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Glycemic variation in elderly diabetic patients with COVID-19

Variação glicêmica em idosos diabéticos com COVID-19

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ABSTRACT
This study aimed to identify the glycemic variation in the elderly with diabetes mellitus and COVID-19 in long stay institutions. Medical records and laboratory test results from 203 elderly residents of 4 LSIE in the municipality of Maringá, pertaining to the period between 2017 and 2022. Of these, 10 were diagnosed with diabetes mellitus, being selected the 5 who were diagnosed with Covid-19 and that had detailed glycemic lab test results from the period in question. Three of them showed glycemic increase, while the other two practically maintained the same glycemic indices before and after Covid-19. All cases had light manifestations of Covid-19, without the need for hospitalization. The results indicate that elderly people with glycemic indices above the normal established for their age may have increased blood glucose when infected with SARS-CoV-2.

Keywords: Blood glucose; COVID-19; Diabetes Mellitus; Long Stay Institutions.

RESUMO
Este estudo teve como objetivo identificar a variação glicêmica de idosos com diabetes mellitus e COVID-19 em instituições de longa permanência. Foram coletados e analisados prontuários e resultados de exames laboratoriais de 203 idosos residentes em 4 ILPIs no município de Maringá, pertinentes ao período entre 2017 e 2022. Destes, 10 idosos apresentavam diagnóstico de diabetes mellitus, sendo selecionados os 5 que apresentaram diagnóstico de COVID-19 e exames de glicemia detalhada durante o período estudado. Três deles apresentaram aumento na glicemia, enquanto os outros dois praticamente mantiveram os mesmos índices glicêmicos pré e pós-COVID-19. Todos os casos apresentaram manifestações leves da COVID-19 sem necessidade de internação. Os resultados indicam que idosos com índices glicêmicos elevados para a sua respectiva idade podem apresentar índices de elevação da glicêmica quando infectados pelo SARS-CoV-2.

Palavras-chave: COVID-19; Diabetes Mellitus; Glicemia; Instituições de Longa Permanência.

INTRODUCTION

According to the IBGE, life expectancy in Brazil increased to 76.4 years old in 2020, and, according to estimates, 25.49% of the Brazilian population will be formed by elders above 65 years old in 2016[1]. Therefore, it is increasingly relevant to study and formulate strategies to optimize care for the elderly. Long Permanence Institutions for the Elderly (LPIs) are public or private facilities for the 60-year-old or older population to live in collectivity. They seek to

provide basic needs, such as food, hygiene, and housing, as well as the specialized care required by the many elders with chronic comorbidities or some degree of dependence[2].

One of the most common comorbidities in the population in this age group is diabetes mellitus. According with estimates from the International Diabetes Federation (IDF), nearly 536 million people from 20 to 79 years old had the disease in 2020. Projections indicate a growing number of cases, approaching 783 million in 20453. This pathology is a multifactorial metabolic syndrome, characterized mainly by hyperglycemia caused by dysfunctions in the production or action of insuline. Type 2 diabetes represents more then 90% of cases[3].

Insulin is the main anabolic hormone. It is produced by pancreatic beta-cells from the islets of Langerhans, responsible to translocate cell membrane proteins that allow the cellular capture of glucose, an essential monosaccharide to carry out physiological metabolic processes[3].

The chronic hyperglycemia caused by uncontrolled diabetes leads to inflammation of the vascular endothelium and to the formation of microthrombi, which, in turn, obstruct the passage of blood to the endothelium, leading to more lesions. These factors contribute for the development of complications from diabetes. These complications can be divided in: microvascular, such as diabetic nephropathy, retinopathy, and neuropathy; and macrovascular, such as a relative increase in the risk of acute myocardial infarction, strokes, and peripheral artery disease[4].

The treatment of diabetes involves patient glycemic control, to avoid the development or worsening of complications. This control is carried out with non-pharmacological measures, such as diets and physical exercise, as well as pharmacological measures, such as the implementation of oral hypoglycemic drugs, or, in more advanced cases, with the use of insulin. Both these types of drugs are made available by the Single Health System[5]. Nearly 70.7% of the diabetic population has access to the necessary drugs free of charge via SUS. However, in 2020, Brazil and the world went through a paradigm shift in regard to public health, due to the beginning of the COVID-19 pandemic[6].

