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NEW APPROACHES RELATED TO THE USE OF POLYAMINE-FREE AND POLYAMINE-DEFICIENT DIETS IN THE LIST OF NUTRITIONAL PRODUCTS FOR COVID-19 PATIENTS

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Abstract

Researches aimed at finding effective means of pathogenic therapy for this viral infection are extremely relevant. Researches of the last three years have established that some human pathogenic coronaviruses – MERS, SARS-CoV and SARS-CoV-2, contain aliphatic polyamines in their structure, which participate in the packaging of genetic material (DNA, RNA), as well as the nucleocapsid. Virus-host cell interactions also provide adhesion processes on the surface of the cytoplasmic membrane of target cells. In the intracellular space, aliphatic polyamines actively affect the translation and replication processes of the genetic material and necessary proteins of the virus itself, as well as the formation of daughter viruses. Long-term persistence in the SARS-CoV-2 infected organism is largely due to the absorption of polyamines by coronavirus localized in target cells of the blood and parenchymatous organs. Unfortunately, the above new facts did not serve as a prerequisite for finding effective means of pathogenetic therapy for COVID-19, based on the inhibition of polyamine-dependent processes that ensure long-term persistence of SARS-CoV-2 in the infected organism. We are talking about specific drugs such as α-difluoromethylornithine and its analogues, which are successfully used in oncology in the complex treatment of malignant neoplasms with the aim of lowering the level of aliphatic polyamines in the affected areas of malignantly transformed organs.

We recommend the use of polyamine-free and polyamine-deficient diets for COVID-19 for the first time.

In the planned study, we will present tables with food products of animal and vegetable origin, characterized by extremely low content and/or absence of aliphatic polyamines in them. At the same time, food products with a high content of aliphatic polyamines should be excluded from the general list of products recommended for COVID-19 patients.

We also recommend the use of a polyamine-deficient diet (with a preventive purpose) during the COVID-19 pandemic to a wide contingent of practically healthy individuals, convalescents, medical staff of specialized infectious disease clinics, as well as family members of SARS-CoV-2 infected patients.

Keywords: *COVID-19, SARS-CoV-2, polyamines, polyamine-free diet, polyamine-deficient diet.*

The search for effective means of symptomatic and pathogenetic therapy for COVID-19 infection is one of the actual problems of modern medicine [*Zilfyan A et al., 2020; Avagyan S et al., 2020; Chen Y et al., 1922; Rosenberg E et al., 2022; Xie Y et al., 2022*].

Currently, the main scientific developments are based on creating vaccines, with the aim of preventing a wide contingent of practically healthy individuals from SARS-CoV-2 infection, including reinfection of convalescents, as well as individuals with chronic diseases [*Zilfyan A et al., 2021; Abu-Raddad L et al., 2021; Hotez P, Bottazzi M, 2022; Zheng C et al., 2022*]. Besides the fact that the effectiveness of all commercial vaccines that have passed the final stage of certification is time-tested, with such an immuno-prophylactic approach, it is necessary to periodically assess the immune status, and, at least, the state of the respi-

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ratory, cardiovascular and digestive systems, both during coronavirus infection, and in clinical recovery period and much later [*Avagyan S et al., 2021; Bajema K et al., 2021; Tenforde M et al., 2021;Cizmeci P et al., 2022; Kobayashi T, Nishiura H, 2022; Lee AR, 2022*].

At present, a different scientific and methodological approach based on finding effective means of symptomatic and pathogenetic therapy for COVID-19 is much less practiced while studying the character of the infectious process caused by SARS-CoV-2 [*Bitsadze B et al., 2020; Howard-Jones A et al., 2022; Kannan M et al., 2022; Rolfo A, 2022; Wang N et al., 2022*].

A number of very informative studies provide data according to which, at all stages of COVID-19 infection, there are significant changes in the metabolism of polyamines localized in virus-sensitive target cells of the macroorganism [*Tabor C, Tabor H, 1984; Löser C et al., 1999; Schipper R et al., 2000; Eliassen K et al., 2002; Gugliucci A, 2004; Moinard C et al., 2005; Larqué E et al., 2007; Ruíz C et al., 2012; Atiya A et al., 2013; Kalac P, 2014; Gómez G et al., 2017; Muñoz-Esparza N et al., 2019; Avagyan S et al., 2020; Zilfyan A et al., 2020; Makhoba X et al., 2022; Xu X et al., 2022*].

