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Original article

The feasibility of a diet which enhances inositol availability

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Summary. *Background:* Supplementation of myo-inositol has proved effective in different pathological conditions associated with insulin-resistance, including polycystic ovary syndrome, diabetes, gestational diabetes, and metabolic syndrome. At the same time, dietary habits in developed countries tend to reduce inositol intake, due to reduced consumption of whole grain foods, legumes, and nuts, rich in phytic acid, the main source of inositol. *Aim:* The review aims at providing a collection of foods with high phytic acid content to be used for diets that can make available as much inositol as is obtained from nutritional supplements commonly present in the market. *Methods:* An extensive review concerning the phytic acid content of foods was obtained from literature; furthermore, we designed an exemplifying phytic acid rich diet in by means of a specific nutritional software. *Results:* Foods with high phytic acid content are: cereals (0.04-3.3% on the dry matter), legumes (0.2-2.4%), oil seeds (0.4-5.7%), and nuts (0.2-9.4%). A moderate amount of phytic acid has been found in root vegetables, tubers and fruits, while low levels are found in the leafy green vegetables. Using these data, we developed an example of weekly diet which provides a mean phytic acid content of 5 g/1660Kcal. *Conclusions:* This study shows that it is possible to increase phytic acid intake, and consequently inositol availability, by means of an appropriate diet as a complementary treatment to dietary supplements. In people who regularly consume fruits and vegetables, the gut microbiota efficiently degrades phytic acid to myo-inositol phosphate products, therefore this diet could be proposed to patients with increased inositol needs, such as those suffering from polycystic ovary syndrome and in insulin resistance.

Keywords: diet, insulin-resistance, myo-inositol, phytic acid

Introduction

Inositol is a cyclitol that exists in nine stereoisomeric forms, myo-inositol being the most common. Myo-inositol is a precursor of phosphatidylinositol and its phosphorylated products, called phosphoinositides, which have been implicated in nearly all aspect of cell physiology. Myo-inositol derivatives perform important cell and metabolic functions, including cell growth and survival, development and function of peripheral nerves, reproduction, and regulation of glucose metabolism, to name just a few. Deregulation of inositol metabolism has been shown to occur in several chronic human diseases, including metabolic syndrome, diabetes, polycystic ovary syndrome, and cancer [(1)]. In particular, depletion of intracellular myo-inositol is commonly observed in diabetic animal models and human subjects [(2, 3)]; indeed, high glucose levels hinder inositol availability by increasing its degradation and by inhibiting both myo-inositol biosynthesis and absorption [(4)]. Myo-inositol and D-chiroinositol supplementation is currently used for the treatment of polycystic ovary syndrome (PCOS), a condition frequently associated with insulin resistance and metabolic syndrome. In women with PCOS, myo-inositol supplementation can restore ovarian activity, and improve hormonal parameters, insulin sensitivity and markers of cardiovascular risk (5). A number of recent studies have shown that inositol consistently improves glucose metabolism, insulin resistance and dyslipidemia in post postmenopausal women with metabolic syndrome (6, 7), and in pregnant women with gestational diabetes, or at risk of developing the disease (8). In addition, myo-inositol supplement has been shown to prevent or delay the development of certain microvascular complications of diabetes in animal models (5) and to improve glycemic control in human patients with type 2 diabetes (9).

Western diets are typically rich in fat and sugar and significantly low in fibers, lacking key components such as inositols and phytates, for which a mechanistic link has been established in the pathogenesis of chronic diseases, including metabolic syndrome, obesity, cardiovascular diseases, PCOS, diabetes, and cancer (4). Myo-inositol is found in the human diet in its free form or as inositol-containing phospholipid in animal-derived foods, or as phytic acid (inositol-hexakisphosphate) or phytates in plant foodstuffs. Dietary intake of myo-inositol has rarely been investigated, and the available data is mainly based on the consumption of phytate-rich foodstuffs rather than on inositol or myo-inositol contained in food. Although the literature shows huge differences between different countries, between urban or rural areas, females and males, young and old subjects, and omnivores and vegetarians, it can be postulated that the mean daily intake of phytic acid is about 500-700 mg for western countries (10), prompting the hypothesis that an increased intake of inositol could be achieved not only by using dietary supplements, but also by dietary means. Accordingly, following an initial attempt to develop a diet with a high myo-inositol content to be prescribed to patients with diabetes mellitus (11), here we designed an exemplifying diet that increases inositol availability, that could be proposed to patients who would benefit from increasing their daily inositol intake due to illness.

