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Article

Concomitant Use of Dietary Supplements and Medicines in Patients due to Miscommunication with Physicians in Japan

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Abstract: We previously reported that some patients used dietary supplements with their medication without consulting with physicians. Dietary supplements and medicines may interact with each other when used concomitantly, resulting in health problems. An Internet survey was conducted on 2109 people who concomitantly took dietary supplements and medicines in order to address dietary supplement usage in people who regularly take medicines in Japan. A total of 1508 patients (two admitted patients and 1506 ambulatory patients) and 601 non-patients, who were not consulting with physicians, participated in this study. Purpose for dietary supplement use was different among ages. Dietary supplements were used to treat diseases in 4.0% of non-patients and 11.9% of patients, while 10.8% of patients used dietary supplements to treat the same diseases as their medication. However, 70.3% of patients did not declare dietary supplement use to their physicians or pharmacists because they considered the concomitant use of dietary supplements and medicines to be safe. A total of 8.4% of all subjects realized the potential for adverse effects associated with dietary supplements. The incidence of adverse events was higher in patients who used dietary supplements to treat their disease. Communication between patients and physicians is important for avoiding the adverse effects associated with the concomitant use of dietary supplements and medicines.

Keywords: dietary supplements; patients; treatment of diseases; medication; adverse effects

1. Introduction

The use of dietary supplements has recently increased worldwide. In the United States, 48.8% of the population used dietary supplements between 2007 and 2010 [1]. Dietary supplementation has also become more common in Japan, with 10.9% of the population using supplements in 2001 [2], 11.0% in males and 16.4% in females in 2003 [3] and 45.8% in older adults in 2008 [4]. Factors, such as sex, age, socioeconomic status and health-related characteristics, have been shown to affect the use of dietary supplements [1,5–8]. Furthermore, the purpose of dietary supplements has changed over time. Dietary supplements were previously used as a nutritional supplement, because malnutrition was a major health issue. However, dietary supplements are now used not only as nutritional supplements, but also in the prevention and treatment of diseases.

The current Japanese system for regulation of dietary supplements is called "Food with Health Claims" and is made up of two categories: (1) "Food with Nutrient Function Claims" for supplementation of vitamins or minerals; and (2) "Food for Specified Health Uses" for specific functions. However, there are a lot of products that people recognize as dietary supplements in the Japanese market other than "Food with Health Claims". These products are not defined by law in Japan, even if they are in the form of capsules or tablets [9,10].

As dietary supplement use increases, associated health problems also increase. Adverse effects caused by dietary supplements, especially hepatotoxicity associated with herbal supplement use [11–13] or stroke and sudden death associated with adulterated supplement use [14,15], have been reported worldwide and have been attributed to two causes. The first cause is the use of low quality or illegal products that contain drug ingredients [16–18]; therefore, the Japanese government constantly surveys and checks these products on websites and retail stores. However, health problems that are caused by using adulterated dietary supplements are rare in Japan. The other cause, which is more important in Japan, is the inappropriate use of dietary supplements, including their excessive intake and the concomitant use of various dietary supplements and/or medicines. Japanese people do not appear to fully understand that dietary supplements are different from medicines, which has led to the use of dietary supplements to treat specific disease as medicines. In particular, inappropriate use of dietary supplements in patients may be associated with severe adverse effects.

We previously surveyed the use of dietary supplements by patients in Japan [19]. We found that some patients used dietary supplements concomitantly with medicines, but did not declare this to their physicians. Several reasons have contributed to this inappropriate use. Since a clear, official definition of dietary supplements does not currently exist in Japan, many dietary supplements claim to treat specific diseases, especially cancer, even though such claims are illegal. Previous studies reported that between 20% and 90% of cancer patients used dietary supplements as complementary and alternative medicines, not only in Japan [20], but also in other countries [21–24]. Furthermore, since dietary supplements are available as capsules or tablets, they have the appearance of medicines and, thus, are often considered to be as effective as medicines. The general public also does not understand the properties of dietary supplements. Physicians have previously expressed concerns regarding the use of dietary supplements by their patients due to the increased risk of dietary supplement-drug interactions [25]. Dietary supplements may interact with some drugs, as well as affect anesthesia and bleeding during

surgery [26]. However, some physicians also do not understand the properties of dietary supplements [27,28].

Therefore, the concomitant use of dietary supplements and medicines may lead to dietary supplement-drug interactions and adverse effects. In the present study, an Internet survey was conducted by concomitant users of dietary supplements and medicines in order to clarify the risk of interactions among subjects in Japan.

2. Methods

2.1. Definition of Dietary Supplements

In Japan, the term dietary supplement has no definition in the law, and some dairy or soybean products are recognized as dietary supplements, even if they are in the form of common foods. Therefore, what dietary supplement means is different for each person. In this survey, we defined dietary supplements as those that had the form of capsules, tablets and powders and that subjects considered to have beneficial effects on their health.