The SARS-CoV-2 virus is the etiologic agent responsible for COVID-19, a major viral inflammatory disease, which mostly affects the lungs and was declared as a pandemic by the WHO in early 2020[7]. The SARS-CoV-2 enters the cell depending on the expression of the angiotensin-converting enzyme (ACE) on the surface of the cell. The spike protein of the virus connects to the receptor, allowing for endocytosis and the subsequent liberation of its genome in the cytoplasm of the host, a process that leads to the lysis of the affected cell. The main complications caused by the disease are severe lung lesions, lung edemas formed by protein

exudate, and lung tissue fibrosis. These changes lead to dyspnea and to a drop in oxygen saturation, often requiring ventilators to stabilize patients in grave condition[8].

The first peak of cases took place in early June 2020, with a mean of 25,000 new cases a day. This number would only increase in the following months, a situation associated with uncertainty about effective methods of treatment and prevention. The lack of personal protective equipment (PPE) and the high demand for beds in the ICUs required a reorganization of all levels of health care in the struggle against the pandemic[9].

In addition to the respiratory system, the virus can damage several other organs where the receptor of the angiotensin-converting enzyme 2 (ECA-2) is expressed, such as the heart and the pancrease[10]. RNA sequencing studies showed that the ECA-2 receptor has a significant cellular expression in the exocrine glands, pancreatic islets, and in the pancreas microvasculature. Its expression was detected especially in beta-pancreatic cells, and research suggest that this expression is increased in diabetic patients[11, 12, 13, 14]. The beta-pancreatic cells have an essential role in cellular metabolism, as they are responsible for stimulating the capture of glucose in most cells of the organism and fpr using it as a source of energy[15].

The mortality rate of COVID-19 is 3.4%. However, the prognosis is even more negative when patients have chronic comorbidities, advanced age, and any degree of fragility[16]. Therefore, it is necessary to evaluate the evolution of diabetic elderly patients who had COVID-19, especially those with a higher degree of dependency, which are often found in LPIs. This data will contribute for the adoption of actions that can contribute to prevent complications and the worsening of diabetes mellitus in this population group.

This study is necessary to understand the relationship between post-COVID complications and diabetes mellitus in the environment of long permanence institutions, since both comorbidities increase the risk of elderly patients, especially in cases that present some degree of dependency.

Considering the above, the goal of this study was to clarify how COVID-19 affected the diabetes mellitus of LPI interns, through an evaluation of the glycemic control of these persons during the pandemic.

METHODOLOGY

This is a retrospective study, part of the research project "The impact of the COVID-19 pandemic on health and factors associated with residents of long permanence institutions in the city of Maringá", which was approved by Opinion 5.333.607. Data was collected from 2020 to

2022, including information on whether the patient was positive for COVID-19. It also included glycemic values, from 2017 to 2020, of elders with diabetes mellitus who lived in four long permanence institutions in a city in the northwest of Paraná.

The administrative system of Maringá mayor's office was used to search for the codes to identify the elders, as well as the records from the Primary Health Care where they were registered.

Data were collected from July to August 2022. From 203 elders in 4 institutions, 91 were included, as they tested positive for COVID-19. From these, we selected 9, who were also diagnosed with diabetes mellitus due to hyperglycemia, found in analyses to determine the presence of glycemia. 4 were excluded as they went through no exams of the sort during the period of the study. To do so, we performed a fasting plasma glucose test and the glucose tolerance test (GTT). Only one patient underwent a glycated hemoglobin test. Data was collected by two researchers who sought the selected names in Excel and Google Drive spreadsheets made available by the Health Secretariat.

Initially, we carried out a descriptive analysis of the data. Qualitative variables were presented in absolute (n) and relative (%) frequencies, and quantitative variables were expressed in mean, standard deviation, and minimum and maximum values. To compare the glycemic values before and after a positive COVID-19 test, we used tables and a chart.