Content of Phytic Acid in Foods

As far as is known, very little data about inositol content in foods has been published to date (11). Given that phytic acid is the main source of myo-inositol, the content of phytic acid in foods was examined, using data obtained from several papers, the Indian Food Composition Tables (12), and the Food Composition Tables of Italian Council for Agricultural Research and Economics (13). Table1 shows the phytic acid content of some common foods. The main sources of phytates in the human diet are cereals, legumes, oil seeds, and nuts. Cereals are rich in phytates and contain approximately 1% phytic acid on the dry matter, ranging from 0.04 to 3.3%. In cereals, most of the phytates are located in the aleurone layer, while the endosperm is almost devoid of phytates (10); for this reason, wholegrain cereals are richer in phytates than refined cereals. In legumes, phytic acid content ranges from 0.2 to 2.4%, occurring predominantly in the protein bodies of the endosperm or the cotyledon. In oily seeds, such as sunflower, sesame and flax, the phytic acid contents varies from 0.4 to 5.7%. In nuts, the range is 0.2-9.4%, with higher level found in almonds (9.42%) and walnuts (6.69%). A moderate amount of phytic acid has been found in root vegetables, tubers and fruits, while low levels are found in the leafy green vegetables (14). The significant variation in the published phytic acid content of various foods should be taken into account, and is a limiting factor when developing a diet high in phytic acid.

Exemplifying Dietary Plan Rich in Phytic Acid

Table 2 shows an example of a weekly diet rich in phytic acid. The diet was developed by means of the Handy Diet software (HandyDiet SRL, Bergamo, Italy), which bases its nutritional analysis on the Food Composition Database for Epidemiological Studies in Italy (15). The diet has been designed for an overweight woman with PCOS, with a daily energy expenditure of 2100Kcal, thus it was computed with a caloric restriction of about 400 Kcal. Nutrient requirements were calculated according to the Italian daily nutritional requirements (16). Phytic acid content was estimated based on the range of values given in Table 1. The diet plan consists of 3 main meals (breakfast, lunch and dinner) and 2 snacks, for which we proposed different options. The diet provides a daily caloric intake of about 1660 Kcal, consisting of 16.11% protein, 33.83% fat, and 44.83% carbohydrates. The macronutrient and

Table1. Phytic acid content of common foods (g/100g dry matter)

Foods	Phytic acid	References
Cereals		
Amaranth grain	0.34-1.51	(12, 38)
Barley	0.39-1.19	(12, 13, 39, 40)
Buckwheat	0.92-1.62	(38)
Bulgur	0.68	(12)
Maize	0.65-2.22	(10, 12, 14, 38)
Maize germ	6.39	(39)
Maize, whole flour	0.79	(41)
Maize, popcorn	0.04-0.61	(13, 42, 43)
Millet	0.18-1.67	(14, 44)
Oat	0.42-1.37	(40, 42)
Oat, flakes	0.84-1.21	(38)
Quinoa grain	0.12	(12)
Rice bran	2.56-8.70	(14, 39, 45)
Rice, brown (parboiled)	1.60	(40)
Rice, brown (raw)	0.52-0.99	(12-14, 40, 42, 43)
Rice, white (cooked)	0.12-0.37	(38)
Rice, white (raw)	0.20-0.60	(14, 40)
Rice, wild (cooked)	1.27-2.2	(10, 38)
Rye	0.54-1.46	(40, 42)
Soghum	0.57-3.35	(39)
Tef	1.05	(46)
Wheat bran	2.02-7.30	(13, 14, 42, 47)
Wheat flour, white	0.12-0.29	(12, 13)
Wheat flour, whole wheat	1.18	(43)
Wheat germ	1.14-4.14	(13, 47)
Cereal-based food		
Bread, French	0.02-0.04	(38, 40)
Bread, maize	0.43-0.82	(38)
Bread, rye	0.05	(43)
Bread, sourdough rye	0.01-0.03	(38)
Bread, whole rye	0.19-0.43	(38)
Bread, oat	0.73-0.21	(38)
Bread, white wheat	0.03-0.73	(13, 38, 40, 43)
Bread, whole wheat	0.60-7.30	(13, 38, 40)

