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Research Paper

Possible effects after a COVID vaccination at the molecular and chemical level for patients with celiac disease

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ABSTRACT

A vaccination against the virus named COVID 19 is now available. Within a few months and intensive international research activities, a vaccine was developed which was first approved in the USA, Canada and then in England. In the EU, too, approval was given on December 21, 2020. There are currently three different active substances that differ from the vaccine type and producer.

Now, since weeks, many members of our celiac disease exchange groups are asking themselves or they are requesting the consultations of various medical specialists belonging to Metabolic Diseases and Diabetology, Gastroenterology, Allergology and Clinical Immunology, Internal and Family Medicine or even Clinical Pharmacists, whether the vaccine can be used for an autoimmune disease such as celiac disease (CD), or whether there is something against it. We have compiled currently available information, using also the existing patient database, adding the organic molecular study as a basis for further recommendations. The absolute novelty is the structural similarity of a part of the studied Gluten molecule (exorphin C and A5) with those of the Spike protein of the COVID 19 virus described in numerous dedicated articles. In addition, it appears that the cell attachment and penetration molecule is common in both cases.[21]

The conclusion of this study reveals that there are no globally known medical reasons to speak against the vaccine for an existing CD, on the contrary we can present the hypothesis of a bilateral benefit both in immunization against the pandemic agent of SAARS - COV 2 and in treating the difficult and often underdiagnosed celiac autoimmune disease.

KEY WORDS*: Gluten, Exorphin, Celiac disease, Spike protein, COVID Vaccination*

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I. INTRODUCTION

With the recent decisions that the Food and Drug Administration, the World Health Organization and the European Medicines Agency (EMA) has granted Emergency Use Authorization for the vaccines against the virus that causes Covid-19, patients with CD [1] are asking for guidance about the advisability of this Covid-19 vaccines in the context of CD, an immune-mediated condition. As medical doctors, pharmacists and scientists taking care of patients with CD, we advise people with CD to receive one of the Covid-19 vaccines that has met the necessary approvals, whether it includes innovative agents withmRNA or peptide (protein) vaccines.

During the last year, there was initial concern that people diagnosed with CD or even undiagnosed but with relevant symptoms [2], might be at an increased risk of severe outcomes from the SARS-CoV-2 infection, given prior studies [3] suggesting risks related to pneumonia and viral infections [4]. Potential factors influencing infections in CD patients are reported in Table 1. [5]

Table - 1: Potential influencing factors in COVID-19 infection affecting patients with CD

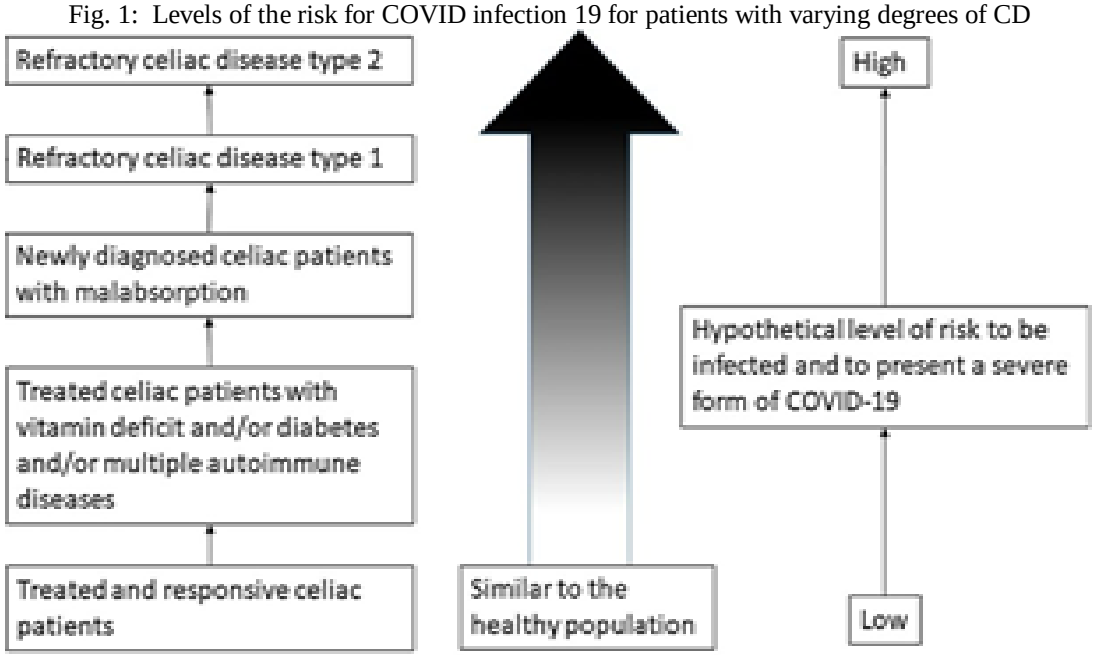
Factor	Type of influence
HLA status	no data about an altered immune response
Immunological factors	no evidence that ILs status or their genetic variants in CD could have any influence

