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Type I Diabetes – Metabolic Disfunction and Changes Induced by Sars-Cov 2 Infection

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Abstract *Diabetes mellitus is a chronic metabolic disease characterized by a deficiency in insulin production and its action or both which leads to prolonged hyperglycaemia with disturbances in most metabolic processes inside the human body. In the case of infection with the new coronavirus SARS-COV-2 (COVID19) these patients have a higher risk of having a severe prognosis. Some studies suggest that diabetes may increase the risk of infection by two to three times, regardless of the presence of other conditions. The role of ferritin in correlation with the severity of COVID-19 patients is unknown. Research hypothesis. The level of blood ferritin. Serum ferritin levels appear to correlate with the severity of COVID-19 patients, which may make them a candidate for the role of biomarker. In this paper I want to show whether ferritin can be a marker of poor prognosis in patients with type I diabetes infected with SARS-COV 2 virus.*

Key words: Diabetes mellitus, Insulin, COVID-19, Ferritin.

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Introduction

The new coronavirus disease (COVID-19) has affected more than 100 million people and caused more than 2 million deaths worldwide. The disease has a poor prognosis, particularly in patients with diabetes. Diabetes mellitus is associated with severe disease, intensive care unit admissions and increased mortality in patients with COVID-19 (Pal, 2020, Huang et al. 2020).

Diabetes is a chronic metabolic disease affecting hundreds of millions of people worldwide, with damaging micro- and macro-vascular effects that are associated with a human and socio-economic burden. For these reasons, diabetes is a global public health problem (Eeg-Olofsson, 2010).

Worldwide, the prevalence of diabetes is increasing. While in 2000 the number of diabetics was 171 million, estimates in 2015 put the number at 415 million, and

predictions for 2040 estimate that the number will rise to 642 million (Chillarón et al., 2010).

Diabetes mellitus is the most common endocrine disorder. More than 150 million people are suffering from the disease worldwide (Tripathi, 2003) and it is likely to increase up to 300 million by 2025. According to WHO, the global prevalence of diabetes is estimated to increase from 4% in 1995 to 5.4% by the year 2025 majorly in the developing countries (Jayaprasad et al., 2011), presently, India, has the largest number of diabetic patients in the world and has been infamously known as the "diabetic capital of the world"(Abate et al., 2007). The classical symptoms of type 1 diabetes are polyuria (frequent urination), polydipsia (increased thirst), polyphagia (increased hunger), and weight loss (Plevyak, 2011).

Diabetes is characterized by hyperglycaemia and disturbances in carbohydrate, fat and protein metabolism. It is associated with an absolute or relative deficiency in the secretion of insulin (Diabetes Mellitus 1, DM1) or with insulin resistance (Diabetes Mellitus 2, DM2) (Savage et al., 2007; Stumvoll et al., 2005). DM 2 is the most common form of the disease, accounting for 85 to 90% of all recorded cases (Tiwari and Rao, 2002).

Insulin is a hormone produced in the pancreas that helps transport glucose (blood sugar) from the bloodstream into the cells so they can break it down and use it for fuel (Preethi, 2013). People cannot live without insulin. The body of a diabetic patient is either doesn't make enough insulin or can't use its own insulin as well as it should in this causes sugars to build up in the blood. Diabetes can cause serious health complications including heart disease, blindness, kidney failure, and lower-extremity amputations.

The novel coronavirus disease (COVID-19) has affected over 100 million people and inflicted over 2 million deaths globally. The disease portends a poor prognosis especially in patients with diabetes mellitus. Diabetes mellitus is associated with severe disease, intensive care unit admissions and increased mortality in patients with COVID-19 (Pal, 2020, Huang et al. 2020).

Adults of any age who have certain medical conditions are at increased risk of having a serious Covid-19 disease, specifically horses who have cancer, chronic kidney disease, heart disease, type 2 diabetes, etc.

Other people may also have a higher risk of Covid-19, namely those with asthma, cerebrovascular disease, high blood pressure, cystic fibrosis, neurological conditions, liver disease, pulmonary fibrosis, type 1 diabetes. In addition, overweight people may also have a higher risk of Covid-19.