2.2. Internet Survey

An Internet-based questionnaire was conducted by Macromill Inc. (Tokyo, Japan) on their research registrants between 18 July and 28 July 2014. Their registrants were more than 2 million in 2014. They could answer this questionnaire on a website and quit any time. This study was conducted with the approval of the Research Ethics Committee of the National Institute of Health and Nutrition. The questionnaire is shown in the supplementary file.

2.3. Preliminary Survey

To select concomitant users of dietary supplements and medicines, a preliminary survey was conducted on 270,083 subjects. Of this, 40,170 subjects completely answered the survey (response rate: 14.9%), and 7869 subjects (19.6%) were using dietary supplements and medicines concomitantly. The part of concomitant users were moved to the actual survey.

2.4. Actual Survey

The actual survey was conducted by 3129 subjects. The questionnaire included demographic characteristics (sex and age), information on their medical status, the purpose of supplementation (maintenance of health, improvements to health, for beauty or weight loss, prevention of diseases and treatment of diseases), the number and types of dietary supplements and medicines that they were taking and understanding of the beneficial and adverse effects. The questionnaire also asked whether subjects informed their physicians of their use of dietary supplements. Of the total subjects, 2109 subjects completely answered the survey (response rate: 67.4%). All subjects provided information on their medical status. Subjects who answered "I am an ambulatory patient (n = 1506)" or "I am an admitted patient (n = 2)" were categorized as patients, and subjects who answered "I am not consulting a doctor (n = 601)" were categorized as non-patients.

2.5. Statistical Analysis

Differences in demographic characteristics or the purposes among groups were tested using the χ^2 test. A univariate analysis to determine the relationship between supplement use and various variables in patients and non-patients was also conducted using the χ^2 test. Statistical analyses were performed using SPSS 18.0J for Windows (IBM Co. Armonk, NY). *p*-Values less than 0.05 were considered significant.

3. Results

3.1. Preliminary Survey

A preliminary survey was conducted on 40,170 people in order to identify those who concomitantly took dietary supplements and medicines. A total of 35.4% of all subjects were currently using dietary supplements; 43.7% took medicines regularly; and 19.6% (n = 7869) took dietary supplements and medicines concomitantly. On the other hand, 17.7% had ceased using dietary supplements for their medication. A part of the subjects taking concomitant medicines were allocated to the main survey in consideration of the population distribution (based on the sex, age and residence) in Japan.

3.2. Characteristics

The characteristics of all subjects (n = 2109) are shown in Table 1. The ratios of age and residence were adjusted by the population distribution in Japan. Among all subjects, 71.5% (n = 1508) were patients, including two admitted patients (Table 1), while the remainder (n = 601) were non-patients, even though they regularly took medicines. The ratio of patients to non-patients increased significantly with age.

Table 1. Characteristics of each group.

	Non-Patients	Patients	Total	*p*-Value
Number of subjects, *n* (%)	601 (28.5)	1508 (71.5)	2109 (100.0)	
Sex, *n* (%)				0.847
Male	302 (50.2)	749 (49.7)	1051 (49.8)	
Female	299 (49.8)	759 (50.3)	1058 (50.2)	
Age, *n* (%)				<0.001
20s	155 (25.8) [a]	188 (12.5)	343 (16.3)	
30s	182 (30.3) [a]	275 (18.2)	457 (21.7)	
40s	120 (20.0)	307 (20.4)	427 (20.2)	
50s	78 (13.0)	338 (22.4) [a]	416 (19.7)	
60s	66 (11.0)	400 (26.5) [a]	466 (22.1)	

Non-patients: subjects who answered "I am not consulting a doctor", even though they regularly took medicine. *p*-Values were calculated using the χ^2 test. [a] Correlation by an adjusted residual analysis ($p < 0.05$).

3.3. Prevalence of Dietary Supplements

Many subjects (53.7% of non-patients and 41.0% of patients) used some type of vitamin or mineral (including multi-vitamins, multi-minerals, or multi-vitamin/mineral products) (Table 2). Vitamins B and C and calcium, iron and zinc were the most commonly used vitamins and minerals, respectively. The preference for vitamin/mineral supplements was significantly greater in non-patients than in patients. Various kinds of non-vitamin, non-mineral dietary supplements were also used (Table 2). Blueberry/lutein products were the most frequently used by both non-patients and patients in this survey, followed by fish oil/n-3 PUFA and glucosamine/chondroitin. The preference for blueberry/lutein, fish oil/n-3 PUFA, glucosamine/chondroitin, black vinegar, garlic and sesamin products was significantly greater in patients than in non-patients. Furthermore, dietary supplements for weight loss, which were labeled as containing several ingredients, including *Coleus forskohlii*, *Gymnema sylvestre*, lactoferrin, α-lipoic acid or others, were also popular in Japan. A subgroup analysis showed that subjects who used dietary supplements to treat their diseases preferred to use non-vitamin/non-mineral supplements (14.8%, n = 236/1591 of non-vitamin/non-mineral supplements users), slightly more than vitamin and/or mineral supplements only (12.7%, n = 66/518 of vitamin and/or mineral supplements only users).