Foods	Phytic acid	References
Bread, unleaven wheat	0.32-1.06	(38)
Breakfast cereal All Bran	3.50	(13)
Cornflakes	0.04-0.15	(13, 38)
Crackers	0.17	(13)
Pasta, durum wheat	0.25	(13)
Pasta, whole wheat	0.52	(48)
Legumes		
Beans, black (cooked)	0.85-1.73	(38)
Beans, faba	0.51-1.77	(10, 13, 38)
Beans, Kidney	0.61-2.38	(13, 38, 45)
Beans, kidney, canned	0.29	(43)
Beans, Lima	0.41-1.27	(38, 49)
Beans, navy	0.69-1.78	(38, 40)
Beans, Pinto	0.60-2.38	(40)
Beans, white	0.96-1.73	(38)
Black gram (Vigna mungo)	0.64-1.03	(14, 49)
Chickpeas	0.28-1.60	(14, 38, 40)
Chickpeas, flour	0.60	(13)
Cowpea (cooked)	0.37-2.90	(10, 12-14, 38, 49, 50)
Green gram (Vigna radiata)	0.85	(14)
Green peas	0.22-1.22	(13, 14, 38)
Lentils	0.21-1.51	(13, 14, 38, 40)
Soy beans	0.92-2.22	(13, 14, 38, 49, 51)
Soy-based food		
Soybean protein concentrate	1.12-2.34	(38)
Soybean protein, isolate	0.24-1.59	(13, 38, 43)
Tempeh	0.45-1.07	(38)
Tofu	0.1-2.90	(10, 38)
Tofu, silken style	0.12	(43)
Nuts and seeds		
Almonds	0.35-9.42	(13, 42)
Almonds, oil roasted	2.11	(43)
Cashews	0.19-4.98	(43, 52)
Cocoa powder	1.92	(13)
Hazelnuts	0.92-2.34	(10, 13, 43)
Linseed	2.15-3.69	(47)
Macadamia nuts, dried	0.15-2.62	(10, 43, 53)
Peanuts	0.17-4.47	(13, 14, 38, 40, 43, 54)

Foods	Phytic acid	References
Pecans	0.18-4.52	(10, 43)
Pine nuts	0.20	(10)
Pistachio nuts	0.29-2.83	(10, 43, 53)
Sesame seeds	1.38-5.72	(14, 38, 42, 53)
Sunflower seeds	3.00	(53)
Walnuts, black, dried	4.03	(43)
Walnuts, English	0.20-6.69	(13, 43, 52)
Tubers		
Potatoes	0.08-0.18	(13, 14)
Fruits		
Apple	0.06	(13)
Apricot, dried	0.194	(12)
Avocado	0.36-0.51	(12, 55)
Banana	0.01	(12)
Black berry	0.01	(12)
Cherries	0.04	(12)
Chestnuts	0.01-0.05	(13, 53)
Coconut	1.38	(13)
Dates	0.13	(12)
Fig	0.05	(12)
Gooseberry	0.05	(12)
Musk melon	0.01	(12)
Pineapple	0.01	(12)
Pomegranate	0.05	(12)
Raisins, dried	0.02	(12)
Strawberry	0.02-0.13	(12, 55)
Vegetables		
Brussels sprout	0.02	(12)
Cabbage, Chinese	0.08	(55)
Cabbage, green	0.01	(12)
Cabbage, violet	0.01-0.03	(12, 55)
Carrots	0.01-0.09	(12, 13, 55)
Cauliflower	0.02-0.05	(12, 55)
Celery stalk	0.03	(12)
Cress, garden	0.02	(12)
Cucumber, green	0.02-0.05	(12, 55)
Eggplant	0.01	(12)
French beans	0.01	(12)

