter – media (DS)	Group IN	Group NIN	p-Value
FBG in hospital (mg/dl)	218,2 (56,86)	193,25 (62,71)	0,0807*
Neutrophil at discharge (%)	79,88 (9,97)	70,42 (17,74)	0,0094*
LDH at discharge (U/L)	271,47 (69,89)	277,25 (98,66)	0,7803*
Fibrinogen at discharge (mg/dL) – media (SD)	355 (98,68)	367,1 (150,7)	0,6980*
Lung damage at discharge (%) – media (SD)	31,93 (8,34)	30,04 (6,76)	0,2761*
Parameter– median (IQR)			
HbA1c at discharge (%)	8,3 (8,1-8,8)	8,0 (7,25-8,25)	0,0135**
CRP at discharge (mg/dl)	37,1 (8,5-56,2)	22,72 (4,73-48,95)	0,6963**
AST at discharge (U/L)	29,2 (21-40)	23,6 (18,35-30,65)	0,2854**
ALT at discharge (U/L)	45,6 (26-67,8)	41,75 (34,5-60,3)	0,6963**
Leucocytes at discharge (10^3/µl)	7,6 (6,5-9,6)	8,66 (7,9-9,4)	0,1389**
Lymphocytes at discharge (10^3/µl)	0,92 (0,73-1,2)	1,2 (1,04-1,5)	0,0004**
Ferritin at discharge (ng/ml)	653 (452-1124)	590 (334-718)	0,0844**
Procalcitonin at discharge (ng/ml) <0,5 / 0,5-2 / 2-10 / >10	30/0/0/0	46/0/2/0	0,6918***
D-dimer at discharge (µg/ml)	0,45 (0,19-1,02)	0,32 (0,24-0,48)	0,6961**
Potassium at discharge	4,1 (3,9-4,3)	4,0 (3,9-4,1)	0,0765**
Natrium at discharge (mmol/L)	133,5 (132-135)	134,1 (133-136,5)	0,1387**
aPTT at discharge (seconds)	19,6 (19,1-20,1)	20,15 (19,2-21,15)	0,0458**
INR at discharge	1,1 (1,04-1,10)	1,1 (1,04-1,19)	0,1162**

IN=insulin-necessity at 6 months after discharge, NIN=non-insulin necessity at 6 months after discharge, DS=standard deviation, FBG=fasting blood glucose, HbA1c = glycated hemoglobin test, CRP=C-reactive protein, AST=aspartate aminotransferase, ALT=alanine aminotransferase, eGFR=estimated glomerular filtration rate, LDH=lactate dehydrogenase, aPTT=activated partial thromboplastin clotting time, INR=International Normalized Ratio; *the Student test for independent groups; ** the Mann-Whitney test.

Statistically significant differences were noted in HbA1c, lymphocyte count, neutrophil (in percentage), and aPTT level at discharge. Elevated HbA1c and neutrophils, along with low lymphocyte counts and aPTT were associated with increased risk of negative diabetes outcomes. Also, during hospitalization, differences were observed in blood glucose levels, ferritin level and potassium level at discharge, but these differences did not reach the threshold of statistical significance. Several criteria related to treatment with dexamethasone and length of stay (LOS) were also recorded and these results are exposed in the following table 4. Neither the specific treatment of the COVID-19 infection, nor the LOS influenced the evolution of NIN DM at hospital admission and after discharge. The results of patient reassessment at 3 and 6 months after discharge can be seen in the following table 4.

Table 4. Criteria related to treatment and duration of hospitalization for the two study groups

Parameter	Group IN	Group NIN	p-Value
Medication routes of administration of antiviral medication (oral/parenteral)	10/20	12/36	0.5912*
Dexamethasone dose (mg/zi) – median (IQR)	16 (16-16)	16 (16-16)	0.5343**
LOS – media (DS)	11.53 (1.43)	11.33 (2.25)	0.6656***

IN=insulin-necessity at 6 months after discharge, NIN=non-insulin necessity at 6 months after discharge, IQR=interquartile range, DS=standard deviation, LOS- lenght of stay; *chi square test with Yates' correction; **Mann-Whitney test; ***the Student test for independent groups.

As we can see, HbA1c at 3 and at 6 months after discharge could predict the evolution towards insulin-dependence of DM, with a statistical significance of 0,0669 at 3 months and 0,0061 at 6 months after discharge (table 5). As we can see, evidently the level of HbA1C at 6 months presents important differences being criteria to continue insulin therapy. Estimated glomerular filtration rate eGFR and BMI remain, in principle, unchanged during this follow-up period (Table 5).