It is established that the level of polyamines in mammals is provided by three sources:

De novo synthesis exclusively by all body cells [Lague *E et al., 2007; Minois N, 2011; Ruiz C et al., 2012*],

Synthesis and/or accumulation by resident microorganisms persisting in macroorganism econiches [*Avagyan S et al., 2019; Muñoz-Esparza N et al., 2019a, b; Romas M et al., 2019; Tofalo K et al., 2019; Zilfyan A et al., 2020*],

Food intake [*Gomez G et al., 2008; Atiya A et al., 2009; 2011; 2013; Ruiz C et al., 2012; Kala P, 2014; Muñoz-Esparza N et al., 2019a, b; Avagyan S et al., 2020*].

Significant amounts of polyamines enter into the macroorganism with various food products that SARS-CoV-2 infected patients consume daily, without taking into account the content of polyamines in them. Thus, the situation is much more complicated, since SARS-CoV-2 is in dire need of polyamines for its activation and long-term persistence. That's why, we offer a polyamine-free and polyamine-deficient diet as auxiliary, but necessary means of symptomatic and pathogenetic therapy for COVID-19, due to which it will be possible to partially stop pathological processes in target organs during this coronavirus infection.

TABLE 1

Polyamine concentrations (nmol/g) in foods for diet groups [*Soda K et al., 2009*]

	Put	Spd	Spm	Total
Low polyamine diet	496	224	143	863
Normal polyamine diet	625	434	160	1219
High polyamine diet	1075	1540	374	2989

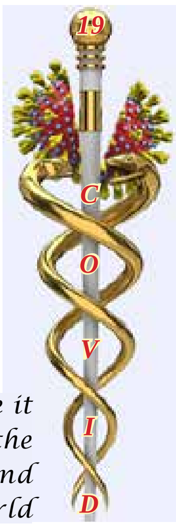
NOTES: Put - putrescine, Spd - spermidine, Spm Spermine

During a paraclinical examination of a wide range of diseases of various etiologies (Parkinson's disease, Helicobacter pylori (H. pylori)-dependent gastritis, viral papilloma, breast, prostate and cervical cancer, colorectal cancer), it was found that all of them have a significantly increased level of aliphatic polyamines in plasma and erythrocytes, as well as in urine [*Lewandowski N et al., 2010; Paik M et al., 2010; Chaturvedi R et al., 2012; Smythies J, 2012; Gondalia S et al., 2013*].

In a number of "polyamine-dependent" diseases, where the levels of polyamines in patients were controlled by diet, the latter was divided into three groups [*Shrestha R et al., 1992, Soda K et al., 2009*]. The levels of polyamines in food products of each group are presented in table 1.

It should be noted that these indicators significantly differ from each other in different countries due to the lack of a single registry for assessing the intake of the optimal level of aliphatic polyamines through food products [*Ralph A et al., 1999; Soda K et al., 2010; Buyukuslu N et al., 2014; Muñoz-Esparza N et al., 2019*].

The average polyamine intakes by adults in countries such as the UK, Italy, Spain, Finland, Sweden and the Netherlands [*Ralph A et al.,*



To overcome it is possible, due to the uniting the knowledge and will of all doctors in the world

1999] were 211,910 *nmol/day* for putrescine, 86,959 *nmol/day* for spermidine and *nmol/day* for spermine. According to the authors, in the United States, mean daily polyamine intakes were 159,133 *nmol/day* for putrescine, 54,697 *nmol/day* for spermidine and 35,698 *nmol/day* for spermine [*Zoumas-Morse C et al., 2007*]. For the population of Central Asia, the daily intake was 93057 *nmol/day* for putrescine, 33122 *nmol/day* for spermidine and 13685 *nmol/day* for spermine [*Buyukuslu N et al., 2014*].

Cipolly B. and co-authors (2003) identified three groups of products according to the content of polyamines. Products of I group (containing less than 100 *nmol*/g) could be taken daily, II group products (101-200 *nmol/g*) could be consumed three or four times a week, and III group products (>201 *nmol/g*) were preferable to avoid (Table 2).

