Nationwide Online Survey to Complement the Current Voluntary Reporting System for Adverse Events Associated with Dietary Supplements: Application to the Case of Skin Manifestations

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Summary The current adverse event reporting system for dietary supplements lacks the ability to collect and analyze ongoing case reports in sufficient numbers to detect health issues. We conducted an online survey to collect data on skin manifestations due to supplement use in consumers and to identify the suspected products and ingredients. An online survey was conducted among 63,737 dietary supplement users in 2016. Those who self-reported experiences of skin anthema or itching caused by supplement use and recognized a causal relationship as almost certain (0.8%) were invited to provide further details of symptoms and products. Most of the users experienced mild symptoms with “itching and/or rash of body part.” After the onset of skin manifestations, 69.3% ceased supplement use, while 26.6% continued supplement use, including those who reduced the amount or frequency of use. Respondents who visited the hospital in response to symptoms accounted for 26.0%, while 53.3% did not seek treatment. The products used were identified in 155 of 300 eligible respondents. Although those products were composed of multiple ingredients, the accumulated data suggested that cutaneous symptoms were related to the following constituents: “Peptides or animal by-products” (31.0%), “Herbal/Botanical” (23.2%) and “Fats and lipid” (13.5%). Conducting an online survey to elicit information directly from consumers identified components of supplements that are involved in skin manifestations that could lead to serious damage, and may fill a void in the current adverse event reporting system.

Key Words dietary supplement, skin manifestation, adverse event, reporting system

Dietary supplements in the form of tablets or capsules contain nutrients or particular components at high concentrations; thus, their safety is of concern even though they originate from known foods or plants. Besides, the quality of supplements varies widely (1), which can be attributed to the addition of many ingredients without scientific evidence, contamination with toxic elements and pharmaceuticals (2), and the inclusion of unlabeled components (3, 4). Therefore, the increase in dietary supplement use in Japan has been accompanied by emerging health concerns regarding adverse reactions (5).

According to previous cases, the accumulation of case reports related to similar products/ingredients is crucial in determining the plausibility of a causal role (6, 7). Incidences of adverse events associated with dietary supplements are consolidated into two major administrative agencies in Japan; those received at public health centers are passed on to the Ministry of Health, Labour and Welfare (MHLW), while those received at the National Consumer Affairs Center of Japan are sent to the Consumer Affairs Agency. Consumers who have experienced adverse events can report the event to any agency or center, yet few reports are made (8, 9). Only a few percent of affected consumers lodge complaints with the manufacturer; however, manufacturers are not obligated to submit adverse event reports if the adverse event is not fatal. Thus, the majority of complaints and/or minor health damage is handled by individual companies without being reported to ministries or government offices (8).

Meanwhile, incidence reports of consumers seeking medical care are made by healthcare professionals to public health centers, but these are usually severe cases and average only about 20 reports per year (9). The lack of capacity to collect case reports is one of the biggest disadvantages of the current spontaneous adverse event reporting system. In situations where most of the symptoms caused by dietary supplements are mild to moderate, a spontaneous reporting system would be unable to supply information on potential adverse event cases (10). Since mild symptoms could indicate future severe damage, the detailed collection of these minor case
reports is needed. Therefore, a new measure to collect minor case reports directly from consumers will be helpful to identify cases that are unreachable under the current system. In a previous pilot study, we collected information on diarrhea, which is the most frequently reported adverse symptom attributed to dietary supplements, from 78,220 supplement users in 2 wk by using a nationwide online survey, and revealed the possible association with herbs and botanicals (11).

Regarding adverse symptoms attributed to supplement use, skin manifestations including rash and urticaria have been reported as the second-most frequently occurring symptom after gastrointestinal symptoms (8, 11, 12). Skin manifestations may indicate the involvement of allergic reactions (13, 14), and may lead to serious allergic symptoms such as anaphylaxis (3, 4). However, allergic patients can use supplements to alleviate symptoms (3), despite the fact that patients with allergies, such as atopic dermatitis, are known to be vulnerable to developing food allergies (15). Moreover, in drug-induced hepatic injury caused by dietary supplements, skin manifestations are a major symptom that develops early (16). It is important to identify cases of adverse skin manifestations; however, to the best of our knowledge, there have been no reports focusing on supplement-induced skin manifestations as a possible indicator of potential severe health damage, or on the detailed symptoms and related products and/or ingredients.

In this study, therefore, we conducted a nationwide online survey to identify cases of skin manifestations as ongoing adverse events from the use of dietary supplements. We also attempted to identify the causative products, ingredients and/or functional components based on the collected cases.