I. Type I diabetes

An autoimmune disease in which the immune system mistakenly destroys the insulin-making beta cells of the pancreas. This causes diabetes by leaving the body without enough insulin to function normally and this is called an autoimmune reaction, or autoimmune cause. It accounts for almost about 5-10% cases of diabetes globally and typically develops more quickly than other forms of diabetes. It is usually diagnosed in children and adolescents, and sometimes in young adults. To survive, patients must administer insulin medication regularly. The following triggers may be involved with this type of diabetes; viral or bacterial infection, chemical toxins within food, unidentified

component causing autoimmune reaction and underlying genetic disposition may also be a type 1 diabetes cause (Mohammad, 2017).

Causes

1. Autoimmune Destruction of Beta Cells

Type 1 diabetes usually develops due to an autoimmune disorder. This is when the body's immune system behaves inappropriately and starts seeing one of its own tissues as foreign. The islet cells of the pancreas that produce insulin are seen as the "enemy" by mistake. The body then creates antibodies to fight the "foreign" tissue and destroys the islets cells leading to their inability to produce insulin. The lack of sufficient insulin then results in diabetes. It is unknown why this autoimmune diabetes develops. Most often it is a genetic tendency; sometimes it follows a viral infection such as mumps, rubella, cytomegalovirus, measles, influenza, encephalitis and polio (Menser, et al., 1978). Certain people are more genetically prone to this happening although why this occurs is not known. Other less common causes of type 1 diabetes include injury to the pancreas from toxins, trauma, or after the surgical removal of the majority (or all) of the pancreas.

2. Genetic Susceptibility

Heredity plays an important part in determining who is likely to develop type 1diabetes. Genes are passed down from biological parent to child. Certain gene variants that carry instructions for making proteins called human leukocyte antigens (HLAS) on white blood cells are linked to the risk of developing type 1 diabetes (Zimmet et al., 1995).

3. Environmental Factors

Environmental factors, such as foods, viruses, and toxins, may play a role in the development of type 1 diabetes, but the exact nature of their role has not been determined. Some theories suggest that environmental factors trigger the autoimmune destruction of beta cells in people with a genetic susceptibility to diabetes (Harikumar et al., 2015).

4. Viruses and Infections

A virus cannot cause diabetes on its own, but people are sometimes diagnosed with type 1 diabetes during or after a viral infection, suggesting a link between the two. Viruses possibly associated with type 1 diabetes include coxsackievirus b, cytomegalovirus, adenovirus, rubella, and mumps (Harikumar et al., 2015).

5. Infant Feeding Practices

Some studies have suggested that dietary factors may raise or lower the risk of developing type 1 diabetes. For example, breastfed infants and infants receiving vitamin D supplements may have a reduced risk of developing type 1 diabetes, while early exposure to cow's milk and cereal proteins may increase risk (Hother et al., 1988).

II. Serum ferritin

Serum ferritin is a globular protein complex that originates from damaged cells and is considered a marker of cell damage. Being predominantly stored in cells of the

reticuloendothelial system, its serum level also reflects the morpho-functional status of the endothelial layer, which is responsible for maintaining circulatory homeostasis. This phenomenon argues the importance of ferritin assessment in COVID-19 because, with certainty, it can be stated that severe hypoxia, anoxia, deteriorates cellular structure (Senjo, 2018).

Elevated serum ferritin levels are associated with malignant states and tissue injury. Hyperferritinemia has recently been investigated in autoimmune diseases (Knovich, 2009).

The serum ferritin test shows increased (indicates hemochromatosis) or decreased levels of ferritin in the body, anemia or iron deficiency. Ferritin expression is under sensitive control and is regulated both transcriptionally and posttranscriptionally by iron, cytokines (tumour necrosis factor-a and interleukin-1a), hormones and oxidative stress (Yildirim et al., 2004).

Some authors believe that SARS-COV 2 attacks haemoglobin causing the dissociation of haem into iron and porphyrin, and then viral proteins take up porphyrin. Thus, the oxyhaemoglobin content decreases and the body will accumulate a quantity of harmful iron ions. These iron ions will initiate inflammatory processes in many tissues, including lung tissue. Because of this the cells produce large amounts of ferritin to bind free iron ions, in this way inflammatory lesions will be diminished (Chen, 2019).