RESULTS

From November 2020 to April 2022, in the four LPI studied, we found 91 elders tested positive for COVID-19. From these, 16 (17.5%) tested positive for the disease more than once, a total of 107 positive tests.

From the 91 elders, 5 (5.49%) were diagnosed with diabetes mellitus. Their age varied from 70 to 88, with a mean of 80±7.96 years (Table 1).

Table 1. Characterization of diabetic elders regard to other comorbidities, sex, and age (Maringá – PR, 2022)

Case No.	Sex	Age (years)	Comorbidities
1	Male	70 years old	Hypertension
2	Male	73 years old	-
3	Male	85 years old	Hypertension Dyslipidemia

			Heart disease
4	Female	84 years old	Hypertension
5	Female	88 years old	Hypertension

Source: The authors (2023).

As table 2 shows, from the 5 diabetic patients, only one (case No. 1) tested positive for COVID-19 twice in the period. One elder (case No. 5), even after receiving the fourth dose of the vaccine, still tested positive for the disease.

Table 2. Date of the positive test and of glycemia before and after the positive test for COVID-19 in pre-diabetic and diabetic elders from the LPIs (Maringá – PR, 2022)

Case No.	**Date of the positive test**	**Pre-COVID Glycemia Date**	**Post-COVID Glycemia Date**
1	21/11/2020 08/02/2021	08/11/2017	24/06/2021
2	20/11/2020	17/10/2017	13/04/2022
3	13/11/2020	24/10/2019	05/03/2021
4	17/05/2021	22/09/2020	27/05/2021
5	12/04/2022	23/03/2022	23/09/2022

Source: The authors (2023).

Figure 1 shows the comparison between the glycemic levels before and after a positive test for COVID-19 in the elders. None of the five elders in this study were hospitalized or used corticosteroid drugs during the COVID-19 infection, which is relevant as these factors can affect their glycemic levels.

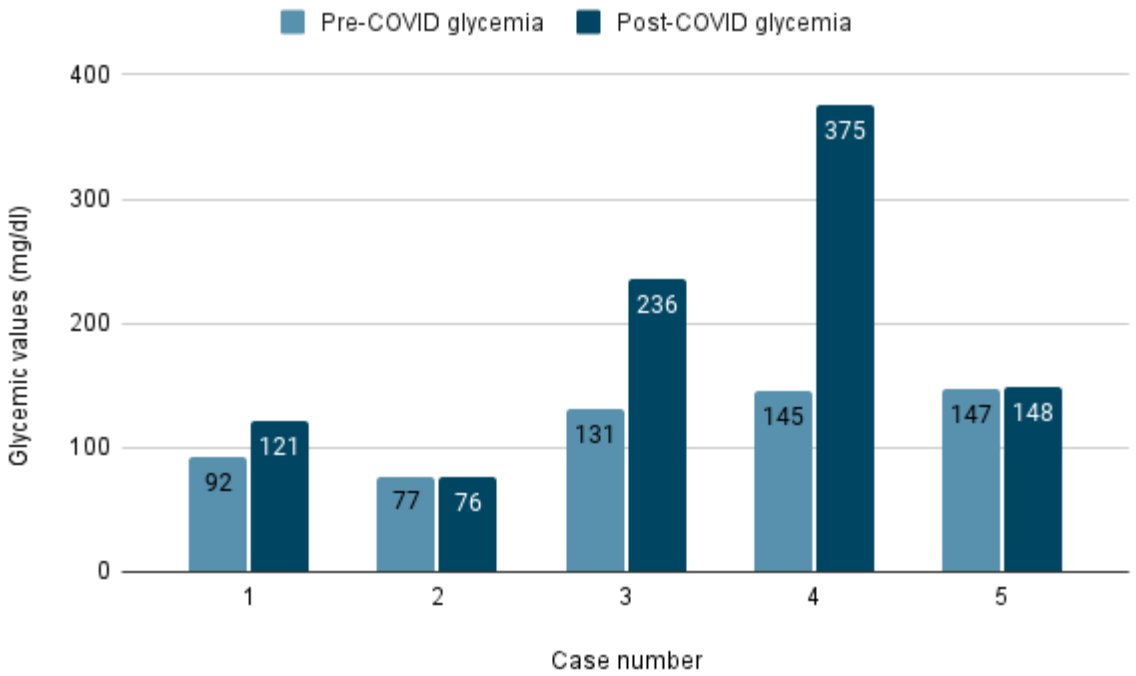

Figure 1. Glycemic behavior of diabetic elders before and after a positive COVID-19 test.
Source: The authors (2023).