MATERIALS AND METHODS

Online survey. The online survey was conducted by an online panel company, Intage, Inc. (Tokyo, Japan), which managed more than 6 million verified and authenticated panelists across the nation (as of December 2016). The panelists were classified into subpanels according to their current events updated every 3 mo. The participants recruited for this study were 18 y and older and from the subpanels of “those who purchased supplements for health and beauty,” “those who purchased weight-loss products” and “those who purchased protein supplements.” There is currently no clear definition for “dietary supplement” in Japan; thus we defined this in the present study as a concentrated dietary component in tablet, capsule, or powder form. The survey company programmed and hosted a survey according to a questionnaire submitted by us and anonymized the collected data prior to handling. The study was conducted between December 13 and 16 (preliminary survey) and between December 19 and 21 (full-scale survey), 2016, with the approval of the Research...
Survey subjects. The preliminary survey was conducted to extract those who had experienced anthema or itching of skin caused by dietary supplement use. Of the 72,997 registrants in the aforementioned subpanels, 63,737 reported the use of dietary supplements in the previous year. Ninety-one percent of supplement users had never experienced any adverse events owing to supplement use. The number who reported anthema or itching of skin was 895 (1.4%). Of these, those who thought a causal relationship between the skin manifestation and supplement use was “Probable” or “Highly probable” were invited to participate in the full-scale survey conducted 3 d later (n=518, 0.8% of supplement users). A total of 382 responded and completed the full-scale survey (response rate: 73.7%). After identification of the products used, 82 were excluded due to medicinal products (n=52) and outside the defined dietary supplements (n=30). Responses to each question item were aggregated for the 300 eligible respondents as well as for those in which all the ingredients in the product had been identified (n=155, referred to as “subgroup”). The flow diagram for the selection of subjects is shown in Fig. 1.

Questionnaire and identification of products and ingredients. Participants of the preliminary survey were asked about dietary supplement use in the previous year (no/yes), experience of adverse events (no/yes, multiple-choice of 10 symptoms) and confidence level of the causal relationship between adverse events and supplement use (“Not sure,” “Possible,” “Probable” or “Highly probable”). In the full-scale survey, participants made either one or multiple responses to the following items: duration and frequency of supplement use; degree of skin manifestation; continuous use of the corresponding supplement, treatment and duration of overall recovery after onset of skin manifestation; other related causes; and circumstances of reporting the incident. The name of the product, manufacturer and any keywords including the active ingredients were also elicited as fillable fields that were required to proceed to the next question. The demographic characteristics of the respondents, including age, sex, and residential area, were obtained from the registered information from the company.

The dietary supplement products were identified based on the manufacturer’s website, which was searched using the entered responses of the name of the product, manufacturer and keywords. When any one or two of the fields indicated “unknown,” we performed a Google search of the words entered in other fields. When

| Table 1. Subject characteristics. | All (n=300) | Products identified subgroup (n=155) |
|----------------------------------|------------|-----------------------------------|
| Sex                              |            |                                   |
| Male                             | 40.3       | 37.4                              |
| Female                           | 59.7       | 62.6                              |
| Age                              |            |                                   |
| <30                              | 3.0        | 3.8                               |
| 30–39                            | 15.7       | 15.1                              |
| 40–49                            | 31.0       | 29.6                              |
| 50–59                            | 33.0       | 31.4                              |
| 60–69                            | 11.7       | 13.8                              |
| >70                              | 5.7        | 6.3                               |
| Residential area                 |            |                                   |
| Hokkaido                         | 3.7        | 2.6                               |
| Tohoku                           | 5.3        | 7.1                               |
| Kanto                            | 43.3       | 43.2                              |
| Chubu                            | 15.7       | 16.1                              |
| Kinki                            | 17.3       | 12.9                              |
| Chugoku+Shikoku                  | 7.0        | 9.7                               |
| Kyushu+Okinawa                   | 7.7        | 8.4                               |
| Use of dietary supplements       |            |                                   |
| Duration                         |            |                                   |
| <1 wk                            | 33.7       | 37.4                              |
| 1–4 wk                           | 30.0       | 31.6                              |
| 1–3 mo                           | 11.3       | 14.8                              |
| 3–6 mo                           | 5.7        | 4.5                               |
| 6–12 mo                          | 2.0        | 2.6                               |
| >1 y                             | 6.0        | 7.1                               |
| Does not remember                | 11.3       | 1.9                               |
| Frequency                        |            |                                   |
| 5–7/wk                           | 80.7       | 87.1                              |
| 3–4/wk                           | 5.0        | 3.2                               |
| 1–2/wk                           | 6.7        | 5.8                               |
| <1/wk                            | 2.7        | 0.6                               |
| Other                            | 5.0        | 3.2                               |
we were unable to identify one specific product, we considered the product to be “unidentified.” Regarding the identified products, only those in accordance with the defined “dietary supplement” were accepted as valid responses, and all ingredient information was obtained from the manufacturer’s website. These products were further classified into supplement types such as “Vitamins/Minerals,” “Peptides or animal by-products,” “Indigestible saccharides,” “Fats and lipid,” “Probiotic bacteria” or “Herbal/Botanical,” based on the ingredients used to gain functional effects. When the ingredient could not be classified into one of the above categories, it was classified as “Combination/unclassifiable product.”