Table 2. Prevalence of the use of each type of dietary supplement.

Type of Dietary Supplement	Non-Patients	Patients	Total	*p*-Value
Number	601	1508	2109	
Vitamin/Mineral				
Multi-vitamins and minerals	24 (4.0)	59 (3.9)	83 (3.9)	1.000
Multi-vitamins	106 (17.6)	190 (12.6)	296 (14.0)	0.003
Multi-minerals	17 (2.8)	40 (2.7)	57 (2.7)	0.939
Each vitamin	161 (26.8)	322 (21.4)	483 (22.9)	0.009
Each mineral	111 (18.5)	196 (13.0)	307 (14.6)	0.002
Any type	323 (53.7)	619 (41.0)	942 (44.7)	<0.001
Non-Vitamin, Non-Mineral (Top 10)				
Blueberry/Lutein	60 (10.0)	205 (13.6)	265 (12.6)	0.029
Fish Oil/n-3 PUFA	37 (6.2)	174 (11.5)	211 (10.0)	<0.001
Glucosamine/chondroitin	30 (5.0)	163 (10.8)	193 (9.2)	<0.001
Collagen	31 (5.2)	79 (5.2)	110 (5.2)	1.000
Black vinegar	18 (3.0)	85 (5.6)	103 (4.9)	0.015
Garlic	13 (2.2)	79 (5.2)	92 (4.4)	0.003
Lactic bacterium	16 (2.7)	70 (4.6)	86 (4.1)	0.051
Sesamin	8 (1.3)	63 (4.2)	71 (3.4)	0.002
Curcuma longa	13 (2.2)	51 (3.4)	64 (3.0)	0.183
CoQ10	12 (2.0)	49 (3.2)	61 (2.9)	0.160
Others				
Weight loss supplements	31 (5.2)	83 (5.5)	114 (5.4)	0.644
St. John's wort	5 (0.8)	0 (0.0)	5 (0.2)	-

Multiple answer p-values were calculated using the χ^2 test.

3.4. Purpose of Dietary Supplement Use

The purpose of dietary supplement use is shown in Table 3 (medical status) and Table 4 (age). When medical status was compared (Table 3), no significant differences were observed in improvements to health, for beauty or weight loss or the prevention of diseases between both groups. However, significantly more non-patients than patients used dietary supplements to maintain health, whereas significantly more patients than non-patients used dietary supplements to treat diseases. When age was compared (Table 4), the use of dietary supplements to maintain health and prevent diseases was greater among older subjects than younger subjects. On the other hand, the use of dietary supplements to improve health and for beauty or weight loss was greater among younger subjects than older subjects. However, no significant difference was observed in the treatment of diseases among generations.

Table 3. Purpose for using dietary supplements (medical status).

	Yes	No	*p*-Value
Maintenance of Health (%)			
All subjects	54.1	45.9	
Non-patients	57.6	42.4	0.047
Patients	52.8	47.2	
Improvements to Health (%)			
All subjects	11.9	88.1	
Non-patients	13.3	86.7	0.206
Patients	11.3	88.7	
For Beauty or Weight Loss (%)			
All subjects	13.4	86.6	
Non-patients	15.0	85.0	0.203
Patients	12.8	87.2	
Prevention of Diseases (%)			
All subjects	8.0	92.0	
Non-patients	8.0	92.0	1.000
Patients	8.0	92.0	
Treatment of Diseases (%)			
All subjects	9.7	91.3	
Non-patients	4.0	96.0	<0.001
Patients	11.9	88.1	

p-Values were calculated using the χ^2 test.

Table 4. Purpose for using dietary supplements (age).

	Yes	No	*p*-Value
Maintenance of Health (%)			<0.001
20s	41.7	58.3 [a]	
30s	50.1	49.9 [a]	
40s	55.0	45.0	
50s	59.6 [a]	40.4	
60s	61.6 [a]	38.4	

Table 4. *Cont.*

	Yes	No	*p*-Value
Improvements to health (%)			<0.001
20s	18.4 [a]	81.6	
30s	13.6	86.4	
40s	12.4	87.6	
50s	9.1	90.9	
60s	7.5	92.5 [a]	
For beauty or weight loss (%)			<0.001
20s	21.0 [a]	79.0	
30s	20.4 [a]	79.6	
40s	13.6	86.4	
50s	8.7	91.3 [a]	
60s	5.2	94.8 [a]	
Prevention of diseases (%)			<0.001
20s	5.2	94.8 [a]	
30s	4.2	95.8 [a]	
40s	7.7	92.3	
50s	9.6	90.4	
60s	12.4 [a]	87.6	
Treatment of diseases (%)			0.372
20s	12.0	88.0	
30s	9.2	90.8	
40s	8.2	91.8	
50s	10.8	89.2	
60s	8.8	91.2	

p-Values were calculated using the χ^2 test; [a] correlation by an adjusted residual analysis ($p < 0.05$).

