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ORIENTATION TOWARDS THE VITAL DECISION OF GLUTEN INTOLERANT PACIENTS FOR VACCINATION

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A vaccination against Covid-19 and the pathogen SARS-CoV-2 is now on the market. 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.[35]

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, Pro-vaccination.

INTRODUCTION

With the recent decisions that the Food and Drug Administration, the World Health Organisation and the European Medicines Agency (EMA) has granted Emergency Use Authorization for the vaccines against SARS-CoV-2, 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 who care for people with CD, we urge people with celiac disease to receive a Covid-19 vaccine that has met the necessary government regulatory approval. This includes inovative agents comprised of RNA and peptide (protein) vaccines.

During the onset of the Covid-19 pandemic in the last year, there was initial concern that people diagnosed with CD or even undiagnosed but with relevant symptoms[2], might be at a slightly increased risk of severe outcomes from SARS-CoV-2 infection, given prior studies[3] suggesting risks related to pneumonia and viral infections[4].

Factors potentially influencing SARS-CoV-2 infection in CD[5] patients are reported in Table 1.

Studies thus far, including the international registry covidceliac.org/celiac.org have indicated no increased risk of severe outcomes. Also SECURE-Celiac = **S**urveillance **E**pidemiology of **C**oronavirus **U**nder **R**esearch **E**xclusion is an international, pediatric and adult database to monitor and report about outcomes of COVID-19 occurring in patients with CD. They encourage clinicians worldwide to report all cases of COVID-19 in patients with CD, regardless of severity, including asymptomatic patients detected through public health screening.

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 destroing effects[7] and we share in the consensus belief by the public health community that mass vaccination is vital.

Table 1

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

HLA status	There is no data suggesting that there is an altered immune response against SARS-CoV-2 virus
Immunological factors	There is no evidence that ILs status or their genetic variants in CD could have any influence
Hyposplenism	May not be considered as a risk factor in this case
Mucosal atrophy	In case of treated and responsive CeD the mucosal state does not seem to have a role
Malabsorption/ Micronutrients deficiencies	Vitamins 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]	The presence of this state may significantly worsen the COVID-19 outcome.

Figure 1 shows the gradual increase in patients' risk.

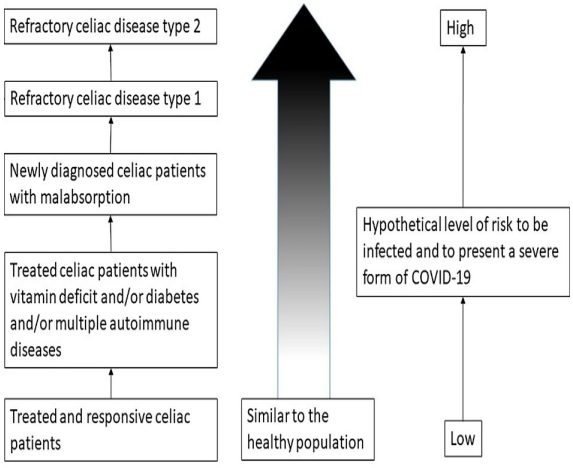


Figure 1. Levels of the risk for COVID infection 19 for patients with varying degrees of CD.

As the safety and efficacy data on Covid 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. All currently available vaccines worldwide that are parenterally administered can be safely taken by celiac patients[9].

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 typ 19[10], on the organic chemistry level.

PART I

We have analised regularly updated summary informations about reported cases of CD, including numbers of cases by city, number of cases by treatment, etc. so that the entire celiac disease community has access to these data. Of course the study contains only de-identified data, in accordance with GDPR implementation of the REGULATION (EU) 2016/679 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (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 celiac disease diagnosed? (serology and duodenal biopsy, serology only, unknown)
7. Serology used (TG2-IgA, DGP-IgG, EMA)
8. Years since diagnosis of celiac disease at the time of COVID-19 diagnosis :<1 year, 1-5 years, 6-10 years, 11-15 years, 16-20 years, 21-25 years, 26-30 years,>30 years, unknown
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. Does the patient have refractory celiac disease? If yes: refractory celiac disease type 1, refractory celiac disease 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? Unrestricted diet; Unrestricted gluten but other foods restricted; Gluten-free diet sometimes; Gluten-free diet most of the time; Trying to follow a gluten-free diet but not always sure; Usually gluten-free with rare intentional gluten consumption; Usually gluten-free with rare unintentional gluten consumption; Strict 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 celiac disease-related medications that were stopped due to COVID 19 All that apply: corticosteroids, azathioprine, 6-mercaptopurine, other