Hyposplenism	cannot be considered as a risk factor in this case
Mucosal atrophy	In treated and responsive CD cases, the mucosal state does not have a role
Malabsorption/ Micronutrients deficiencies	A Vitamin deficit may lead to increased susceptibility to infections. Although there is no evidence concerning COVID-19. Verify the nutritional state of the pacient!
Refractory CD[6]	may significantly worsen the COVID-19 outcome.

Studies thus far, including the international registry covidceliac.org/celiac.org have indicated no increased risk of severe outcomes. Also, SECURE-Celiac is an important instrument of surveillance for the adult or pediatric cases of patients with CD and concomitant COVID 19 infection. Clinicians worldwide can report on this platform cases of asymptomatic, mild or severe COVID-19 in patients with CD.

Even though the risk among persons with CD is comparable to that of the general population, we have seen that Covid-19 can nevertheless have destroying effects [7] and we share in the consensus belief by the public health community that mass vaccination is vital. Figure 1 shows the gradual increase in patients' risk.

Fig. 1: Levels of the risk for COVID infection 19 for patients with varying degrees of CD



As the safety and efficacy data on Covid-19 vaccination has emerged, there is no evidence to suggest that people with CD would be more prone to an adverse effect of vaccination [8].

CD is not considered an allergy, and by itself does not prompt additional precaution when proceeding with vaccination. Patients with concerns about vaccination and their particular situation should interact with a specialist/clinician or their health care provider. They should undergo Covid-19 vaccination as soon as it is offered and we urge our patients to do so. [9]

II. MATERIAL AND METHODS

Our study includes two parts:

I. An initial retrospective study on the incidence of SAARS-COV2 disease in patients diagnosed with CD, on the medical level, and

II.A descriptive study with in deep structural features of the Gluten molecule, as exorphin C and A5 variants, compared to the Spike proteins of the Corona Virus type 1910, on the organic chemistry level.

Part I

We have analyzedinformationconcerning cases of CD by city, diagnostic type, treatment, etc., offering to the CD community a data base. Of course, the study relies to the GDPR (General Data Protection Regulation).

CD QUESTIONAIRE

1.Age of the patient (under 18 or ≥90)

2.Residence State, City

3.Gender [Male, Female, Other]

4.Race/Ethnicity

5.Patient's weight (kg)
6.How was CD diagnosed? (serology and duodenal biopsy, serology only, unknown)
7.Serology used (TG2-IgA, DGP-IgG, EMA)
8.Years since diagnosis of the CDwhen diagnosed with COVID-19
9.Did the patient ever have a follow-up duodenal biopsy?
10.Most recent follow-up biopsy result: normal villi (Marsh 0, 1, or 2); villus atrophy (Marsh 3)
11.Was there a tissue transglutaminase antibody value measured within 1-year preceding COVID-19 diagnosis?
12.Tissue transglutaminase value: elevated, normal or unknown
13.Refractory CD? If yes: type 1, type 2 or unknown
14.At the time of COVID-19 diagnosis, what was the patient's degree of adherence to the gluten-free diet?
15.Immunosuppressive medications at time of COVID diagnosis (please include medications stopped within two weeks of time of diagnosis). Indicate all that apply. Only include oral or parenteral medications. (corticosteroids, azathioprine, 6-mercaptopurine, other) with the dosing interval (round to closest interval): Daily (includes daily and > once daily), Greater than daily but less than weekly, weekly, Q2 weeks, Q3 weeks, Q4 weeks, Q5 weeks, Q6 weeks, Q7 weeks, Q8 weeks, Q9 weeks, Q10 weeks
16.Were any of the previously specified celiac disease-related medications stopped due to COVID 19?Specify CD-related treatment stopped. All that apply: corticosteroids, azathioprine, 6-mercaptopurine, other
17.Does the patient have any of the following comorbidities: Cardiovascular disease, Diabetes, Asthma, COPD, Other Chronic Lung Disease (NOT asthma/COPD), Hypertension, Cancer, History of stroke, Chronic renal disease (CKD, etc.), Chronic liver disease (PSC, NAFLD, cirrhosis, etc.)
18. Current or former cigarette/Tabak smoker
After the personal, clinical and paraclinical information, we have dedicated a special part to the records about SAARS-COV19, which are of absolute importance for the correct distribution of the patient on wards or hospital departments.
COVID-19 INFORMATION
Year of diagnosis of COVID 19 (2020, 2021)
Specify approximate number of days of symptoms from COVID 19 (if known)
Have patient's symptoms resolved at the time of this report? [Yes, No, Unknown, Patient never developed symptoms (just tested positive)]
Did the patient develop new gastrointestinal symptoms at the time of COVID 19 infection?
What were the patient's gastrointestinal symptoms at the time of COVID 19 infection? (Abdominal pain, Diarrhea, Nausea, Vomiting, Other)
Specify the patient's gastrointestinal symptom at the time of COVID 19 infection
Were any medications and/or investigational therapies used to treat COVID-19 in this patient? Remdesivir, chloroquine/hydroxychloroquine, oseltamivir, lopinavir/ritonavir, tocilizumab, corticosteroids (only if for COVID and not celiac), other
Did the patient die of COVID 19 or other complications caused by or contributed to by COVID 19?
Was the patient evaluated in a hospital ER?
Has the patient been hospitalized? If yes, Name of hospital and Length of stay (days)
Did the patient require a ventilator?
Did the patient require admission to an intensive care unit (including step-down units)?