3.5. Concomitant Use of Dietary Supplements and Medicines

As discussed above, 19.6% of participants (7869/40,170) in the preliminary survey took dietary supplements and medicines concomitantly, while the actual survey was only conducted on subjects who took dietary supplements and medicines concomitantly. Table 5 shows the number of subjects taking dietary supplements and medicines concomitantly. The most common pattern was one kind of dietary supplement and one kind of medicine (n = 440, 20.9%). However, 82 subjects (3.9%) took more than five dietary supplements and more than five medicines concomitantly.

Table 5. Number of dietary supplements and medicines used concomitantly.

	Number of Medicines				
	1	2	3	4	≤5
Number of dietary supplements					
1	440	233	125	69	152
2	126	191	87	38	93
3	63	50	74	27	57
4	17	19	15	34	27
≤5	33	15	21	21	82

3.6. Declaration of Dietary Supplement Use to Physicians or Pharmacists

Only 25.7% of all subjects (16.0% of non-patients and 29.7% of patients) declared dietary supplement use to their physicians or pharmacists. In other words, more than 70% of patients used dietary supplements on their own without consulting with their physicians. Furthermore, neither of the admitted patients declared dietary supplement use to their attending physicians. Table 6 shows the reasons for not declaring dietary supplement use to physicians or pharmacists. Most subjects regarded dietary supplements as food and, therefore, safe and, as a consequence, did not consider interactions with their medication. In addition, "physicians or pharmacists never asked about dietary supplement use" was also a major reason for miscommunication between patients and physicians or pharmacists.

Table 6. Reasons for not declaring dietary supplement use to physicians or pharmacists.

Reasons	*n*
Dietary supplements are just food	653
There are no influences on medication (self-judgment)	509
There are no problems with using dietary supplements	369
Physicians or pharmacists never ask about dietary supplement use	360
Use dietary supplements only when needed	74
Physicians or pharmacists may deny dietary supplement use	31
Others	12

Multiple answers.

3.7. Beneficial or Adverse Effects due to the Use of Dietary Supplements

Only 41.1% of all subjects (40.8% of non-patients and 41.2% of patients) felt better by using dietary supplements. On the other hand, 8.4% of all subjects (8.2% of non-patients and 8.6% of patients) developed adverse effects from the use of dietary supplements, with the most common being diarrhea (32.7% of non-patients and 30.2% of patients), nausea and vomiting (14.3% and 25.6%), stomachache (22.4% and 12.4%), constipation (12.2% and 15.5%), fatigue (6.1% and 15.5%), headache (8.2% and 14.0%), interaction with medication (14.3% and 10.9%), rash and prurigo (6.1% and 10.1%), palpitations (2.0% and 8.5%), effects on health examination data (2.0% and 4.7%), and others. No significant difference was observed between non-patients and patients. A subgroup analysis showed that subjects who used any kind of non-vitamin/non-mineral supplement (8.7%) developed more adverse effects than those who only used vitamin and/or mineral supplements (7.7%). Furthermore,

subjects who used dietary supplements to treat diseases (16.6%) had more adverse effects than those who used them for other purposes, such as the maintenance of health (8.4%), improvements to health (11.9%), for beauty or weight loss (10.3%) or the prevention of diseases (11.1%).

4. Discussion

We previously reported the inappropriate usage of dietary supplements by Japanese patients, some of whom used dietary supplements and medicines concomitantly without consulting with their physicians [19]. Some ingredients in dietary supplements have been shown to interact with drugs. Therefore, the concomitant use of dietary supplements and medicines by patients without the physician's knowledge may lead to dietary supplement-drug interactions and adverse effects. In the present study, we investigated the concomitant usage of dietary supplements and medicines by patients in Japan.

The prevalence of dietary supplements has been surveyed, and vitamin/mineral supplements were revealed to be the most commonly used [4,29]. Consistent with a previously conducted survey, approximately half of our subjects used vitamin/mineral supplements. Deficiencies in vitamins/minerals cause health problems that can be prevented by vitamin/mineral supplements. The use of vitamin/mineral supplements was found to be increased in patients diagnosed with cancer [30]. In addition, vitamin/mineral supplements were shown to have beneficial effects in nutritionally deficient patients in China [31,32]. On the other hand, a cohort study in Japan [33] and a systematic review of vitamin/mineral supplements [34] showed that vitamin/mineral supplements did not affect the incidence of cardiovascular diseases and cancer or total mortality. It still remains unclear whether excessive amounts of vitamins/minerals are beneficial or harmful.