Foods	Phytic acid	References
Kale	0.13	(55)
Knol-khol, leaves	0.05	(12)
Lettuce	0.04	(12)
Parsley	0.05	(12)
Pepper	0.02	(12)
Pumpkin, green	0.02	(12)
Radish	0.11	(55)
Spinach, leaves	0.01-0.07	(12, 14)
Tomato	0.01-0.31	(12, 13, 55)
Zucchini	0.01	(12)

Table 2. Dietetic plan enriched in phytic acid

MEAL	FREQUENCY (days/week)	FOOD (g)	OPTIONS (g)	PHYTIC ACID (g)
Breakfast 1	3	Milk, semi-skimmed (200)		-
		Coffee (50)		-
		Muesli (50)		0.78-1.15
Breakfast 2	2	Yogurt, whole milk (125)		-
		All Bran cereals (40)		0.92
		Fruits[1] (180)		0.05-0.07
Breakfast 3	2	Milk, semi-skimmed (200)		-
		Coffee (50)		-
		Bread, whole wheat (60)		0.36-4.38
		Jam (15)		-
		Almonds (21)		0.07-1.88
Snack 1	5	**Walnuts** (24)	**Almonds** (21)	0.06-1.74
Snack 1	2	Fruits[1] (180)		0.05-0.07
Lunch 1	3	**Pasta, whole wheat** (60) *with* vegetables (150)		0.34
		Tofu (60) or **legumes** (50)		0.16-1.25
		Raw vegetables[2] (150)		0.01-0.15
Lunch 2	2	**Brown rice** (70) *with*	**Green peas** (75)	0.53-1.61
			or **Almonds** (20)	0.49-2.68
			or **Walnuts** (25)	0.41-2.36
		Leafy green vegetables[3] (80)		0.02-0.04
Lunch 3	1	**Whole maize polenta** (70) *with*	Stewed meat (120)	0.55
			or Ragu (120)	
			or Stewed fish (120)	
		Cooked vegetables[4]		0.06-0.08

MEAL	FREQUENCY (days/week)	FOOD (g)	OPTIONS (g)	PHYTIC ACID (g)
Lunch 4	1	**Bulgur wheat** (80)	**Barley** (80)	0.42-0.74
		Stewed **Pinto beans** (40)	Stewed **lentils** (55)	0.18-0.89
		Cooked vegetables[4] (200)		0.06-0.08
Snack	7	Fruits (180)		0.05-0.07
Dinner 1	3	Vegetable soup with **tef** (20) and **amaranth** (20)	*or* Vegetable soup with **oat** (20) and **buckwheat** (20)	0.22-0.55
			or Vegetable soup with **green peas** (20), **kidney beans** (10), and **durum wheat pasta** (20)	
		Eggs (100)	*or* Cheese (50)	-
			or Low-fat meat (100)	-
		Cooked vegetables[4] (200)		0.06-0.08
		Bread, whole wheat (60)	**Bread, whole rye** (60)	0.20-2.32
Dinner 2	2	Fish (120)		-
		Cooked vegetables[4] (200)	Raw vegetables[2]	0.06-0.08
		Bread, whole wheat (60)	**Bread, whole rye** (60)	0.20-2.32
		Fruits[1] (180)		0.05-0.07
Dinner 3	1	Ravioli (90)		-
		Raw vegetables[2] (150)		0.01-0.15
		Fruits[1] (180)		0.05-0.07
Dinner 4	1	Salad with **beans** (50),		
		Avocado (50)		0.53-3.04
		Bread, whole wheat (60)	**Bread, whole rye** (60)	0.20-2.32

1 To choose among: apple, banana, blackberry, cherries, fig, gooseberry, musk melon, pineapple, pomegranate, strawberry

2 To choose among: carrots, celery, cucumber, green or violet or Chinese cabbage, garden cress, spinach, pepper, radish, tomatoes

3 To choose among: chicory, green or Chinese cabbage, green radicchio, lettuce, raw spinach

4 To choose among: broccoli, Brussels sprout, cauliflower, chard, chicory, eggplant, French beans, Kale, knol-khol leaves, mushroom, opposite-leaved saltwort, pumpkin, spinach, zucchini

micronutrient content lies within the range of recommended requirements, except for the carbohydrate content, which would be classified as borderline based on the guidelines of the Italian Society of Human Nutrition [16] for a female in her 30s. Table 3 shows the macro- and micronutrient content of the proposed diet. In addition, the diet provides a mean daily intake of phytic acid that ranges from 1.85 g to 8.09 g.