17. Does the patient have any of the following comorbidities (check all that apply)? Cardiovascular disease (coronary artery disease, heart failure, arrhythmia.), 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.), Current cigarette smoker

After the personal, clinical and paraclinical informations, we have dedicated a special part to the records avout 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.

RESULTS AND DISCUSSION

PART I

Table 2 summarizes the data collected in this study on patients with CD during the pandemic.

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 Celiac Disease					
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%)
Remdesivir					
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.

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.

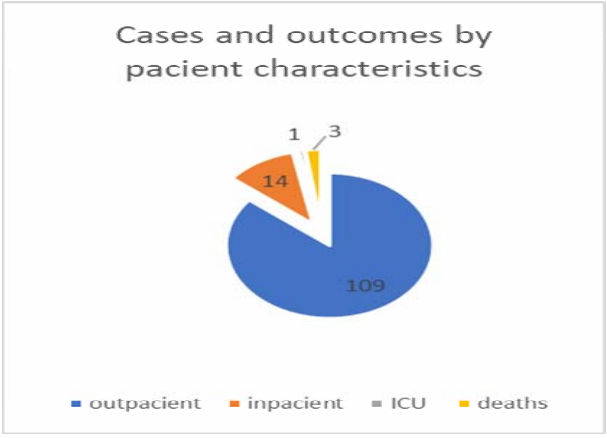
Graph 2 shows the distribution by age groups.

It is obvious that the middle age groups were the most affected, while the extreme groups less.

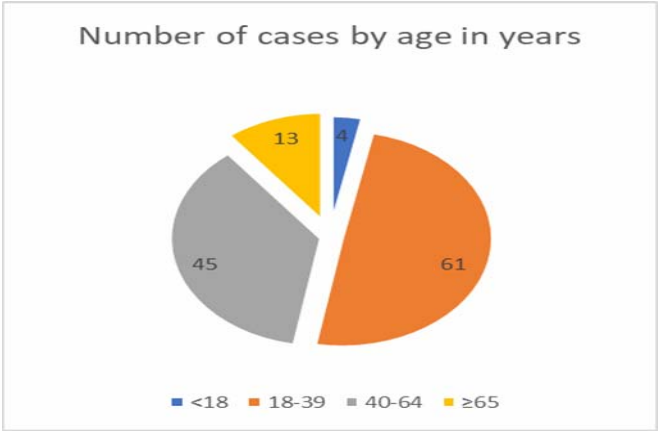
Graph 3 below, shows the number of cases by gender of patients.

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.

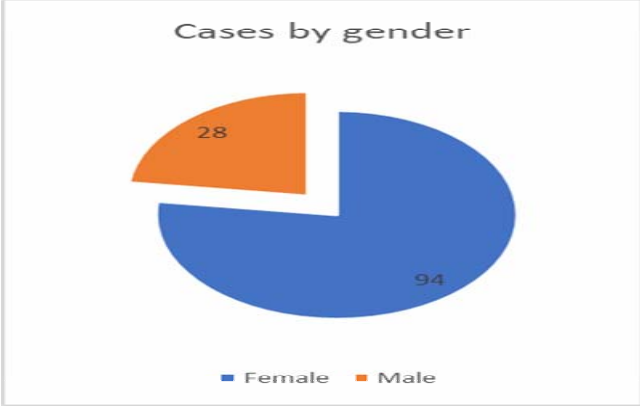
Graph 4 shows that the involvement of patients with CD was generally long-term when they came in contact with the COVID virus.