**Statistical analysis.** Differences in the distributions of responses among all respondents and between subgroups were examined using the chi-square or Fisher’s exact test. Association analyses between two variables were tested by the Wilcoxon signed-rank test. Statistical analyses were performed using R version 3.4.1, and two-tailed p values less than 0.05 were considered to indicate significance.

**RESULTS**

**Characteristics of subjects**

The adverse event frequency of anthema or itching was 1.4% of dietary supplement users, of which 57.9% self-reported the causal relationship between the symptom and dietary supplement as probable or highly probable. The characteristics of all subjects in the final analyses (n=300) and the subgroup in which all ingredients were identified (n=155) are shown in Table 1. Subjects consisted of more females than males, and more people in the age order of 50s, 40s and 30s. The duration of supplement use showed over 60% of subjects answered...
Online Survey to Collect Supplement-Related Skin Manifestations

“less than 1 mo.” and the frequency showed approximately 80% used the supplement almost every day. The distributions of subjects’ characteristics in Table 1 were similar among all subjects and the subgroup.

**Adverse symptom of skin manifestation**

In all subjects, 83.3% experienced mild symptoms with “itching and/or rash of body part.” Although 14.7% reported a generalized rash, there were no serious events such as shock symptoms (Table 2). After the onset of skin manifestation, 69.3% ceased dietary supplement use, while 26.6% continued using supplements, including those who reduced the amount/frequency of use. In response to adverse symptoms, 26.0% of subjects visited the hospital, while 53.3% did not seek treatment. More persons who experienced generalized rash went to the hospital than those who experienced partial manifestation (45.5% and 22.8%, respectively, \( p = 0.001 \)). Symptoms did not improve for days for 49.3% of subjects and for weeks or months for 26.3%. The length of recovery did not differ between the presence and absence of allergic diathesis as a factor related to skin manifestation (\( p = 0.703 \)). However, continuous use of products delayed recovery for weeks or months in more people (62.5%, \( p = 0.017 \)) in the presence of allergic diathesis. None of the subjects reported the event to an administrative agency; instead, 20.3% contacted the manufacturer or retail store. The distributions of responses in Table 2 were similar among all subjects and the subgroup.

**Functional components and ingredients**

The types of dietary supplements suspected by the subgroup respondents (\( n = 155 \)) as causative of the skin manifestation are shown in Fig. 2. “Combination/unclassifiable product,” which included products containing multiple types of ingredients, accounted for 19.4%. Sixty-eight percent consisted of “Peptides or animal by-products” (31.0%), “Herbal/Botanical” (23.2%) and “Fats and lipid” (13.5%). The most frequently added ingredients to products for functional components were as follows: collagen peptide (collagen peptides derived from pig, chicken or fish, or extract from chicken cartilage, 35.4% of all “Peptides or animal by-products” products), glucosamine (glucosamine derived from prawns and crabs, 16.7%), chondroitin (extract from shark cartilage, 16.7%), hyaluronic acid (hyaluronic acid or extract from crista galli, 14.6%), and placenta (placenta concentrate, 8.3%). In “Herbal/Botanical,” there was no particular ingredient frequently used, but products containing more than 5 plant extracts (27.8%) and more than 5 plant fermented extracts (27.8%) accounted for the majority. Fish oil was the predominant ingredient (85.7%) in “Fats and lipid.” Although not a functional ingredient, all of the products in “Fats and lipid” contained gelatin for capsule preparation.

**DISCUSSION**

In the present study, we conducted a nationwide online survey for collection of information on ongoing adverse events of skin manifestations associated with dietary supplement use. As a result, the survey of 72,997 persons over 9 d showed 0.8% of dietary supplement users experienced skin manifestation and self-reported the cause to be probably or highly probably due to supplement use. Most respondents experienced mild symptoms, but approximately 20% sought medical treatment at a hospital. In addition, the information collected from over 100 subjects enabled us to determine the types of causative ingredients as “Peptides or animal by-products,” “Herbals/Botanicals” and “Fats and lipid.”