Part II

The study was dedicated to the structural implications of the molecules causing cell damage in the case of CD, respectively Gluten and in SAARS-COV2, respectively COVID virus19. Apparently, they do not bring the idea of similarity but, focusing on the structural analysis using computational virtual Molview modeling of specific fractions of the Gluten molecule (exorphin C and A5), as well as the analysis of COVID 19 virus's radiated crown spikes and the common cell adhesion intermediate N-Acetyl-d-galactosamine-6-phosphocholine, we obtained relevant results.

III. RESULTS AND DISCUSSION

Part I

The data collected in this study on patients with CD during the pandemic are summarized in the following Table 2.

Table -2: Results of the retrospective study about cases of patients suffering from CD infected with COVID-19

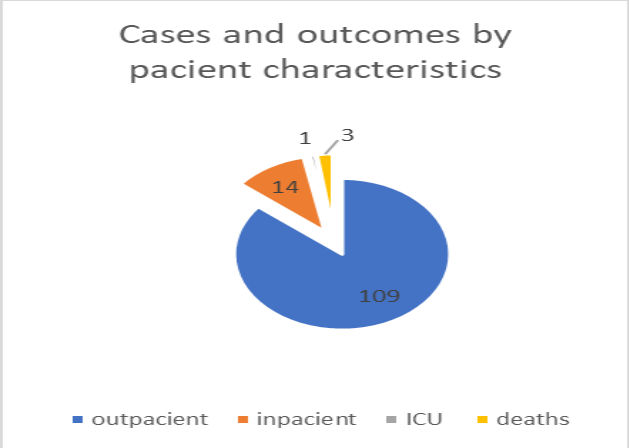
Characteristics	Total	Outpatient	Inpatient	ICU	Deaths
Overall	123 (100%)	109 (89%)	14 (11%)	1 (1%)	3 (2%)

Age					
< 18 years	4 (3%)	4 (100%)	0 (0%)	0 (0%)	0 (0%)
18 - 39 years	61 (50%)	57 (93%)	4 (7%)	0 (0%)	1 (2%)
40 - 64 years	45 (37%)	38 (84%)	7 (16%)	0 (0%)	2 (4%)
≥65 years	13 (11%)	10 (77%)	3 (23%)	1 (8%)	0 (0%)
Gender					
Female	94 (76%)	85 (90%)	9 (10%)	0 (0%)	2 (2%)
Male	28 (23%)	23 (82%)	5 (18%)	1 (4%)	1 (4%)
Years Since Diagnosis					
< 1 year	14 (11%)	14 (100%)	0 (0%)	0 (0%)	0 (0%)
1 - 5 years	33 (27%)	31 (94%)	2 (6%)	0 (0%)	0 (0%)
6 - 10 years	29 (24%)	27 (93%)	2 (7%)	0 (0%)	2 (7%)
11 - 15 years	18 (15%)	15 (83%)	3 (17%)	1 (6%)	0 (0%)
16 - 20 years	14 (11%)	11 (79%)	3 (21%)	0 (0%)	0 (0%)
21 - 30 years	4 (3%)	4 (100%)	0 (0%)	0 (0%)	0 (0%)
> 30 years	9 (7%)	6 (67%)	3 (33%)	0 (0%)	0 (0%)
Unknown	2 (2%)	1 (50%)	1 (50%)	0 (0%)	1 (50%)
Refractory Celiac Disease					
Type 1	4 (3%)	3 (75%)	1 (25%)	0 (0%)	0 (0%)
Type 2	5 (4%)	3 (60%)	2 (40%)	(0 (0%)	0 (0%)
No	82 (67%)	73 (89%)	9 (11%)	1 (1%)	0 (0%)
Unknown	32 (26%)	30 (94%)	2 (6%)	0 (0%)	3 (9%)
Adherence to Gluten Free Diet					
Strict gluten-free	79 (64%)	72 (91%)	7(9%)	1 (1%)	2 (3%)
Usually gluten-free, rare unintentional gluten	22 (18%)	20 (91%)	2 (9%)	0 (0%)	0 (0%)
Usually gluten free, rare intentional gluten	3 (2%)	3 (100%)	0 (0%)	0 (0%)	0 (0%)
Gluten-free most of the time	1 (1%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)
Gluten-free sometimes	2 (2%)	1 (50%)	1 (50%)	0 (0%)	0 (0%)
Trying to be gluten-free but not always sure	6 (5%)	5 (83%)	1 (17%)	0 (0%)	0 (0%)
Unrestricted gluten with other foods restricted	2 (2%)	1 (50%)	1 (50%)	0 (0%)	0 (0%)
Unrestricted diet	7 (6%)	6 (86%)	1 (14%)	0 (0%)	1 (14%)
Unknown	1 (1%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)
Disease Activity					
Marsh 0, 1, 2	40 (33%)	35 (88%)	5 (13%)	0 (0%)	0 (0%)
Marsh 3	12 (10%)	9 (75%)	3 (25%)	0 (0%)	0 (0%)
Unknown	71 (58%)	65 (92%)	6 (8%)	1 (1%)	3 (4%)
Immunosuppressive therapy for CD					
Steroids	9 (7%)	6 (67%)	3 (33%)	1 (11%)	0 (0%)
Biologics	2 (2%)	2 (100%)	0 (0%)	0 (0%)	0 (0%)
No	112 (91%)	101 (90%)	11 (10%)	0 (0%)	3 (3%)
Comorbidities					