By analyzing current data on the level of polyamines in food products, it is possible to make both a polyamine-free and polyamine-deficient diet specifically for patients suffering from polyamine-dependent diseases.

First of all, one can single out a polyamine-free diet, which is used in the practice of treating oncological diseases [*Moulinoux J et al., 1991; Cipolla B et al., 2003; 2007*].

Table 2

Polyamine contents in regular food
[*Cipolla B et al., 2003*]

Permitted every day (<100 *nmol/g*)	Permitted once in a while (101-200 *nmol/g*)	Forbidden (>201 *nmol/g*)
• Bread • Meats, beef, veal, pork, poultry • Eggs • Fish (fresh) • Milk and white cheese • Pasta and rice • Tomatoes, onions, mushrooms, lettuce, spinach, potatoes, beetroot • Apples, pears, peaches, strawberries, grapes • Flour, margarine, butter, oil • Salt and pepper • Biscuits • Water, coffee, tea	• Yoghurt • Pasteurized cheese • Jams • Wine	• Carrots • Radishes • Celery • Green beans • Oranges and juice • Bananas • Prunes • Grapefruit • Melon • Liver • Fermented cheese: stilton, Roquefort, gorgonzola, camembert

Table 3

Polyamine-free products

Food products	Put	Spd	Spm	Cad	Total
Butter	bdl	bdl	bdl	bdl	bdl
Salt	bdl	bdl	bdl	bdl	bdl
White pepper	bdl	bdl	bdl	bdl	bdl
Black coffee	bdl	bdl	bdl	bdl	bdl
Ceylon tea	bdl	bdl	bdl	bdl	bdl
Champagne cider	bdl	bdl	bdl	bdl	bdl
Cola beverage	bdl	bdl	bdl	bdl	bdl
Curdled milk	bdl	bdl	bdl	bdl	bdl
Skimmed milk	bdl	bdl	bdl	bdl	bdl
Cream	bdl	1	bdl	bdl	1
Milk (semi-skinned, low fat)	1	bdl	bdl	bdl	1
Natural yoghurt	0.3	0.4	0.4	bdl	1.1
Egg white (freshly-laid)	1	bdl	bdl	bdl	1.0
Whisky	bdl	1	bdl	bdl	1
Cognac	bdl	1	bdl	bdl	1
Rice (white)	2.0	bdl	bdl	bdl	2.0
Soft cheese	bdl	1	1	1	3
Caster sugar	3	bdl	bdl	bdl	3.0
Very thin pancake (crepe)	bdl	5	1	1	7.0
Chocolate eclair	2	3	bdl	2	7.0
Wine vinegar	8	bdl	bdl	bdl	8.0
Mayonnaise	1	4	1	3	9.0
Honey	8	1	bdl	1	10.0
Cookie (sweet biscuit)	2	6	1	1	10.0

Notes: Put - putrescine, Spd - spermidine, Spm Spermine, Cad - cadaverine, bdl- below detection limits

As can be seen from table 3, there are products in which aliphatic polyamines are not detected, and a group of products in which they are detected in extremely low quantities. We suggest products in which the total amount of polyamines is less than 10 *nmol/g* [*Ralph A et al., 1999; Cipolla B, 2003; 2007; Buyukuslu N et al., 2014; Muñoz-Esparza N et al., 2019*].

According to Cipolla B. and co-authors, the content of polyamines is very significant in some products, such as meat and meat products, culinary products, bread products, vegetables, spices, canned foods, so they cannot be offered as polyamine-free products.

Secondly, products that can be consumed in a polyamine-deficient diet are presented in table 4 [*Cipolla B et al., 2003*].

Analyzing all the data presented in table 4, the levels of individual polyamines are found in the same food product, which are identical in content (Frankfurter sausage, White bread), or, conversely, significantly differ from each other. For example, Stout beer and Red table wine have much higher levels of putrescine than other polyamines. Pear and Green cabbage have much higher levels of spermidine, compared to other polyamines.

It should be especially noted that in different countries the standards for daily polyamine intake significantly differ from each other [*Ralph A et al., 1999; Zoumas-Morse C et al., 2007; Muñoz-Esparza N et al., 2019; Buyukuslu N et al., 2014, Avagyan S, 2021*], therefore the data of Cipolla B. and colleagues are unacceptable for other countries (USA, Japan, Turkey).