Increased serum ferritin concentration is often associated with immune and inflammatory response in various infections. Some studies have shown that patients with bacterial infection had higher ferritin levels compared to viral infection (Lalueza, 2020, Sanaei Dashti, 2017).

Material and methods

The study includes 40 patients, of both genders (18 women and 22 men), aged between 34 and 90 years, with type I diabetes diagnosed with COVID-19 grouped in a single group and hospitalized at the Medgidia Municipal Hospital (period July 2021 - March 2022).

Monitoring of the patients included other biological blood tests, namely serum glucose, glycosylated hemoglobin (HbA1C), LDH (lactate dehydrogenase), AST (Aspartate amino-transferase), ALT (Alanine amino-transferase), serum creatinine, ureea, c-reactive protein serum ferritin.

Biochemical variables:

Serum glucose was determined, à jeun, by the colorimetric enzymatic method (spectrophotometric).

Glycated haemoglobin (HbA1c) was collected à jeun and measured by immunoturbidimetric method.

Serum creatinine was determined photometrically using an enzymatic method.

AST, ALT (transaminases) and LDH were determined by spectrophotometric method.

Serum ferritin levels were measured at the time of diagnosis using the chemiluminescence technique.

The apparatus used for testing samples: immunological (serum ferritin) is the Mindray CL 2000, and for biochemical is the Mindray BS 800.

Clinical variables are: age, sex, origin, smoking, death and secondary diagnosis (cardiovascular disease - C, pulmonary disease - P).

Of the 40 patients with type I diabetes and COVID-19, 13 had heart disease, 27 of whom were diagnosed with viral pneumonia.

Of all patients included in the study, 12 died within 8-10 days of admission.

Results

Serum ferritin values in 40 patients were studied in correlation with diabetes mellitus and SARS-COV 2 virus, including 6 with mildly elevated serum ferritinemia, 17 with severe serum ferritinemia and 17 with critical serum ferritinemia. Of the 17 patients with critical serum ferritin values, 12 died.

A directly proportional correlation was found between high serum ferritin values and increased C-reactive protein (acute phase inflammatory marker) statistical representation with p<0,001.

Table 1. Descriptive Statistics

Descriptive Statistics

	N	Minimum	Maximum	Mean	Std. Deviation
Varsta (ani)	40	36.00	90.00	65.90	11.56

Descriptive Statistics

Sex		N	Minimum	Maximum	Mean	Std. Deviation
M	Varsta (ani)	22	36.00	79.00	62.00	10.78
F	Varsta (ani)	18	51.00	90.00	70.67	10.93

Table 2. Descriptives - Independent Samples Test (biochemical variable)

	Deces	N	Minimum	Maximum	Mean	SD	p
Ferritin (ng/ml)	Da	12	1010.45	4772.61	2655.84	1128.55	< 0.001
	Nu	28	66.04	1113.74	543.34	351.61	
HbA1C (%)	Da	12	7.90	15.40	9.94	2.19	0.759
	Nu	28	8.10	15.40	10.16	2.05	
Glucose	Da	12	206.00	514.00	339.00	96.87	0.316

(mg/dl)	Nu	28	114.00	519.00	305.43	95.25	
LDH (U/L)	Da	12	157.00	1344.00	520.00	346.43	0.115
	Nu	28	184.00	896.00	342.82	170.58	
AST (U/L)	Da	12	11.00	121.00	58.75	33.27	0.028
	Nu	28	14.00	106.00	38.18	22.58	
ALT (U/L)	Da	12	24.00	196.00	71.17	59.20	0.165
	Nu	28	11.00	90.00	36.96	22.18	
Creatinine (mg/dl)	Da	12	.64	3.55	1.12	.85	0.382
	Nu	28	.50	1.77	.89	.32	
Urea (mg/dl)	Da	12	18.00	262.00	72.67	65.47	0.344
	Nu	28	19.00	113.00	53.57	22.83	
CRP (mg/L)	Da	12	68.60	533.20	161.89	130.41	< 0.001
	Nu	28	8.50	102.20	46.72	29.98	
Raport Ritis	Da	12	.44	2.16	1.01	.53	0.649
	Nu	28	.30	3.25	1.11	.63	

Normally distributed variables: mean ± SD;

Note: there are significant differences between mean values of ferritin, AST, CRP in patients who died and patients who survived only for variables marked yellow ($p < 0.005$).