0	76 (62%)	71 (93%)	5 (7%)	1 (1%)	3 (4%)
1	37 (30%)	31 (84%)	6 (16%)	0 (0%)	0 (0%)
≥2	10 (8%)	7 (70%)	3 (30%)	0 (0%)	0 (0%)
GI symptoms at COVID diagnosis					
Diarrhea	37 (30%)	32 (86%)	5 (14%)	0 (0%)	0 (0%)
Abdominal Pain	24 (20%)	21 (88%)	3 (13%)	0 (0%)	0 (0%)
Vomiting	6 (5%)	5 (83%)	1 (17%)	0 (0%)	0 (0%)
None	69 (56%)	65 (94%)	4 (6%)	1 (1%)	2 (3%)
Other/Unknown	10 (8%)	8 (80%)	2 (20%)	0 (0%)	1(10%)
Investigational therapies for COVID					
Corticosteroids	3 (2%)	3 (100%)	0 (0%)	0 (0%)	0 (0%)
Chloroquine/Hydroxychloroquine	8 (7%)	4 (50%)	4 (50%)	1 (13%)	0 (0%)
Lopinavir/Ritonavir	2 (2%)	2 (100%)	0 (0%)	0 (0%)	0 (0%)
Other (e.g. Azithromycin, adjunct therapies)	17 (14%)	14(82%)	3(18%)	0 (0%)	0(0%)
None	93 (76%)	87 (94%)	6 (6%)	0 (0%)	1 (1%)
Unknown	3 (2%)	3 (100%)	0 (0%)	0 (0%)	2(67%)

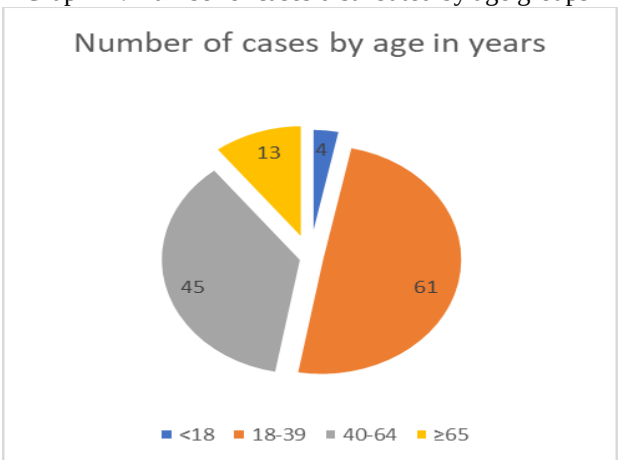
After analyzing the results, Graph 1 resulted