Polyamine-dependent diseases include neurological, cardiovascular and viral diseases. Their dependence on polyamine level has already been established. Taking into account the achievements of many researchers in studying the level of polyamines in products and their accessibility in the digestive tract upon their exogenous entry into the body, in some countries, it is also suggested to follow a polyamine-dependent diet for the treatment of patients with polyamine metabolism-related diseases, with the purpose of regulating the level of polyamines in the macroorganism.

Polyamine-dependent diet preparation is a very laborious process, and requires professional skills of not only nutritionists, but also general practitioners, depending on the contingent of patients who should adhere to the polyamine diet.

It has been stated that cancer patients, who have very high level of aliphatic polyamines in blood, urine and malignantly degenerated cells, are also suggested to follow a polyamine deficient diet in order to lower the level of polyamines in the macroorganism. In our opinion, decreased concentration of polyamines (spermine, spermidine and putrescine) in the body can significantly slow down

Table 4

Products (a partial list) that can be consumed in a polyamine-deficient diet [*Cipolla B et al., 2003*]

Foods	Put	Cad	Spd	Spm	Total
White wine (Burgundy)	9.0	bdl	1	bdl	10.1
Apple juice	11.1	bdl	2	bdl	13.1
Grape juice	9.0	bdl	5.1	bdl	14.1
Apricot juice	8.0	bdl	7.0	bdl	15.0
Dried milk	2.0	bdl	7.0	7.0	16.0
Prune	6.1	1	10.1	2	19.2
Pear	0.4	0.7	18.4	0.2	19.8
Freshly-laid egg	20.5	bdl	bdl	bdl	20.5
Pear	4.3	0.7	20.3	bdl	25.3
Stout beer	21.2	1	bdl	bdl	22.2
Red table wine (Bordeaux)	22.3	bdl	bdl	bdl	22.3
Peach	7.4	1	18.4	bdl	26.8
Egg yolk (freshly-laid)	43.7	bdl	bdl	bdl	43.7
Onion	5.7	3.3	35.4	bdl	44.3
Diced bacon	3	12.1	7.0	26.3	48.3
Tomato juice	35.5	1	13.2	1	50.7
Apple	30.3	0.9	22.1	bdl	53.3
Semolina	25.1	1	5.0	23.1	54.2
Red grapes	34.2	6.4	15.2	0.1	55.8
Fresh pasta	13.0	3	35.1	6.0	57.1
Green pepper	21.6	5.3	30.4	4.1	61.4
Normal ripe carrot	7.7	0.8	53.6	2.7	64.8
Toulouse sausage	3	1	16.3	46.2	66.5
Green cabbage	6.0	1	55.7	6.4	69.1
Spicy sausage (merguez)	8.1	1	12.2	48.3	69.6
Lemon	53.8	0.8	18.4	0.9	73.8
Strawberry	18.5	4.3	40.3	13.7	76.8
Chipolata	3	1	24.2	50.3	78.5
Beet, beetroot	51.7	0.2	29.1	bdl	81.0
Frankfurter sausage	11.1	14.2	27.0	31.1	83.4
Skinned potato	31.4	5.1	46.1	4.3	86.8
Pork (roast)	4	3	9.3	72.3	88.6
Turkey (wing)	14.1	2.0	10.1	68.3	94.5
White bread	13.0	15.3	54.2	13.2	95.7
String beans	65.2	bdl	27.2	6.0	98.4

Notes: Put - putrescine, Spd - spermidine, Spm Spermine, Cad - cadaverine, bdl- below detection limits the course of the pathological process.

While creating a polyamine-deficient diet for patients, we analyzed the diet proposed by Ralph A. and co-authors (1999), where the daily food intake was 1500-1600 *g* per day, and the level of polyamines in this food was 309.54 *µmol*.