Table 5. Patient reassessments at 3 and at 6 months after discharge for the two study groups

Parameter– media (SD)	Group IN	Group NIN	p-Value
HbA1c at 3 months (%)	7,67 (0,73)	7,32 (0,83)	0,0669*
HbA1c at 6 months (%)	7,13 (0,61)	6,70 (0,68)	0,0061*
BMI at 3 months (kg/m²)	28,46 (3,19)	28,29 (3,02)	0,8084*
BMI at 6 months (kg/m²)	28,00 (2,99)	27,87 (2,80)	0,8524*
Parameter– median (IQR)	**Group IN**	**Group NIN**	**p-Value**
eGFR at 3 months (ml/min/1,73m²)	98,6 (96,3-99,3)	97,9 (95,6-98,95)	0,5785**
eGFR at 6 months (ml/min/1,73m²)	98,7 (97,5-99,5)	97,7 (94,9-99,6)	0,4229**

IN=insulin-necessity at 6 months after discharge, NIN=non-insulin necessity at 6 months after discharge, IQR=interquartile range, DS=standard deviation, IQR=interquartile range, HbA1c=glicated hemoglobin test, eGFR=estimated glomerular filtration rate, BMI=body mass index; *the Student test for independent groups; **the Mann-Whitney test.

The logistic regression model built for the conversion of diabetes from NIN to IN for all variables found with statistically significant difference identified only 2 independent risk factors: white blood cell count (odds ratio = 1.7136, CI 95%: 1.06-2,75) and aPTT level (odds ratio = 0.6484, CI95%: 0.44-0.95) at the time of admission.

The decision to introduce insulin in the treatment of the patient with DM based on the level of HbA1c, we also calculated the Pearson correlation coefficient between the level of HbA1c at 6 months after discharge and the level of leukocytes, respectively aPTT at the time of admission. The results were negative, the correlation between these values not being linear (for leukocytes – r=0.1159, CI 95%: -0.16 – 0.38, p=0.4230 and for aPTT – r=0.0486, CI95 %: -0.23 – 0.32, p=0.7374).

DISCUSSIONS

Management of diabetes in the context of COVID-19 infection is difficult in case of corticotherapy. All patients need to receive insulin therapy with strict monitoring of blood sugar levels during their hospitalizations in order to guarantee a good balance and a good evolution [7,8]. A review by Attri, B., Goyal, A., Gupta, Y. et al [9] provides a practical guidance on the use of the basal-bolus insulin regimen in patients with diabetes mellitus hospitalized with COVID-19. RECOVERY trial provides evidence that treatment with dexamethasone at dose of 6 mg once daily for up to 10 days reduces 28-day mortality in patients with COVID-19 who received respiratory support [10]. In our study we did not found statistically significant differences in case of corticotherapy for our two study groups.

The severity and COVID-19 outcomes are correlated with the extensive infiltration of neutrophils in the lung and neutrophil numbers in the peripheral blood, and the magnitude of neutrophilia is suggestive of the intensity of inflammatory responses [11]. Statistically significant differences were noted in lymphocyte count and neutrophil (in percentage) in our study for leucocyte p=0,0002 (during hospitalization), neutrophile at discharge p=0,0094 and lymphocytes at discharge p=0,0004. Elevated neutrophils, along with low lymphocyte counts were associated with increased risk of negative diabetes outcomes. Significantly higher levels of inflammatory biomarkers indicate that COVID-19 is a potent trigger of inflammatory responses that could be associated with poor clinical outcomes [12]. No differences were observed in case of inflammatory biomarkers (ferritin, CRP, procalcitonin) for our two study groups.

For hospitalized patients' insulin therapy is preferred, in case of moderate and severe COVID-19 disease. Better outcomes have been reported in COVID-19 patients receiving Metformin as therapy for diabetes mellitus [13].

Among the patients who were receiving oxygen, the use of dexamethasone was associated with a lower risk of invasive mechanical ventilation. In both these groups, the use of dexamethasone increased the chance of being discharged from the hospital alive within 28 days.

In our study a higher leukocyte level and a shorter aPTT, at the time of admission, were associated with a higher probability of introducing insulin in the treatment of diabetic patients with COVID-19 infection.

Age remains the strongest risk factor for severe COVID-19 outcomes. In our group media of age was around 65 years, but without reaching statistically significant differences between the two groups. Regarding death reports in the follow-up period, we had 100% survivors on participants in this study.

CONCLUSIONS

At hospitalized diabetic patient with COVID-19 infection under corticotherapy, statistically significant differences were noted in HbA1c, lymphocyte count, neutrophil (in percentage), and aPTT level at discharge. Elevated HbA1c and neutrophils, along with low lymphocyte counts and aPTT were associated with increased risk of negative diabetes outcomes. As we can see, HbA1c at 3 months after discharge could predict the evolution towards insulin-dependence of DM. In our study patients with NIN DM at admission for Covid-19 infection, need insulin therapy at 6 months in a percentage of 38,6%. For that reason, the periodic diabethological follow- up is necessary for more than 6 months.

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