Discussion

The utility of inositol supplementation has been demonstrated in different pathological conditions, including PCOS [17], diabetes [9], gestational diabetes [18], and metabolic syndrome [6]. On the other hand, it is notable that dietary habits in developed countries tend to reduce inositol intake due to reduced consumption

Table 3. Macro- and micro-nutrient composition

Proteins (%)		**16.11**	
Fat (%)		**33.83**	
Carbohydartes (%)		**44.83**	
Minerals		**Vitamins**	
Fe (mg)	16.4	B1 (mg)	1.30
Ca (mg)	718	B2 (mg)	1.62
Na (mg)	1476	C (mg)	235
K (mg)	3548	Niacin (mg)	16.14
P (mg)	1133	B6 (mg)	2.04
Zn (mg)	9.00	Folic acid (μg)	459
Mg (mg)	204	Patothenic acid (mg)	2.67
Cu (mg)	1.03	Biotin (μg)	19.59
Se (μg)	253	B12 (μg)	7.24
Cl (mg)	1000	retinol (μg)	92.46
I (μg)	72.8	E (mg)	15.46
Mn (mg)	1.42	D (μg)	3.25
S (mg)	310		

of whole grain foods, legumes and nuts. Accordingly, a diet rich in inositols, may optimize inositol intake in people who could benefit from the properties of this particular nutrient.

Since little information concerning myo-inositol content of individual foodstuffs is available in the literature, we collected foods with a high content of phytic acid, which is the main source of inositol, and proposed an example of diet with a high content of this nutrient. This raises some concerns: phytic acid has long been considered an antinutrient, due to its ability to form insoluble complexes with divalent cations, thus reducing their bioavailability, and minerals whose bioavailability is particularly affected include zinc and non-haeme iron. However, recent studies have demonstrated that the antinutrient effect of phytic acid only occurs when large quantities of phytic acid are consumed in combination with a diet low in trace elements [19]. In the diet computed for this study, most of the minerals satisfy the nutritional requirements, with the exception of iron (16.4 mg vs. 18 mg); however, whereas the Italian guidelines recommend a daily iron intake of 18 mg for a woman of 30 years of age, the European Food Safety Authority guidelines (EFSA, 2017) recommend 16 mg. Moreover, this potential shortage is balanced out by the high amount of vitamin C (235 mg vs. 85 mg), a strong reducing agent which reduces ferric to ferrous state, thereby increasing the iron absorption. When designing an inositol-rich diet, therefore, it is important to ensure optimum mineral intake to prevent deficiencies, to provide an adequate amount of riboflavin, and to recommend an increased intake of food rich in organic acid, such as ascorbic or malic acid, shown to enhance iron absorption [20]. For this reason, and to further increase inositol intake through diet, it is important to consider that various types of fruit, such as melon, grapefruit, citrus fruits, kiwifruit, and nectarines, have a high content of myo-inositol, which can provide about 150 mg of myo-inositol in a 150 g portion [11], along with a considerable quantity of organic acids. Moreover, certain food preparation processes such as soaking, germination and fermentation should be recommended because they have proven effective in hydrolysing phytic acid to lower phosphorylated inositol phosphates[21]. Additionally, a growing body of evidence points to the health benefits of phytic acid and its preventive effects on a number of pathologies, such as coronary heart disease, diabetes, renal lithiasis, and even different kinds of cancer [22, 23]. Indeed, phytic acid has been shown to be an antioxidant [24], to lower serum cholesterol and triglyceride levels [25, 26], to improve blood glucose response [27] and modulate insulin secretion[28].

M*yo*-inositol should be considered a conditionally essential nutrient, because although the human body can produce it up to 4 g/day from glucose, deregulation of its metabolism has been shown to occur in several human diseases [1], meaning that a higher intake is required. Unfortunately, reference intakes have not yet been established for inositol, and even its intake through diet has rarely been investigated. Indirect estimates, based on the consumption of phytic acid-rich food, show daily intakes not exceeding 500-700 mg/day for western countries, where a level of 1000 mg/day is considered high [10]. The diet proposed in this study has a phytic acid content of between 1.85 g and 8.09 g/1660Kcal, which can be considered a significant increase obtained without the use of supplements.