Graph -1: Patient cases by type



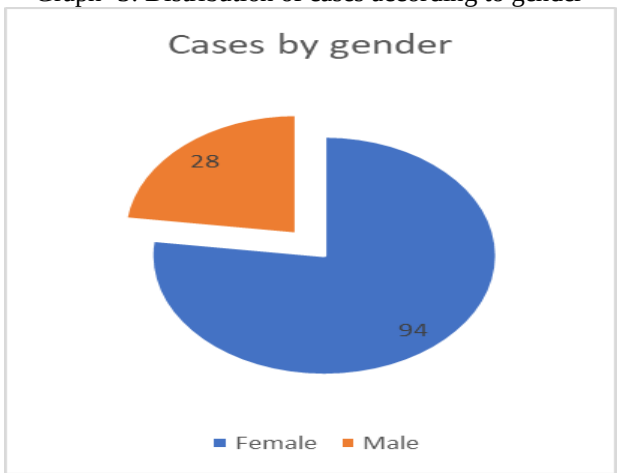
Out of the total number of patients with CD affected by COVID 19, we observe a very small percentage of patients hospitalized in the ICU (ATI) and also a few lethal cases.Graph 2 shows the distribution by age groups

Graph -2: Number of cases distributed by age groups



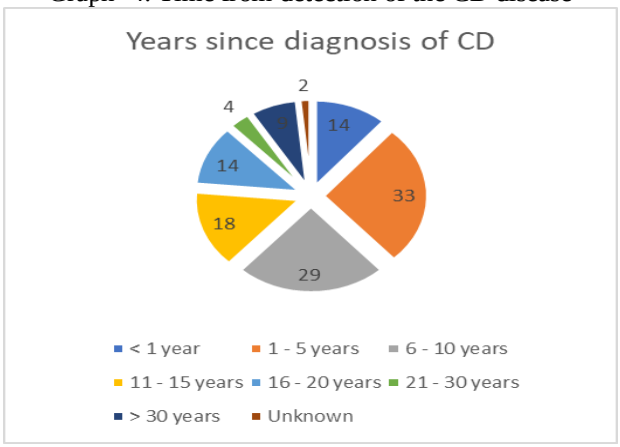
It is obvious that the middle age groups were the most affected, while the extreme groups less. And the Graph 3 below, shows the number of cases by gender of patients.

Graph -3: Distribution of cases according to gender



The distribution of genders in the population of the studied cases is similar to the general one of patients with CD, reflecting the prevalence of the female gender, usually more affected.
Graph 4 shows that the involvement of patients with CD was generally long-term when they came in contact with the COVID virus.

Graph -4: Time from detection of the CD disease



And the discussions can be continued based on the characteristics stated in the study hypothesis, revealing the prevalence of non-refractory cases of CD strictly on a gluten elimination diet, with a Marsh index activity of grade 0, 1 or 2, without having a drug immunosuppressive therapy for CD, without gastrointestinal symptoms upon confirmation of the diagnosis of COVID and without specific COVID treatments.
This would be the analytical portrait of the CD patient with concomitant COVID impairment to whom the protective vaccination against COVID should be preferred.

Part II

The specific molecule involved in CD pathology, Gluten, which we have studied exhaustively, has revealed surprising details, especially in the context of COVID 19. Gluten exorphins are a group of opioid peptides formed during digestion of the Gluten protein, categorized in: A5, B4, B5 si C. The focus of the study was on exorphins C and A5, more often cited as causing gluten intolerance. Gluten Exorphin C has the structure: H-Tyr-Pro-Ile-Ser-Leu-OH and the chemical formula: C29H45N5O8 with a molecular weight of 591.70 g/mol while Gluten exorphin A5 the structure: H-Gly-Tyr-Tyr-Pro-Thr-OH with the chemical formula: C24H37N5O9 and a superior molecular weight: 599.64 g/mol. You can see their percentage composition in the following Table 3.

Table -3: The elemental and percentage composition of the two types of exorphins: C and A5

Elements	**Exorphin C**		**Exorphin 5A**	
C	12.0107 u × 29	0.5887	12.0107 u × 29	0.5809
H	1.00794 u × 45	0.0767	1.00794 u × 37	0.0622
N	14.0067 u × 5	0.1184	14.0067 u × 5	0.1168
O	15.9994 u × 8	0.2163	15.9994 u × 9	0.2401

Thus, the compositional differences are highlighted in the following we will present the non-superposable structural details. Exorphin C to the left and Exorphin A to the right as structural formula (Figure 2), model 3D (Figure 3) and Molview translucent model (Figure 4).