Considering that the average daily intake of total polyamines for healthy individuals of the European contingent is 315.1 µmol/day (putrescine – 160.3 µmol/day, spermidine – 96.7 µmol/day and spermine – 58.1 µmol/day) [*Ralph A et al., 1999*], and according to Cipolla B. and colleagues (2003), we offer 120-130 *µmol/day* maximum level of polyamines in this volume of food for the polyamine-deficient diet. Under these conditions, in our opinion, it is necessary to exclude some products with a large amount of polyamines (marked with one asterisk in table 5) from the diet proposed by Ralph A. and co-authors (1999) specifically for residents of the United Kingdom, and, at the same time, adding some food products to this list that do not contain (or contain negligible amounts) polyamines (marked with two asterisks), and suggest a polyamine-deficient diet as an example (Table 5).

In this aspect, polyamine levels as diagnostic markers have not been the subject of a special study despite the fact that both coronaviruses (SARS-CoV and SARS-CoV2) need polyamines in the persistence process in an infected organism. It is for neurological, oncological and viral diseases, we propose to include a polyamine-deficient diet in the list of nutritional products, in order to reduce the level of aliphatic polyamines in the macroorganism.

Apparently, the inclusion of a polyamine diet for COVID-19 patients, in general terms, was proposed by us earlier [*Avagyan S et al., 2021*].

It should be especially noted that the third source of polyamine intake, with their subsequent absorption by macroorganism cells, resident microorganisms and, especially, viruses, in an infected organism was not the subject of a special study.

In this aspect, some human pathogenic coronaviruses – MERS, SARS-CoV and SARS-CoV-2, need polyamines localized in target cells and resident microorganisms in the process of long-term persistence in the macroorganism, in order to maintain their functional activity-adhesion on the

TABLE 5

Daily dietary polyamine intake in the UK in 1995 (including eating out) [*Ralph A et al., 1999*] ♯

Food	Intake *(g/d)*	*Total (µmol/d)*	
		For Normal polyamine Diet	*For polyamine-deficient diet*
Other cereal	69	9.371	9.371
Biscuits, cake	42	0.964	0.964
Milk, cream, yogurt	100	0.81	0.81
Eggs	14	0.079	0.079
Vegetables	166	45.207	45.207
Chocolate, sweets, jam	34	0.549	0.549
Meat	34	8.678	8.678
Poultry	34	13.256	13.256
Fish	25	3.975	3.975
Soft drinks	166	2.157	2.157
Miscellaneous	36	9.468	9.468
Bread*	119	18.669	–
Cheese*	16	15.117	–
Potatoes*	157	80.698	–
Fruit*	147	48.818	–
Meat products*	66	15.816	–
Alcohol/wine	129	9.131	–
Oils, fats	uq	0	0
Spinach**	uq	0	0
Mayonnaise**	uq	0	0
Raisin**	uq	0	0
Tuna (in oil)**	uq	0	0
Garlic**	10	0.07	0.07
Dill**	10	0.07	0.07
Kiwi**	30	0.21	0.21
Pineapple**	30	0.21	0.21
Total	1466	309.54	125.07

*Notes: ♯ Таблица представлена с рекомендациями авторов, * - пиша, которая нами удалена из диеты, ** - пиша, в которой отсутствуют полиамины, uq -unlimited quantity* surface of target cells, translation and replication of daughter viruses [*Mounce B et al., 2016 a,b; Avagyan S et al., 2020; Firpo M, Mounce B, 2020; Firpo M et al., 2020; Zilfyan A et al., 2020*]. Moreover, aliphatic polyamines are involved in the nucleocapsid packaging of some human pathogenic coronaviruses.

It was the "vital" need of polyamines for SARS-CoV-2, which largely ensure the processes of long-term persistence of the coronavirus in the body, that served as the basis for the recommendations to include agents blocking the exchange of polyamines in the infected organism in the general registry of symptomatic therapy for COVID-19 [*Mounce B et al., 2017; Zilfyan A et al., 2021; Avagyan S et al., 2021*]. These agents include α-difluoromethylornithine (DFMO), which inhibits the initial steps of aliphatic polyamine synthesis by blockade of ornithine decarboxylase [*Meykens F, Gerner E, 1999*]. Unfortunately, such an approach, based on the use of DFMO as a complex therapy for COVID, has not been properly evaluated yet. It should also be noted that at present we do not have even minimal information about the features of aliphatic polyamine metabolism in a SARS-CoV-2 infected organism. In our opinion, this situation requires the implementation of scientific and organizational measures in specialized clinical laboratories, where the levels of aliphatic polyamines – putrescine, spermidine and spermine should be determined in the bioassays taken from COVID-19 patients.