In addition to vitamin/mineral supplements, our subjects used various kinds of dietary supplements. The most popular ingredient in the dietary supplements used by our subjects was blueberry/lutein. Blueberry/lutein is also popular among non-medicated subjects in Japan, because it is considered beneficial for eye conditions, especially the prevention of cataracts and glaucoma. Blueberry/lutein products are marketed with such claims despite the lack of sufficient evidence, and the general public believes them in Japan. The second most popular ingredient was fish oil/n-3 PUFA, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). EPA is also regulated as a drug ingredient for hyperlipidemia in Japan and has anti-platelet and anti-coagulant effects. Therefore, these dietary supplements are as effective as EPA-drugs, which are approved in Japan if they are of good quality. However, functional claims, such as for medicines, are not allowed to EPA-dietary supplements. Similar to EPA, chondroitin sulfate is regulated as a drug ingredient for rheumatoid arthritis in Japan. However, if efficacy is not claimed, chondroitin sulfate could be available as a dietary supplement. Most chondroitin supplements contain glucosamine, which is regulated as a drug ingredient for rheumatoid arthritis in Europe, but not in Japan, and are, thus, used by rheumatoid arthritis patients. A previous study reported that 60% of rheumatoid arthritis patients in Japan used dietary supplements, of which 40% are components of cartilage that contains chondroitin [35].

Dietary supplements have been shown to interact with drugs. The most well-known example is St. John's wort (*Hypericum perforatum* L.). St. John's wort contains hyperforin, which increases the expression of cytochrome P450 (CYP), especially CYP3A4, and affects drug metabolism in the

liver [36]. In the present study, five non-patients used St. John's wort, and none of them had declared this use to their physicians (pharmacists). Two subjects used sodium loxoprofen (a CYP2C9 substrate), with one reporting an interaction with their medication. Other subjects used paroxetine hydrochloride hydrate (a CYP2D6 substrate), vitamin B or folic acid with St. John's wort. St. John's wort does not interact with these medicines. If these subjects used St. John's wort with this knowledge, it would not be considered problematic; however, they did not. Other herbs (e.g., black cohosh, *Coleus forskohlii*, echinacea, garlic, ginkgo, ginseng, green tea, kava and milk thistle) [37–41] and ingredients (e.g., catechins [42], curcuminoids [43], isoflavones [44], quercetin [45], polyphenols [46] and resveratrol [47]) also affect drug-metabolizing enzymes. In the present study, many subjects used these dietary supplements without consulting with their physicians.

Physicians need to be aware of the dietary supplements being used by their patients in order to avoid interactions between medication and dietary supplements. If there is insufficient evidence to warrant safety concerns, physicians need to advise their patients to cease the concomitant use of dietary supplements and medicines. However, 17% of all subjects answered that they did not discuss these supplements with their physicians or pharmacists, because they were never asked about it, which is consistent with previous findings [48]. This may have been associated with both patients' and physicians' insufficient recognition of the interactions between dietary supplements and medications, not only in Japan [43], but in other countries [49–52].

More subjects in the present study (8.4%) developed adverse effects due to the use of dietary supplements than in our previous study (3.3%) [19], even though most cases were not severe. No significant differences were observed in the incidence of adverse effects between non-patients and patients. This result suggests that the concomitant use of dietary supplements and medicines may increase the incidence of adverse effects. In this survey, we asked subjects which types of dietary supplements and medicines they were taking and found that most used several dietary supplements and medicines concomitantly. The possibility of dietary supplement-drug interactions is increased by the concomitant use of a larger number of dietary supplements and drugs. Therefore, we could not determine any relationship between dietary supplements and adverse effects.

There were some limitations to this study. This survey was conducted via the Internet, the utilization of which has recently expanded. The Ministry of Internal Affairs and Communications reported that the rate of Internet utilization was greater than 95% in those under 40s, 85% in those in their 50s, 63%–72% in their 60s and 49% in their 70s in 2012 in Japan. A gap may still exist between Internet users and non-users, especially in elderly people. Furthermore, Japanese people do not understand the difference between dietary supplements and medicines. A previous survey showed that 22% of the Japanese population did not understand the distinction between dietary supplements and medicines. In this study, some subjects inserted the name of a dietary supplement as a medicine name and *vice versa*. We also asked subjects for the names of the dietary supplements that they used, but a lot of subjects answered with just the main ingredient of the dietary supplement. Most products in Japan currently contain multiple ingredients. For example, if one product is being promoted as a glucosamine supplement, this product typically contains chondroitin, hyaluronic acid, collagen and other ingredients. Therefore, we were unable to clarify interactions between dietary supplements and medicines in this study.