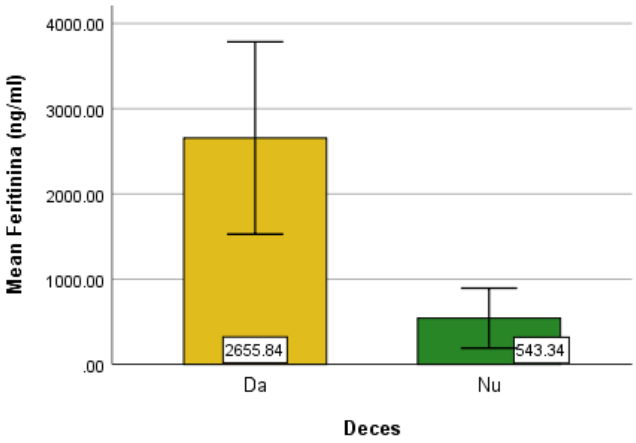

Fig.1. Bar+Error-Bar plot of the **Ferritin** variable as a function of death, p<0,001

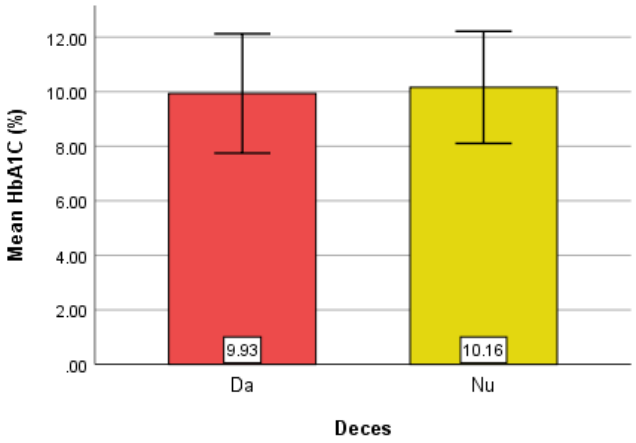

Fig.2. Bar+Error-Bar plot of the **HbA1C** variable as a function of death, p= 0,759

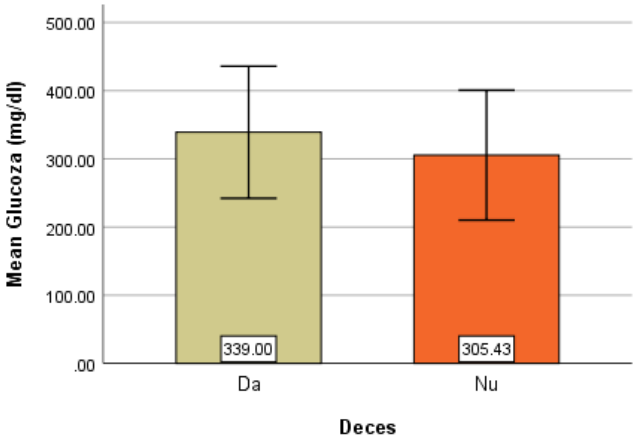

Fig.3. Bar+Error-Bar plot of the **Glucose** variable as a function of death, p=0,316

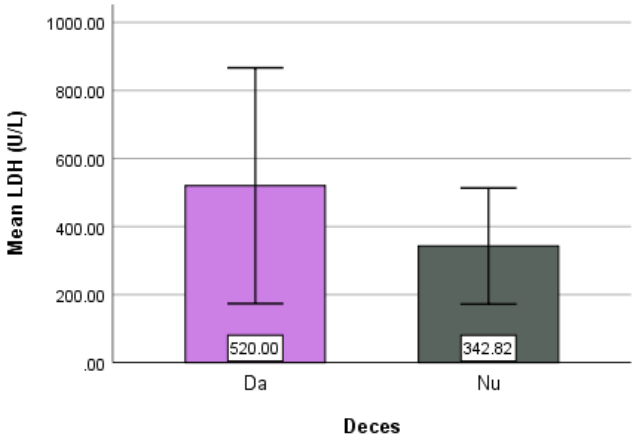

Fig.4. Bar+Error-Bar plot of the **LDH** variable as a function of death, p=0,115