Fig. 2: Structural formulas of Exorphin C (left) and Exorphin A5 (right)

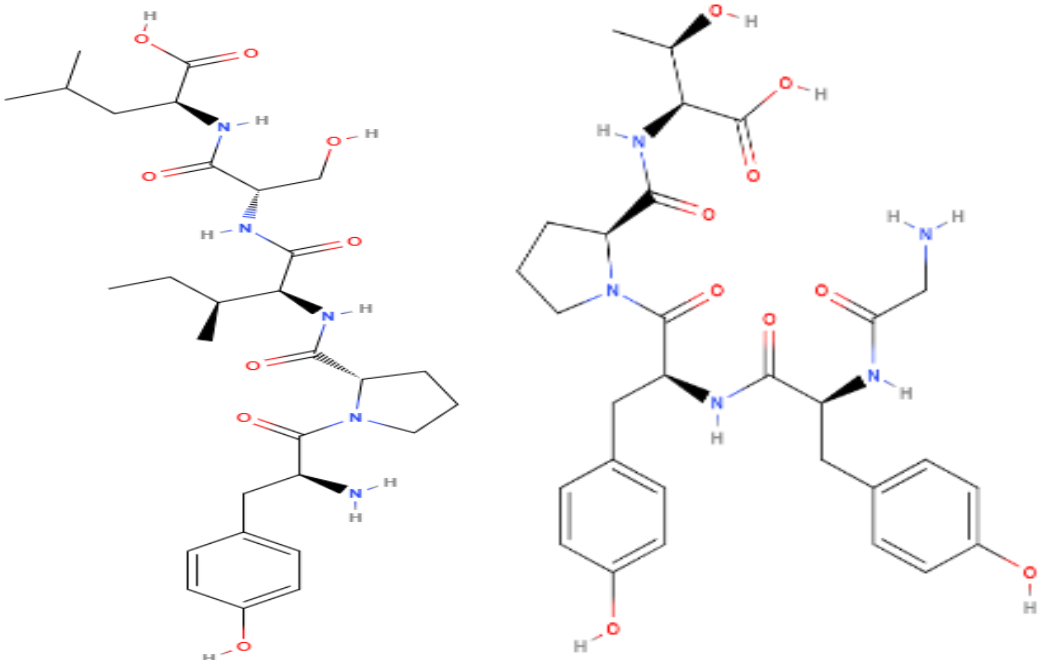


Fig. 3: Model 3D (sticks and balls) of the molecules Exorphin C (left) and Exorphin A5 (right)

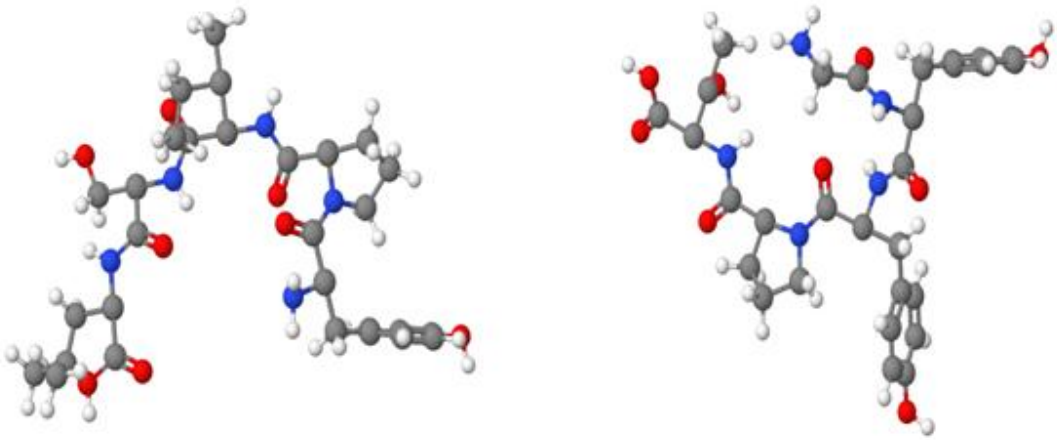
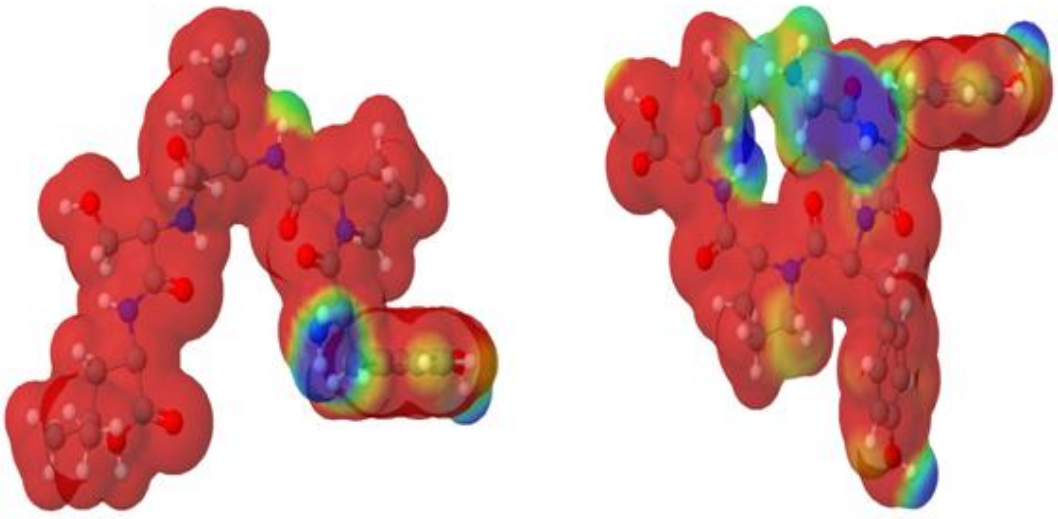