5. Conclusions

It is important for physicians to ask patients about dietary supplement use and for patients to inform their physicians about these supplements if physicians do not ask about them. In addition, patients need more information on the dietary supplements that they use. Education about dietary supplements is important for patients in order to avoid the adverse effects associated with dietary supplements.

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Author Contributions

Tsuyoshi Chiba designed the questionnaire, analyzed the data and wrote the manuscript. Yoko Sato analyzed the data and checked the manuscript. Sachina Suzuki checked the data and the manuscript. Keizo Umegaki designed the questionnaire and checked the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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調査・資料

ワルファリン服用者におけるビタミンK摂取量の許容範囲に関する系統的レビュー

(平成27年3月5日受理)

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A Systematic Review of the Acceptable Intake Level of Vitamin K among Warfarin Users

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The interaction of warfarin and vitamin K is a clinically significant issue. This study investigated the acceptable intake level of vitamin K among warfarin users by means of a systematic review. We searched two databases (PubMed and "Igaku chuo zasshi") for articles about adverse events arising from interaction of warfarin and vitamin K, published until October 2014. Of 1,310 citations retrieved, 16 studies met the selection criteria for examination of the upper limit, and 6 studies dealt with amounts below the limit. The intake of vitamin K in warfarin patients was acceptable in the range of 25–325 μg/day, with a maximum daily variation of 292 μg, and a value of 150 μg/day seemed optimum. When these results were applied to usual foods, except for dietary supplements or health foods, the only prohibited foods were fermented soybean (natto) and foods containing it, while green leafy vegetables could be acceptable if their intake is limited.

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Key words: ワルファリン warfarin; ビタミンK vitamin K; 相互作用 interaction; 系統的レビュー systematic review

緒 言

ワルファリンは，古くから血栓塞栓症の予防・治療薬として使用されてきた医薬品であり，現在，国内では100万人以上の服用者がいると推計されている*1．一方，ビタミンKは，グルタミン酸からγカルボキシグルタミン酸を生成する際のカルボキシ化に必要な栄養素で，肝臓ではビタミンK依存性凝固因子の第II（プロトロンビン），VII，IX，X因子の生合成に寄与している[1]．ワルファリンは，ビタミンKエポキシドからのビタミンKの再生を抑制することによって還元型ビタミンKを枯渇させ，その抗凝固作用を発揮する．その薬効の増強は皮下，消化管，頭蓋内の出血，逆に薬効の減弱は血栓形成を引き起こし，いずれも致死的な症状につながる可能性がある．そのため，ワルファリン服用者にはワルファリンの薬効を一定に保つため，定期的な血液凝固能のモニタリングが行われるとともに，ワルファリンと拮抗して相互作用を起こすビタミンKの食事やサプリメントからの摂取について注意喚起が行われている*2．

ビタミンKは正常な血液凝固の維持とともに，オステオカルシンの活性化を介して骨形成にも重要な役割を担っている[2]．ちなみに，骨形成には血液凝固よりも多量のビタミンK摂取が必要とされている[3]．日本人の食事摂取基準2015年版におけるビタミンKの基準は，正常な血液凝固を維持するのに必要な目安量として成人では150 μg/日となっている*3．天然型のビタミンKには過剰症は認められないため，耐容上限量は定められていない．

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*2 エーザイ株式会社 Warfarin適正使用情報第3版 http://www.eisai.jp/medical/products/warfarin/proper-use/

*3 厚生労働省 「日本人の食事摂取基準（2015年版）策定検討会」 報告書 http://www.mhlw.go.jp/stf/shingi/0000041824.html

天然型のビタミンKには，緑黄色野菜などの植物性食品に由来するビタミンK_1（フィロキノン），動物性食品や納豆などの細菌に由来するビタミンK_2（メナキノン）がある．緑黄色野菜ではクロロフィル濃度が高いほどビタミンK_1含有量が多く[4]，青汁などの製品には多量にビタミンK_1が含まれている[5]．また，納豆にはメナキノン-7が多量に含まれている．そこでワルファリン服用者に対しては，特に青汁や納豆の摂取に対する注意喚起がなされている．しかし，医療従事者の中にはワルファリンとビタミンKの相互作用を過度に捉え，通常の食事から適量で摂取している緑黄色野菜についても，摂取禁止や厳しい制限を行う必要性を感じていることがある．しかし，そのような過度な食品の摂取制限は，かえって食事バランスの乱れによる栄養不足や，患者のQuality of life（QOL）の低下につながる可能性があるとともに，骨の健康維持など，ビタミンKが有する血液凝固以外の働きに悪影響を与える可能性がある．さらに近年，ワルファリン服用者の抗凝固能の安定化には，一定量のビタミンKの経口摂取が有効であるとの考え方も示されている[6]．