Since there are no significant changes in this issue, a polyamine-deficient diet should be considered today as possible effective means of symptomatic and, especially, pathogenetic therapy for COVID-19.

In fact, we propose an alternative approach based on the significant elimination of food products containing high levels of aliphatic polyamines entering into the infected organism. Due to this approach, it will be possible to minimize the level of polyamines in target cells and, thereby, achieve a noticeable inhibition of polyamine-dependent processes responsible for the persistence and enhancement of the biological activity of SARS-CoV-2 in an infected organism.

It should be especially noted that the entire list of foods that we will present as a polyamine-deficient diet, along with numerous products of animal and vegetable origin, is used in everyday life, without any restrictions for a healthy contingent of people living in many regions of the globe, as well as in a wide range of somatic diseases, including those of infectious origin. At present, the diet of COVID-19 patients also includes food products with a high content of aliphatic polyamines – putrescine, spermidine and spermine.

As we mentioned above, our recommendations are based on one important scientific and methodological principle in the process of studying the COVID-19 pathogenesis, in which SARS-CoV-2 urgently needs polyamines for its persistence. That's why, on the one hand, we propose, if possible, to exclude a wide range of food products that are rich in polyamines. On the other hand, we adhere to the maximum intake of those foods that are characterized by the lowest content of polyamines or their complete absence.

In this article we provide a list of products of animal and vegetable origin as a "polyamine-deficient" diet, which should be followed by both COVID-19 patients and a wide contingent of apparently healthy individuals and convalescents (table 5). Unfortunately, to date, there is no such experience associated with the use of a polyamine-deficient diet in patients infected with SARS-CoV-2 in any country.

Apparently, this is our first attempt to introduce the principle of a polyamine-deficient diet for COVID-19 patients, which may undergo corrections with the introduction of new recommendations.

It should be noted that our own recommendations on the need for a polyamine-deficient diet for COVID-19 were summarized in our previous publication [*Avagyan S et al., 2021; Cipolla B et al., 2003; Muñoz-Esparza N, 2019*] with several tables (due to the synthesis of numerous highly informative data) that presented a wide range of animal and vegetable products, characterized by both high and low content of aliphatic polyamines. Due to this circumstance, there was a need for new recommendations on the use of more specific, most commonly used products, with a low content of aliphatic polyamines, regardless of the region of residence of a healthy and SARS-CoV-2 infected contingent of individuals.

Polyamine-deficient products of animal and vegetable origin recommended by us for COVID-19 patients, both during the period of SARS-CoV-2 infection and the height of the disease, and during clinical recovery (at least for several years after infection) are presented in table 5.

Food products with a high content of putrescine in them should be excluded from the general diet of COVID-19 patients. As an example, it's enough to cite very informative data on the content of aliphatic polyamines in food products, which are presented in a summary table [*Ali A et al., 2011*]. The same data of the above-mentioned authors are given in our book and review article [*Avagyan S, Zilfyan A, 2019; Avagyan S et al., 2020*].

To ensure vitamin C intake, it is recommended to eat foods with a high content of vitamin C (even several times higher than its content) and with a low content of polyamines instead of some fruits in which the content of polyamines is very high (oranges, grapefruits, tangerines). Rose hips, green peppers and some other products can be very effective in replacing citrus for COVID-19 patients, as their vitamin C content is several times higher than that of citrus fruits, and the level of polyamines is much lower.

Drinking red wines is not excluded, as well as chocolate in relatively minimal quantities.

Reviewing and analyzing the obtained results, we found necessary to exclude those food products (from the list of products taken during COVID-19) that contain the highest content of putrescine: sauerkraut, green peppers, fried potatoes and green onions, ketchup. Among the meat products and their derivatives is goose and chicken liver pate.

The distribution of aliphatic polyamines in various food products of animal and vegetable origin often varies widely. Therefore, physicians and nutritionists should follow the principle of selective approach when prescribing a polyamine-deficient diet to COVID-19 patients and convalescents. When choosing a diet, clinicians should be based on chromatographic study results (high performance liquid chromatography) aimed at determining the level of aliphatic polyamines in the blood of COVID-19 patients and convalescents: putrescine, spermidine and spermine.