Fig. 4: Molview translucent 3D model of Exorphin C (left) and Exorphin A5 (right)



The decisive point we reached in the study was to detect the attachment molecule through which both aggressive mucosal agents end up docking at the target cell: an N-acyl-D-glucosamine 6-phosphate that is the N-acetyl derivative of D-glucosamine 6-phosphate which is a component of the aminoacid metabolism. The Molview model reveals also in this case the similarity to the Exorphins on the one hand and on the other hand it figures the possibilities of attachment to the Spike protein by O linkage or N linkage [11]. The following Figures 6,7 and 8 are also visually suggestive.

Fig. 6: Molecular structural formula N-acyl-D-glucosamine 6-phosphate highlighting possible O or N link attachment sites

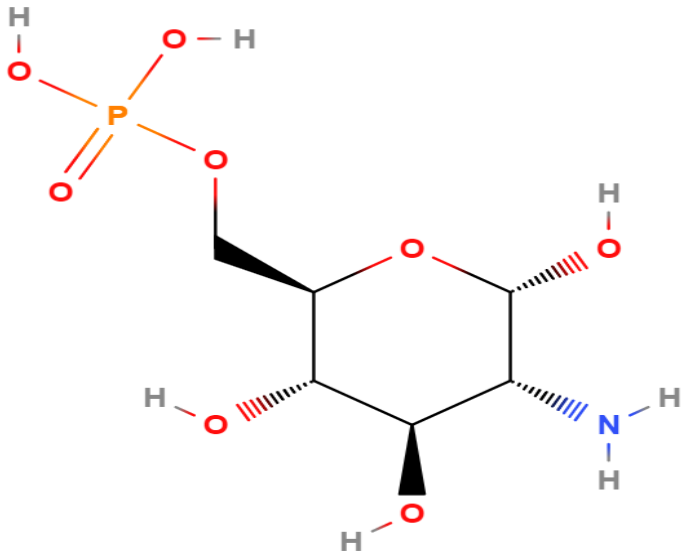


Fig. 7: The three - dimensional model of the molecule of N-acyl-D-glucosamine 6-phosphate