This wide range of values is due to the considerable variations in the published phytic acid content of foods in literature (see table 1) and is a limiting factor when developing such a diet. On one hand, this significant variation in phytic acid content reflects the real content in foodstuffs, due to the different cultivar of seeds, various environmental or climatic conditions where crops are grown, and the different stages of seed maturation; on the other, the methods used to determine its concentration. Not least, food processing may also play a role in phytic acid concentration in food [10], hence the difficulty in the exact amount of phytic acid in the diet.

Finally, another fundamental issue is the quantity of inositol that the human body is able to obtain from phytic acid. Studies in human show that 37-66% of dietary phytic acid is degraded during digestion in the stomach and small intestine, if the diet is rich in food phytases (10). The phytase activity of the human gut is very low (29), and therefore not useful for phytic acid hydrolysis, while gut microbiota phytases could lead to significant phytic acid degradation in the colon, depending on the usual diet: in the study by Markiewicz and co-workers [30], a diet rich in fruit and vegetables caused changes in gut microbiota composition that led to a degradation of up to 100% of phytates to myo-inositol phosphate products. Indeed, probiotic lactobacilli, and other species of endogenous digestive microbiota can produce phytases [31], therefore subjects who consume more prebiotics will have a healthier microbiota characterized by a higher diversity of bacteria [32], being able to benefit from foods that contain phytic acid. A tight correlation between microbiota, phytate and gut health has been recently shown by Wu and coworkers (33), who revealed that microbiota derived inositol phosphate activates the mammalian histone deacetylase 3 (HDAC3) to promote epithelial repair. Thus, phytate, degraded by commensal bacteria into inositol-1,4,5-trisphosphate, enables improved recovery of injured erythrocytes by promoting epithelial proliferation and repair.

On the other hand, it is noteworthy that gut microbiota is reported to change with diet [34], thus it may adapt to a myo-inositol-rich diet; this can explain why some volunteers can adjust to a high-phytate diet [35]. However, the type and the amount of intermediate inositol-phosphates arising from phytase hydrolysis that are absorbed is not known. Inositol supplementation in clinical trials ranges from 2 to 4 g /day [36]; a balanced diet containing 5 g of phytic acid can provide as much inositol as can be obtained from nutritional supplementation, a realistic scenario in subjects who regularly consume adequate portions and a variety of fruit and vegetables, due to the increase of phytate-degrading strains in the microbiota.

Conclusions

in conclusion, although it is difficult to estimate the precise quantity of inositol that can be obtained from a diet, and although further evaluations of inositol foodstuff content and its metabolism are necessary, this study shows that the development of a diet that increases inositol availability is feasible. Particular attention should be paid to patients with bipolar mood disorder treated with lithium; indeed, it has been shown that lithium reduces the cellular concentration of myo-inositol, and this was proposed as the therapeutic mechanism in the treatment of the disease [37]. No other side effects are attributable to an inositol-rich diet; on the contrary, as suggested by Markiewicz and colleagues [30], such a diet may increase the potential of intestinal microbiota to degrade phytates, thus improving its function. The diet proposed here may be useful for different kinds of patients, especially in conditions associated with insulin-resistance; a phytic acid rich diet represents an alternative or a complementary approach to the use of inositol supplements, considering that foods rich in phytic acid are a source of many other different healthy nutrients. Further clinical studies are needed to evaluate the efficacy and side effects of the diet on long-term patient management.

Authors' Contributions

Ramona Frida Moroni, Emanuela Cazzaniga, and Paola Palestini contributed to the collection of data about the content of phytic acid in foods. Ramona

Frida Moroni and Michele Sculati contributed to the development of the diet. All authors contributed to the development of the manuscript. All authors are in agreement with the manuscript and declare that the content has not been published elsewhere.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported by the authors

Ethical Approval/Patient Consent

This study did not involve human patients or animals, thus it did not require ethical approval or patient consent

Availability of Data and Materials

The authors confirm that the data supporting the findings of this study are available within the article and the cited references

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