None of the subjects reported the adverse event of skin manifestation to an administrative agency, and over 70% did not report it to anyone, even though one in four sought medical treatment at a hospital. Some of the subjects contacted the manufacturer or retail store; however, the information collected by these companies is unlikely to be reported to any governmental office, since companies are not mandated to report non-fatal adverse events in Japan, and approximately 90% of the gathered information comprises of complaints (9). Instead, health professionals are responsible for reporting severe
adverse events suspected to be caused by supplement use to public health centers. However, the dietary supplement history of patients is infrequently obtained in the medical setting because of the lack of specialized training to detect harm from supplements (17). In addition, physicians and pharmacists are unable to definitively prove the cause-and-effect relationship of adverse events (8). These circumstances dissuade health care professionals from reporting to public health centers. It is important to prophylactically detect an ongoing health anomaly to prevent further damage. Therefore, collecting real-time adverse events by periodically conducting surveys directly with consumers, as performed in the present study, is suggested to function effectively within the current system.

Meanwhile, the large number of reports in the present study facilitated the identification of common types of supplements among the respondents as follows: “Peptides or animal by-products,” “Herbals/Botanicals” and “Fats and lipid.” Herbal products are often suspected to be the causative agents of adverse reactions (12, 13, 18). In addition to herbals, our results suggested that “Peptides or animal by-products” may also be a possible cause of skin manifestations. As adverse reactions attributed to herbals are generally noted to be due to lack of standardization, contamination, adulteration, plant misidentification/substitution, improper use or innovated preparation methods rather than pharmacological/toxicology effects (12), the extract from an animal tissue or a concentrate may contain a variety of constituents as well as the functional components. In fact, there have been cases of anaphylactic reaction caused by the ingestion of allergenic protein contaminants in dietary supplements (3, 4).

Furthermore, fish oil accounted for the majority of “Fats and lipids” products, which was the third most used supplement type involved in adverse events of skin manifestations. Interestingly, instead of the anti-inflammation properties of eicosapentaenoic acid and docosahexaenoic acid that are expected to be effective in the prevention and treatment of allergic reactions (19, 20), our result showed that fish oil was a suspected cause. Yet, evidence that factors in fish oil cause skin manifestations is lacking. During our thorough investigation of the ingredients, gelatin was found in all products of “Fats and lipid” as a capsule component. Gelatin allergy is often recognized as a side effect of gelatin-containing vaccination; thus, gelatin-free vaccines have been available since 1999 in Japan. Nonetheless, a case of anaphylaxis from the ingestion of a gelatin-containing oral medication, with suspected sensitization by gel capsules, was reported in 2014 (21). Given these facts, the gelatin used in the formation of capsules, though not the principle substance of supplements, has emerged as a suspicious cause of skin manifestation.

Even if the functional components are labeled on the product package, there is no guarantee that the actual ingredients are purified components. Rather, extracts or concentrates, which consist of a complex mixture of intended/unintended components, are often used as the source. Moreover, supplements generally contain multiple ingredients and additives, as in the case of fish oil products, and some products even contain multiple functional components (accounting for 19.4% in our survey). These manufacturing conditions of dietary supplements make it more difficult to identify the causative ingredient or component of adverse events, especially with few case reports. In these circumstances, extracting commonalities among hundreds of accumulated reports from consumers, as performed in the present study, will facilitate the identification of potentially harmful ingredients, components or products.

With respect to the quality control of the online survey, the survey company had procedures in place to eliminate duplicate registrants and fraudulent respondents. As an added measure, we limited the full-scale survey to those who were confident in the causal relationship between skin manifestations and supplement use, thereby collecting only reliable responses. However, the information we obtained was all self-reported and adverse events were not necessarily evaluated from a medical perspective. Thus, there may be over/underestimation of the severity of symptoms and of the causal relationship. In addition, the supplemental products used were clearly identified in only half of the subjects. In an online survey, unknown factors may influence the results, and problems interpreting the data remain. Nevertheless, nationwide online surveys remain a valuable tool to investigate large populations in a short period of time and to collect and accumulate reports directly from consumers for ongoing adverse events in real-time.

**CONCLUSION**

In the present study, a survey of 63,737 dietary supplement users revealed that 0.8% reported a possible adverse event of skin manifestation. Of the products 155 respondents reported as suspicious, the types of supplements deemed noteworthy were: “Peptides or animal by-products,” “Herbals/Botanicals” and “Fats and lipid.” It was also demonstrated that periodically conducting a nationwide online survey to elicit information directly from consumers, and identifying commonalities among the accumulated reports, could fill a void in the current adverse event reporting system. The survey findings will serve to further educate consumers as well as guide supplement manufacturers.

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