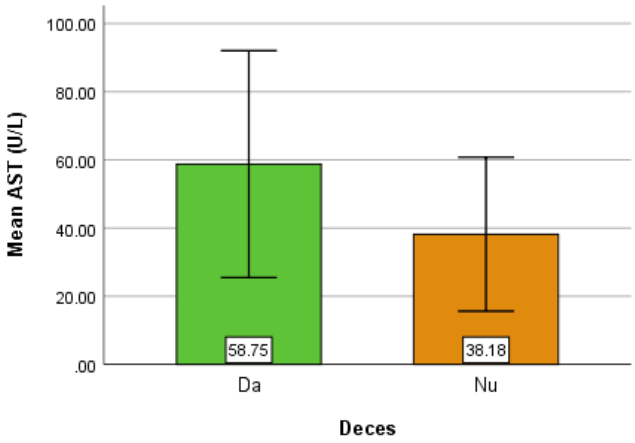

Fig.5. Bar+Error-Bar plot of the **AST** variable as a function of death, p= 0,028

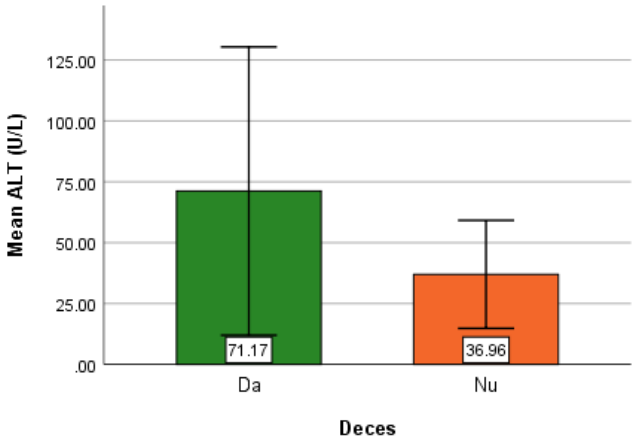

Fig.6. Bar+Error-Bar plot of the **ALT** variable as a function of death, p=0,165

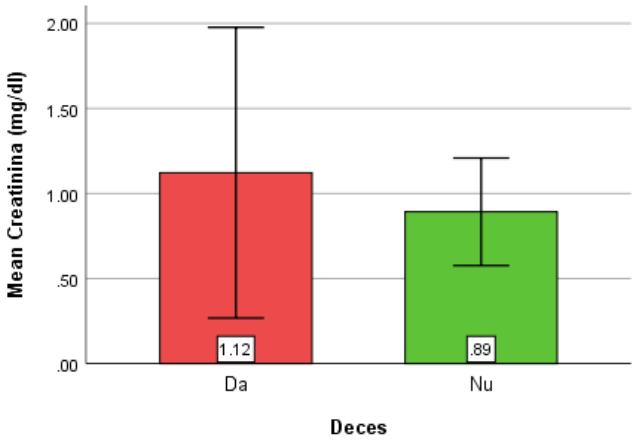

Fig.7. Bar+Error-Bar plot of the **CREATININE** variable as a function of death, p= 0,382

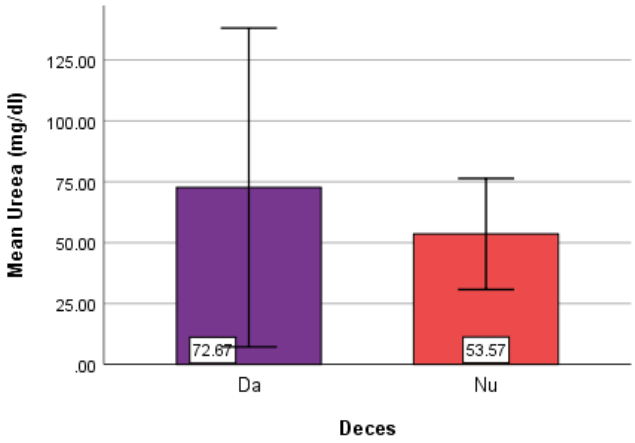

Fig.8- Bar+Error-Bar plot of the **UREA** variable as a function of death, p= 0,344