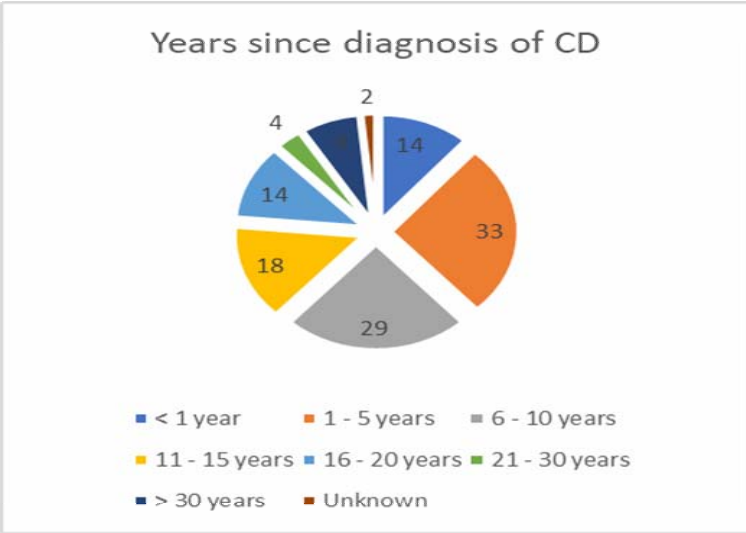
Graph 1. Patient cases by type



Graph 2. Number of cases distributed by age groups.



Graph 3. Distribution of cases according to gender.



Graph 4. Time from detection of the CD disease.

And discussions can continue 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: $C_{29}H_{45}N_5O_8$ 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: $C_{24}H_{37}N_5O^9$ 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	0.58866	12.0107 u × 29	0.58087
H	1.00794 u × 45	0.076656	1.00794 u × 37	0.062194
N	14.0067 u × 5	0.11836	14.0067 u × 5	0.11679
O	15.9994 u × 8	0.21632	15.9994 u × 9	0.24014

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 (Fig. 2), model 3D (Fig. 3) and Molview translucent model (Fig. 4).

So far, the nCoV-2019 has been reported to share 96% sequence identity to the RaTG13 genome (EPI_ISL_402131). However, the S1 Receptor Binding Domain (RBD) of the nCoV-2019 genome was noticeably divergent between the two at amino acid residues 350 to 550.

We aimed to identify coronaviruses related to nCoV-2019 in viral metagenomics datasets available in the public domain. In a recently published dataset describing viral diversity (PRJNA573298 344) we used VirMAP 147 to reconstruct a coronavirus genome (approximately 84% complete from samples SRR10168377 134 and SRR10168378 65) that shared 97% amino acid identity across the same RBD segment.

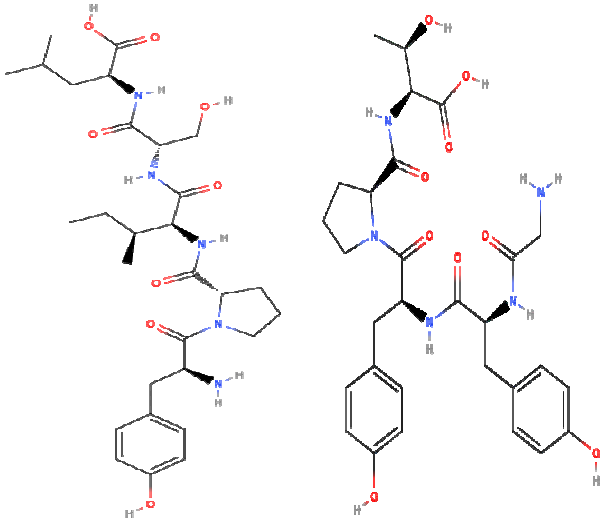


Figure 2. Structural formulas of Exorphin C (left) and Exorphin A5 (right).

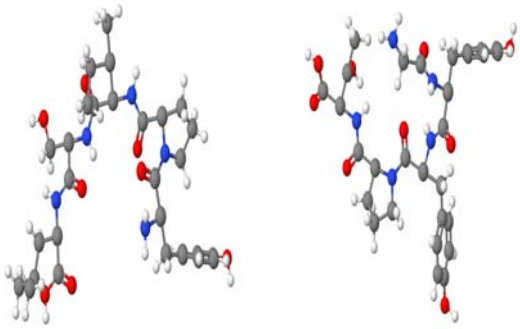


Figure 3. Model 3D (sticks and balls) of the molecules Exorphin C (left) and Exorphin A5 (right).