In this selective approach, we recommend the use of freshly made pomegranate juice, or the pomegranate itself with seeds, and green tea, since the expected effect depends on the properties of both products. Firstly, pomegranate is characterized by the absence of polyamines in it. Secondly, and more significantly, both products have a unique ability to inhibit the synthesis of aliphatic polyamines in the macroorganism, by blocking the ornithine decarboxylase activity, thereby preventing the synthesis of putrescine from ornithine.

For prophylactic purposes we also recommend to use all food products offered during the pandemic as a polyamine-deficient diet to a wide contingent of practically healthy individuals, convalescents, medical staff of specialized clinics, as well as family members of SARS-CoV-2 infected patients.

All the fruits listed in table 6, which have high levels of aliphatic polyamines, must be excluded from the list of nutritional products of not only COVID-19 patients, but also practically healthy individuals, medical personnel of specialized infectious diseases clinics, as well as family members of SARS-CoV-2 infected patients.

While preparing polyamine-free and polyamine-deficient diets, one should, in our opinion, adhere to the following tactics.

First, it is necessary to determine the levels of polyamines in plasma, erythrocytes and urine of patients with modern methods of diagnostic tests. It is advisable to determine not only the levels of putrescine, spermidine and spermine, but also to

Table 6

Aliphatic polyamine levels in fruits that have to be excluded from the list of nutritional products of COVID-19 patients

Fruits	Polyamine (*μmol/g*)		
	Put	Spd	Spm
Orange	620-1360	27-93	-
Philippine mango	903	199	16
Tangerine	860	80	-
Ruby grapefruit	580	20	-
Grapefruit	292	19	3
Banana	180-466	60	-
Grape	105	87	-
Cherry	53	19	-

Notes: Put - putrescine, Spd - spermidine, Spm Spermine include cadaverine and agmatine in this list, given that high performance liquid chromatographic (HPLC) analysis allows them to be determined simultaneously in the same sample [*Hockl P et al., 2000; Taibi G et al., 2000; Aflaki F et al., 2014*].

Secondly, a nutritionist must necessarily participate in preparing a diet, who must be familiar with the results of laboratory biochemical studies for the determination of polyamines.

When formulating a polyamine-deficient diet, the nutritionist should pay special attention to the fact that the levels of polyamine combinations in different products manifest themselves in different ways. For example, if the levels of putrescine in patient's blood are higher than spermine and spermidine based on a diagnostic test, the nutritionist should exclude specific food products containing high levels of putrescine from the general diet. A similar approach should be followed by a nutritionist when taking into account the indicators of spermidine and spermine in patient bioassays.

Conclusion

It is necessary to study the changes in polyamine levels and establish diagnostic indicators characteristic of each disease in patients with "polyamine-dependent" diseases, particularly with viral infections.

We propose the above list of food products for the first time as a polyamine-deficient diet for COVID-19 patients, a wide contingent of practically healthy individuals, medical personnel of specialized infectious disease clinics, as well as family members of SARS-CoV-2 infected patients.

In our opinion, the recommended polyamine-deficient diet is based on scientifically substantiated study results of a number of advanced scientists and the results of our own observations.

The polyamine-deficient diet is mainly based on COVID-19 pathogenesis, which, in particular, is expressed by the "uptake" of polyamines from target cells by SARS-CoV-2. As a result, long-term persistence of the coronavirus in the macroorganism is ensured by activating its adhesive properties, intracellular translation and replication of daughter viruses.

That is why the proposed polyamine-deficient diet seems to be most likely pathogenetically justified, since it will, to a certain extent, significantly inhibit the SARS-CoV-2 persistence in the infected organism.

This is our first attempt to include in the diet such food products of animal and vegetable origin that contain an extremely low content of aliphatic polyamines – putrescine, spermidine and spermine.

The "scheme" of the polyamine-deficient diet, proposed by us, is, of course, not exhaustive and, moreover, a panacea. The choice of all the products included in the list of the polyamine diet at the same time cannot serve as a prerequisite. The attending physicians should adjust the use of food products themselves after prior consultation with "competent" nutritionists, however, always subject to the conditions for choosing exactly those products that we recommend as a polyamine-deficient diet for COVID-19 patients.

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