Case 1 was a male patient, 70 years old, an intern of the São Vicente de Paula LPI since 2017. His comorbidities were systemic arterial hypertension, pre-diabetes mellitus, and cognitive deficit. He made continuous use of hydrochlorothiazide 25mg and doxazosin mesylate 2 mg. He had a positive result in a RT-PCR test on 11/21/2020, and again in 02/08/2021. He was telemonitored for 20 days in both cases, and in both cases his clinical state improved. His fasting glycemic and glycated hemoglobin exams, carried out periodically by the LPI, showed an increase in fasting glycemia from 92 mg/dL on 11/08/2017 to 121 mg/dL on 06/24/2021; there was also an increase in glycated hemoglobin from 5,5% on 11/08/2017 to 6% on 06/24/2021. The patient's glycemia was not monitored from 11/08/2017 to 06/24/2021.

Case 2 was a male patient, 73 years old, an intern of the São Vicente de Paula LPI since 2017. He had type 2 diabetes mellitus and used metformin 850 mg every 12 hours. He presented a detectable PT-PCR test in 11/20/2020 and was telemonitored for the three next weeks. The diabetes mellitus treatment continued during this period and his clinical state improved throughout. An analysis of the results of the periodical fasting glycemia and glycated hemoglobin tests the LPI carried out showed a decrease in fasting glycemia, from 77 mg/dL on 17/10/2017 to 76 mg/dL on 04/13/2022, and a decrease in glycated hemoglobin from 5.6% on 27/10/2017 to 5.2% on 04/13/2022. The glycemic levels of the patient were not monitored from 17/10/2017 to 04/13/2022.

Case 3 was a male patient, 85 years old, an intern of the São Vicente de Paula LPI since 2019, with systemic arterial hypertension, dyslipidemia, nonspecific heart disease, and type 2 diabetes mellitus. The patient was a smoker and made continuous use of enalapril 10mg, furosemide 40 mg, carvedilol 6.25 mg, omeprazole 20mg, gliclazide 30mg, acetyl-salicylic acid 100 mg, simvastatin 40 mg, doxazosin 2 mg, and human insulin with NPH, 10 UI at breakfast and 15 UI before going to bed. He presented a detectable RT-PCR test in 11/13/2010, and was telemonitored during the three following weeks, during which the diabetes mellitus treatment continued. His clinical state improved after this period. The periodic fasting glycemia tests carried out by the LPI showed an increase from 131 mg/dL on 10/24/2019 to 236 mg/dL on 03/05/2021. The glycemic levels of the patient were not monitored from 24/10/2019 to 03/05/2021.

Case 4 was an 84-year-old female, an intern of the Benedito Franchini Home LPI since 2021. She had systemic arterial hypertension and type 2 diabetes mellitus. She made continuous use of insuline NPH 3mL, regular insuline 3mL, levothyroxine 100 mcg, fluoxetine 20 mg, and ferrous sulphate 40 mg. She presented a detectable PT-PCR test on 17/05/2020 and was telemonitored for the two next weeks. The diabetes mellitus treatment continued during this period and her clinical state improved afterwards. The periodic fasting glycemia tests carried out by the LPI showed an increase from 145 mg/dL on 09/22/2020 to 375 mg/dL on 05/27/2021. Even after four months, the patient's glycemia is still not normal, remaining at a total of 197 mg/dL on 09/01/2021. The patient's glycemia was not well monitored during the pandemic as there was a single fasting glycemia verification in the entire year of 2020.