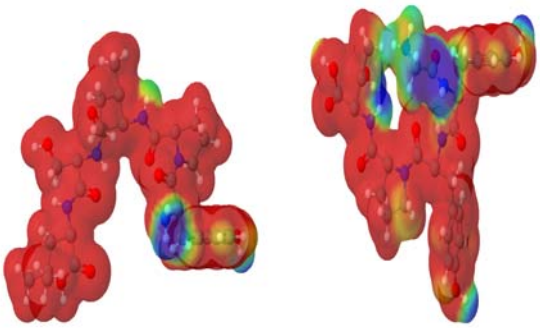


Figure 4. Molview translucent 3D of Exorphin C (left) and Exorphin A5 (right).

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surface glycoprotein [Wuhan seafood market pneumonia virus]

Sequence ID: YP_009724390.1 Length: 1273 Number of Matches: 6

See 5 more title(s)

Range 1: 350 to 550 GenPept Graphics Next Match Previous Match

Score	Expect	Method	Identities	Positives	Gaps	Frame
384 bits(986)	1e-126	Compositional matrix adjust.	181/201(90%)	190/201(94%)	0/201(0%)	+2

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Sbjct  530    STNLVKNKCVNFNFNGLTGTG  550
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Figure 5. Printscreen of the search in VirMAP 147.

This result indicates a potential recombination event for nCoV-2019. From the coordinates shown in this preprint 450, it looks like most of the differences between RaTG13 and nCoV-2019 are restricted to loop 2 of the receptor binding motif (positions ~450-500).

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].

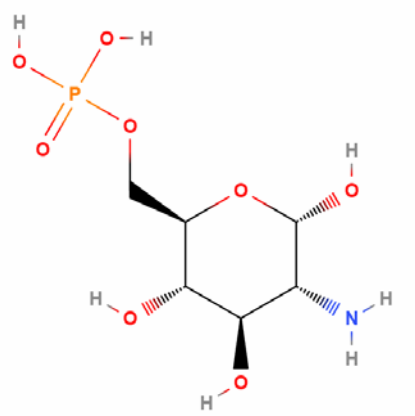

Figure 6. Molecular structural formula N-acyl-D-glucosamine 6-phosphate highlighting possible O or N link attachment sites.

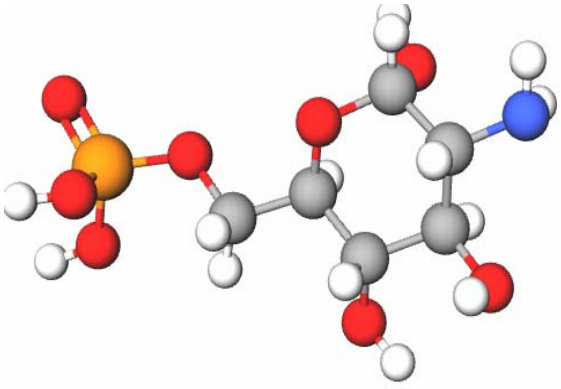

Figure 7. The three-dimensional model of the molecule of N-acyl-D-glucosamine 6-phosphate.

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.

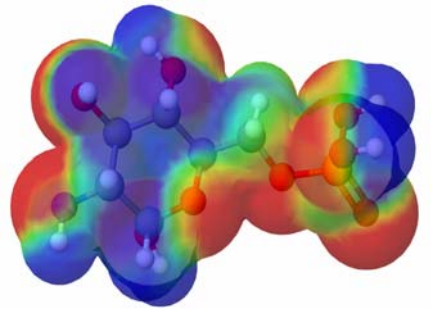

Figure 8. Molview's exceptional visual application of the activated N-acyl-D-glucosamine 6-phosphate molecule

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].

Aknowledgement. Special thanks to the Department of Organic Chemistry.

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