食品成分に関する有効性や安全性は，いずれも定性的に捉えられており，成分の摂取量という定量的な考え方がとられていない．ビタミンKとワルファリンについても，相互作用を回避すべき摂取量や許容できる摂取量についてはあまり意識されておらず，断片的な有害事象報告を基にして相互作用が判断されている．ワルファリンの抗凝固作用には，患者の薬物代謝酵素の遺伝的な影響[1]，年齢，併発疾患や併用薬などさまざまな要因が関与し，個人差が大きいために一定した見解を出すことは容易でない．そのような中で，ワルファリンの抗凝固能の指標であるプロトロンビン時間国際標準比（International normalized ratio; INR）とビタミンK摂取量の関係を検討し，ワルファリン服用者が摂取可能なビタミンKの上限量を250 μg/日と推定した報告がある[6]．この報告は，各論文の人数の差異が考慮されていない，系統的レビューとはなっていない，日本語文献が検索されていないなど，若干不十分な点がある．

そこで本研究では，この先行研究の結果[6]を踏まえ，ワルファリン服用者にとって許容できるビタミンKの摂取範囲（下限量と上限量）を検討するための系統的レビューを実施した．また，その結果を基に，ワルファリン服用者にとってビタミンKの摂取が許容できる食事メニューについて検討した．

方　　法

1. 論文の検索

検索は，2014年10月3日に，PubMed，医学中央雑誌Web版（医中誌）のデータベースを用いて実施した．検索式は先行研究[6]を参考に設定した．すなわち，PubMedにおいては，キーワードをvitamin K, warfarin，リミット条件をhuman，English OR Japanese，Clinical Trial OR Case Reports OR Meta-Analysis OR Randomized Controlled Trialとし，さらに，キーワードにcohort studyまたはcase control studyを追加してArticle typesのリミット条件を解除したものの合計3回の検索を実施した．医中誌においては，キーワードをビタミンK，ワルファリン，リミット条件をヒト，会議録を除くとした．

2. 対象論文の選択

つづいて，論文のスクリーニングを以下の採択基準に基づいて実施した．採択基準は，①原著・短報・資料・実践報告であること（総説，解説，特集，Q&A，講義，図説は除く），②臨床研究・症例報告・メタ分析・無作為化比較試験・コホート研究・症例対照研究のいずれかであること，③ビタミンKとワルファリンの相互作用に関する内容であること，④遺伝子多型によるワルファリン治療の検討ではないこと，⑤ワルファリンによる副作用をビタミンK投与により治療した内容ではないこと，の5点とした．

1次スクリーニングではデータベース検索により抽出された論文について，表題および抄録を精読し，重複した論文，採択基準に合致しない論文を除外した．採択基準に達しているか判断しかねる論文については，2次スクリーニングで評価することとした．2次スクリーニングでは全文を精読し，1次スクリーニングと同様に論文を除外した．また，選別された論文における引用文献について，1次スクリーニング，2次スクリーニングと同様の作業を実施し，基準を満たす論文を抽出した．

さらに，3次スクリーニングにて，①ビタミンK摂取量が記載されている，②ビタミンK摂取を開始して有害事象が生じた，③ビタミンK摂取前後の血液凝固能検査値としてINRまたはトロンボテスト値が記載されている，の3点を満たすものを抽出し，上限量の検討に使用した．また，①ビタミンK摂取量が記載されている，②ビタミンK摂取により抗凝固能が安定した内容を含む，の2点を満たすものを抽出し，下限量の検討に使用した．以上の作業は，筆者のうち2名で行い，2名の判断が異なった場合は協議のうえで決定した．

3. 上限量の検討

採択された論文より，ワルファリン服用者において有害作用が生じた際のビタミンK摂取量とINRの変化量の関係について，人数による重みづけ回帰分析を行った．トロンボテスト値の記載しかない論文については，既報の換算表[7]によりINR値に変換した．INRまたはトロンボテスト値がグラフのみで示されたものに関してはグラフより目視で値を読み取った．

さらに，原因食品以外からの食事によるビタミンK摂取量を考慮した総ビタミンK摂取量（原因食品からの摂取量＋その他食事からの摂取量）とINRの変化の関係についても同様に検討した．食事からのビタミンK摂取量が記載されていない論文については，該当国または近隣国の栄養調査報告によるビタミンK摂取量を推定値として利用した．

僧帽弁形成術後の症例に対するINRは2.0～2.5，人工弁置換術後の症例に対するINRは2.0～3.0を目指すことが推奨されているように，ワルファリンの各適応症に対し推奨されるINRは0.5～1.0の幅がある*2．したがって，既報[6]に従ってINRの変動が0.5以内であれば抗凝固治療に悪影響を及ぼさないと仮定し，得られた回帰直線式よりワルファリン服用者に対するビタミンK摂取量の上限値を算出した．