Case 5 was a female, 88 years of age, an intern of the Wajunkai LPI since 2018, with SAH and type 2 diabetes mellitus. She made continuous use of losartan 50 mg, acetyl-salicylic acid 100 mg, amlodipine 5 mg, simvastatine 20 mg, and metformin 500 mg. She presented a detectable PT-PCR test on 04/12/2020 and was telemonitored for the two next weeks. The diabetes mellitus treatment continued during this period and her clinical state improved afterwards. The fasting glycemia tests carried out periodically by the LPI showed a small increase, from 147 mg/dL on 03/23/2022 to 148 mg/dL on 09/23/2022.

DISCUSSION

Even considering elderly patients with comorbidities, which, according with literature, suggests a worse prognosis, COVID-19 manifested mildly in all cases, with an eventual resolution and no need for hospitalization, specific treatment, or acute respiratory syndromes[17].

One of the potential explanations for the glycemic increase in the patients of this study is the pancreatic damage caused by the SARS-CoV-2 virus, which affects pancreatic islets and microvasculature, directly and indirectly affecting the endocrine functioning of the pancreas[14].

In the case of patient 4, there was a glycemic peak 10 days after the positive RT-PCR test. Her clinical state was consistent with that of a hyperglycemia caused by an acute pancreatic lesion, but four months later the glycemic levels were not back to normal, pre-COVID-19 levels. This can be explained by an acceleration of the natural type 2 diabetes mellitus history, involving a process of lesions and reparation in pancreatic tissues and microvasculature, in addition to a cytokine storm that can be caused by SARS-CoV-2[18]. These pathological processes are made more intense by the fact that the patient is in an advanced type 2 diabetes mellitus clinical state, requiring NPH and regular insulin as opposed to oral antidiabetic drugs. This factor is related to a greater expression of the ECA-2 receptor, which is the entryway of the SARS-CoV-2 virus into the cell[12].

In patients 2 and 5, there was nearly no change in glycemic levels. Both patients used metformin, an oral antidiabetic drug classified as a biguanide. Its main function is activating the AMP-activated protein kinase (AMPK), which has a role in anabolic inhibition and systemic catabolic activation. In addition, metformin increases the use of glucose by intestinal cells[19, 20]. These effects do not depend on insulin. Therefore, this could explain the maintenance of glycemic levels in both patients, regardless of the COVID-19-related pancreatic lesion processes.

Metformin is used in isolation as an early type 2 diabetes mellitus treatment. Its use by patients 2 and 5 indicates that these cases are no quite advanced, and, therefore, the pancreatic expression of the ECA-2 receptor is not as strong.

Cases 1 and 3 presented a glycemic increase consistent with the hypothesis of an acute pancreatic lesion; however, glycemic levels did not go back to pre-COVID levels. The same is true for patient 4. A potential explanation for this acceleration of the natural evolution of type 2 diabetes mellitus in these cases would be the association of an acute pancreatitis case caused by COVID-19 with the increased functioning of angiotensin 2, leading, consequently, to a decrease in the expression of the angiotensin converting enzyme 2 (ECA-2) during the SARS-CoV-2 infection[21]. Angiotensin-2 has several systemic effects, such as the induction of inflammatory responses via stimulation of pro-inflammatory cytokines, and stimuli to increased arterial pressure via activation of the renin–angiotensin–aldosterone system[22].

The pancreatic tissue damage caused by the SARS-CoV-2 infection, associated with microvasculature lesions caused by the same virus and an increased angiotensin-2 action, can

be the mechanisms responsible for a negative progress of diabetes mellitus in the elderly studied after COVID-19.

To be concluded, it should be mentioned that case reports with a low number of participants have a low evidence level, which is a limitation of this study. Another limitation, also related with the number of participants, is the impossibility of calculating inferential statistics to reach conclusions and be able to create inferences. Furthermore, glycemic exams were carried out irregularly during the pandemic, which is another limitation.

Even considering these limitations, this type of research is an early study to support the elaboration of further investigations with larger samples, which would then be able to represent the population as a whole.

CONCLUSION

Although this is a case report, results suggest that patients with glycemic levels above the normal range for their age can have these levels increased further by SARS-CoV-2.

Regardless of the fact the study involved elders in LPIs, we suggest that the glycemic levels of elders with positive SARS-CoV-2 tests should be watched carefully with more frequent tests, considering that medium-to-long term COVID-19 effects are still unknown

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