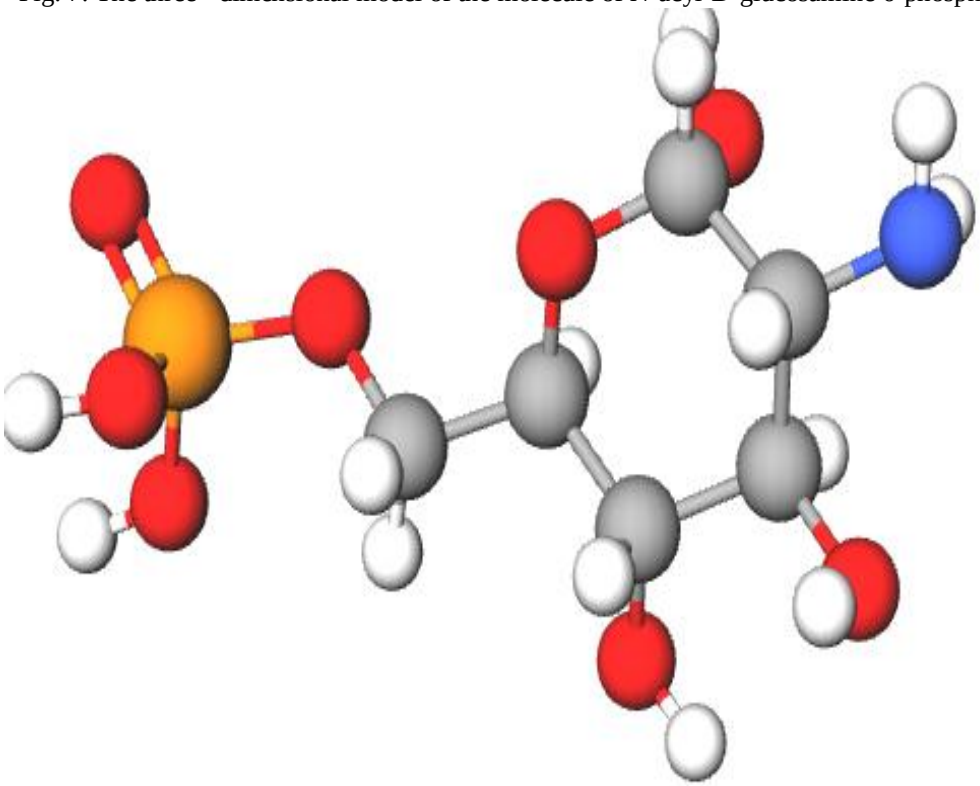
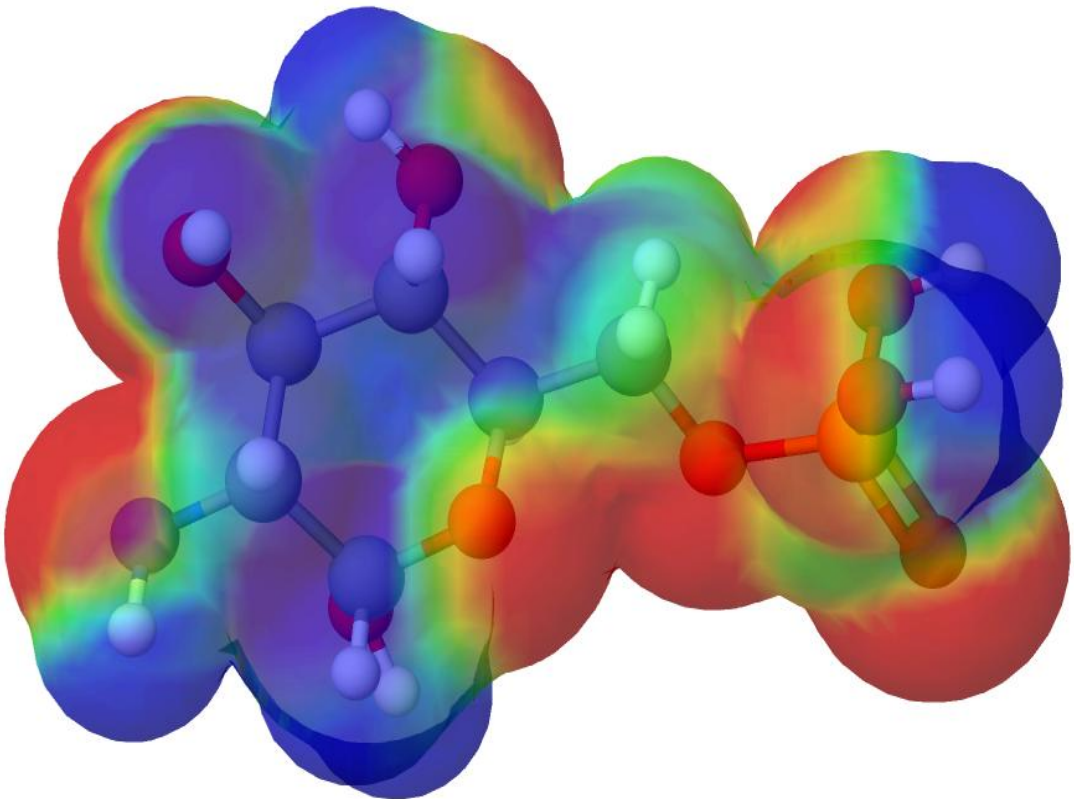


Fig. 8:Molview's exceptional visual application of the activated N-acyl-D-glucosamine 6-phosphate molecule



This means that mucosal attachment, whether gastrointestinal to CD or respiratory to SAARS-COV2, the causative agent, can be successfully prevented by creating and administering these COVID vaccines that target exactly some fragments of Spike proteins.

Translating the action to the intestinal level, we can extrapolate and provide a protective action at this level as well.

IV. CONCLUSION

The public perception of vaccines is that they are effective for adults of all ages including the elderly alike are suitable. One therefore intuitively sees the population as a large, uniform mass waiting for "the" vaccine. In the case of COVID-19, above all older people as well as people with certain pre-existing conditions to the high-risk groups in which an infection leads to particularly severe courses can lead to death. Among the most affected comorbidities were the autoimmune ones, including CD.

European statistics estimate that 1% of the population suffers from CD. The same quotas are valid for Romania and for its western region, studied by us. And in all these cases, well-studied molecules are involved, which now reveal their importance and actions, and through their structure we are increasingly convinced of the opportunity to display them as a chance and an opportunity for healing.

The results of the detailed analysis of this article encourage these patients and all medical and pharmaceutical and research staff to achieve a positive adherence to the national program, in accordance with the European, international and even global, vaccination against COVID. Also developing ideas and approaches to improve the effectiveness of vaccines also contribute to improve people's lives [12].

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