以上の解析にはStata 13を用いた．

4．下限量の検討

採択された論文について，エビデンステーブルを作成し，ビタミンK摂取によりINRの変動が安定した報告の結果をまとめた．

5．メニュー例の選択

平成24年国民健康・栄養調査結果*4を参考に，日本人のビタミンK供給源として大きく寄与している食材を用いたメニュー1食分のビタミンK摂取量を既報のメニュー例[8]より抽出した．このうち，ビタミンK含有量が検討結果で得られた上限量を超えるものを，ワルファリン服用者にとって摂取を避けるべきメニュー，1日3食摂取すると仮定し，上限量の1/3を超えるものを摂取時注意が必要なメニューとした．また，これらのメニューについて，上限量の1/3を超えずに摂取できる量を許容目安メニューとした．

結果および考察

1．論文の抽出について

論文の検索および抽出結果をFig. 1に示した．

検索された論文1,130報のうち，229報は原著・短報・資料・実践報告のいずれにも該当せず，9報は臨床研究・症例報告・メタ分析・無作為化比較試験・コホート研究・症例対照研究のいずれにも該当しなかった．また，530報はビタミンKとワルファリンの相互作用に関する内容ではなく，179報は遺伝子多型がワルファリン治療効果に及ぼす影響について検討したものであった．ビタミンKはワルファリンの作用を減弱させることから，ワルファリンによる出血等の副作用をビタミンK投与により治療した症例報告も多く，今回の検索でも112報が該当したが，本研究はビタミンK摂取による有害事象報告をまとめることが目的であるため，これらの論文は除外した．

以上の条件で抽出された79報について，内容を精査し16報をワルファリン服用者におけるビタミンK摂取の上限量の検討に，6報を下限量の検討に採択した．ビタミンK摂取の影響によりワルファリンの効果が減弱した報告のうち，具体的なビタミンK摂取量とワルファリンの抗凝固能指標であるINRの変動値が両者とも記載されていたものは少なく，多くの論文が採択できなかった．有害事象の検討を治療中のヒトを対象として行うことは倫理的観点から難しいため，1つ1つの症例報告が貴重なデータとなる．より詳細な検討を行うためには，ビタミンKとワルファリンの相互作用による有害事象の報告において，ビタミンK摂取量とそれに伴うINRの変動が記載されていることが理想的であろう．

2．上限量の検討

上限量の検討に採択した16報の詳細をエビデンステーブルに示した（Table 1）．有害事象の原因食品は，マルチビタミンミネラルサプリメント（3報，5件）が最も多く報告されていた．通常食品の摂取によるもの（栄養剤やサプリメント以外）は4報（6件）あり，それらはブロッコリー，豚レバー，ホウレンソウ，アサクサノリであった．日本人のビタミンK摂取源として大きく寄与している*3食材の納豆が挙げられていないのは，症例報告はあるものの，論文中に摂取量およびINR変化量の記載がないために採択できなかったからである．論文中に記載されていたビタミンK摂取量は，疫学研究では食事からの総摂取量，臨床研究と症例報告では原因食品の含有量，または食事からの総摂取量のいずれか一方のみが示されていた．ビタミンK摂取量とワルファリンの効果減弱の程度を詳細に検討するためには，臨床研究および症例報告において，ビタミンKの総摂取量および原因食品からの摂取量の両者がそろった報告が理想的であるが，そのような論文は見当たらなかった．

16報において，記載されていたビタミンK量を用いた場合（A）と，推定値を用いて算出した総ビタミンK摂取量を用いた場合（B），それぞれにおけるビタミンK摂取量とINR変化量の関係をFig. 2に示した．

食事からの摂取量を加味した場合（B）でも，各報告の分布に大きな違いは認められなかった．Fig. 2において，Landau-Moulda[9]とChowら[11]の2点が他の報告と離れていたため，これらのデータを除いて同様の解析を行った結果，それぞれの回帰式はTable 2のとおりとなった．

ワルファリンの各適応症に対するINRの変動の目標値には0.5～1.0の幅が示されていることから*2，各回帰式を用いてINRの変動幅が0.5のときのビタミンK摂取量を算出した．その結果，記載されていたビタミンK量のみを用いた場合は292～311 μg，食事によるビタミンK摂取量を加味した場合は325～333 μgであった（Table 2）．本研究は有害作用のリスクが高まる値の検討であるため，より安全側の値を採り，ビタミンK摂取量の変動が292 μg/日，総ビタミンK摂取量が325 μg/日を超える場合に有害作用のリスクが高まると考えるのが妥当と考えられる．先行研究において，ワルファリン服用者のビタミンK摂取量が250 μg/日を超える場合，有害作用のリスクが高まる可能性があると報告されている[6]が，この報告では各論文における人数の差異が考慮されておらず，通常の食事からのビタミンK摂取量も考慮されていない．これらの点を改善した本研究の結果は，少し多めのビタミンK摂取が許

*4 厚生労働省　平成24年国民健康・栄養調査結果　http://www.mhlw.go.jp/bunya/kenkou/eiyou/h24-houkoku.html