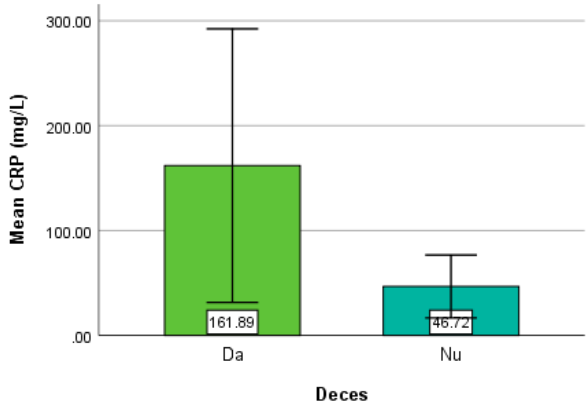

Fig.9. Bar+Error-Bar plot of the **CRP** variable as a function of death, p= <0,001

Table 3. Link between sex and death

Sex * Death Crosstabulation

			Deces		
			Da	Nu	Total
Sex	M	Count	10	12	22
		% of Total	25.0%	30.0%	55.0%
	F	Count	2	16	18
		% of Total	5.0%	40.0%	45.0%
Total		Count	12	28	40
		% of Total	30.0%	70.0%	100.0%

There is an association, a link between the variables Sex and Death: X2stat = 5.560, df = 1, p = 0.018 < 0.05. The risk of death in men is 6.667 times higher than in women: OR = 6.667, 95% Confidence Interval for Odds Ratio = (1.227, 36.226).

Table 4. Link between smoking and death

Smoking * Death Crosstabulation

			Death		
			Da	Nu	Total
Smoking	F	Count	9	20	29
		% of Total	22.5%	50.0%	72.5%
	NF	Count	3	8	11
		% of Total	7.5%	20.0%	27.5%
Total		Count	12	28	40
		% of Total	30.0%	70.0%	100.0%

No there is an association, a link between the variables Smoking Status and Death: X2stat = 0.054, df = 1, p = 0.817 > 0.05. The risk of death in smokers is equal to that of non-smokers: OR = 1.200, 95% Confidence Interval for Odds Ratio = (0.257, 5.612).

Table 6. Link between diagnosis and death

Diagnosis * Death Crosstabulation

			Death		
			Da	Nu	Total
Diagnosis	C	Count	5	8	13
		% of Total	12.5%	20.0%	32.5%
	P	Count	7	20	27
		% of Total	17.5%	50.0%	67.5%
Total		Count	12	28	40
		% of Total	30.0%	70.0%	100.0%

No there is an association, a link between the variables Diagnosis and Death: X2stat = 0.657, df = 1, p = 0.418 > 0.05. The risk of death in C patients is equal to that of P patients: OR = 1.786, 95% Confidence Interval for Odds Ratio = (0.436, 7.317).

Table 7. Link between origin and death

Origin * Deces Crosstabulation

			Deces		
			Da	Nu	Total
Origin	U	Count	5	16	21
		% of Total	12.5%	40.0%	52.5%
	R	Count	7	12	19
		% of Total	17.5%	30.0%	47.5%
Total		Count	12	28	40
		% of Total	30.0%	70.0%	100.0%

No there is an association, a link between the variables Provenance and Death: X2stat = 0.807, df = 1, p = 0.369 > 0.05. The risk of death in urban patients is equal to rural patients: OR = 0.536, 95% Confidence Interval for Odds Ratio = (0.136, 2.109).

Discussions

The risk of death caused by increased serum ferritin in men is 6.667 times higher than in women.

Our study demonstrated a directly proportional correlation of serum ferritinemia and C-reactive protein.

Elevated serum ferritin is often associated with the immune and inflammatory response in various infections.

Serum ferritin is a sign of cellular and mitochondrial distress, as well as an indicator of severe endothelial injury, and the correlation in this study demonstrate that may serve as a marker of advanced severity of pathology.

Conclusions

1. Decompensated diabetes is accompanied by increased iron storage in the body.
2. Decompensation in diabetic patients is accompanied by renal failure which worsens as the carbohydrate profile decompensates.
3. Inflammatory syndrome is present in all patients with elevated ferritin. Thus, iron deposits accentuate the inflammatory syndrome.
4. Death occurred in patients with accentuated inflammatory syndrome, liver failure, renal failure and increased iron deposits.

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