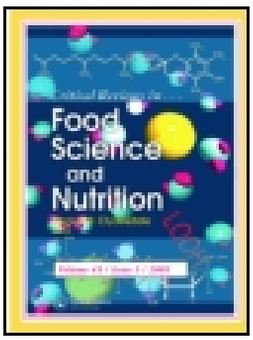

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SYSTEMATIC REVIEW

Differences in efficacy evaluation endpoints in clinical trials for claiming reduction of post-prandial glycemic response between Japan and the European Union

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ABSTRACT

When evaluating the efficacy of foods with health claims (FHC), each country sets different standards for efficacy evaluation endpoints in clinical trials, which may result in a barrier, namely the case that the claim that is allowed in Japan cannot be used on the label in another region and vice versa. We aimed to investigate the efficacy evaluation endpoints used in clinical trials of FFCs containing ID and submitted in Japan, in reference to the EU requirements for substantiating the claim, namely "reduction of post-prandial glycemic responses". We detected only one difference in efficacy evaluation endpoints, which was insulin levels. We found 67 such clinical trials cited in systematic literature reviews on finished products or functional substance(s). Of these, 43 (64%) trials lacked insulin assessment. Particularly, for foods that were claimed to reduce post-prandial glycemic responses, the EU does not consider a claim to be substantiated unless insulin levels have been evaluated. Our findings suggest the need for standardization of requirements for FHC between Japan and the EU. This consideration will strengthen the evidence for clinical significance of ID and allow products labeled with this health claim to be more widely distributed.

KEYWORDS

Clinical trial; foods with functional claims; indigestible dextrin; efficacy evaluation; post-prandial glycemic response; Japan

Introduction

In research conducted in 1984 with funds provided by the Japanese Ministry of Education, Culture, Sports, Science and Technology, for the first time in the world, a new definition for the role of foods that improved health was given and these foods were labeled as "functional foods" (Yano 1987). In 2015, the Consumer Affairs Agency of Japan introduced a new labeling system for Food with Health Claims (FHC), made up of the three categories: 1) Food with Function Claims (FFC), 2) Food for Specified Health Uses (FOSHU), and 3) Food with Nutrient Function Claims. The Japanese evaluation system of FFC requires to prove the efficacy of FFC using systematic literature review(s) on either a finished product or functional substance (s) (SRs), OR using at least one clinical trial on a finished product (equivalent to the level of evidence for FOSHU). A guideline is available on the necessary efficacy evaluation endpoints in clinical trials published for FOSHUs, including FFCs (Consumer Affairs Agency 2018a).

In 2017, a total of 10 million people were reported to be prediabetic by the National Health and Nutrition Survey, a fundamental statistical survey conducted in Japan (Ministry of Health, Labor and Welfare 2018), and an equivalent number of patients had type 2 diabetes mellitus. Individuals with prediabetes have high blood glucose levels without diagnosis or symptoms and have an increased risk of developing arteriosclerosis (Tominaga et al. 1999). They also have an increased risk of death from cardiovascular diseases as reported by the Funagata diabetes study (Tominaga et al. 1999). Therefore, FHCs that lead to the "reduction of post-prandial glycemic responses" may be effective in preventing the progression of myocardial infarction in at-risk but otherwise healthy individuals.

Indeed, FHCs containing indigestible dextrin (ID), which is purported to reduce sugar absorption, are popular in Japan (Yano Research Institute Ltd 2016). ID is also known as "resistant dextrin" in the European Union (EU) and is widely used for its health benefits because of its easy-to-use physical properties, safety, and sufficient evidence for physiological benefits. It was designated as Generally Recognized As Safe (GRAS) by the United States Food and Drug Administration (Food and Drug Administration, 1981), and approved as a FOSHU by the Ministry of Health and Welfare (currently the Ministry of Health, Labor, and Welfare 2018) in Japan in 1992 (National Institutes of Biomedical Innovation, Health and Nutrition 2018).

However, internationalization of food trade has made it increasingly difficult to complete food production processes within a single country. For example, foods that are claimed to have health benefits derived from probiotics are not authorized by the European Food Safety Authority (EFSA)

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(EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) 2009). Therefore, food labels with health claims related to probiotics had to be altered (JETRO 2014), even for effective FHCs that had been released into the market in Japan; this example shows that there may be cases in which health claims of FHCs must be changed accordingly before being imported to other countries. Therefore, FHCs with new heath claims such as "good for digestion" are more difficult to gain entry into the EU market.

The Codex Alimentarius was established in 1961 to protect the health of consumers and to facilitate the international standardization of relevant regulations (Codex Alimentarius 1961). Its activities comprise making global recommendations for food labeling, risk assessment, and the use of foods for special dietary purposes. However, the recommendations and guidelines published by the Codex Alimentarius Commission (CAC) are not legally binding and only serve as guidelines for local governments to develop legislation. Despite the global guidelines provided by the CAC, the regulatory system for FHCs is not standardized among countries and regions (Malla, Hobbs, and Sogah 2013; de Boer and Bast 2015). Therefore, effective criteria for efficacy evaluation endpoints in clinical trials at the local level should be further discussed for the next step of globalization, as countries with a global market use varying criteria to evaluate health claims only to meet local needs and regulations deeply rooted in their own society and culture.

Here, we aimed to investigate the efficacy evaluation endpoints used in clinical trials of FFCs containing ID and submitted in Japan, in reference to the EU requirements for substantiating the claim, namely "reduction of post-prandial glycemic responses".

Materials and methods

Target food with health claims and material selection

FOSHU can be validated by the results of clinical trials only, and not SRs. The application dossiers for FOSHU are kept confidential; therefore, we instead targeted clinical trials cited in SRs of FFC made in Japan. In Japan, all the application dossiers describing scientific evidence on efficacy evaluation of FFCs, including the review process of SRs, have to be publicly available through the database on the website published by the Consumer Affairs Agency (https://www.fld.caa.go.jp/caaks/cssc01/). We therefore obtained the results of all clinical trials cited for SRs, which were related to the health claim "reduction of post-prandial glycemic responses" in the submitted dossiers and contained the functional substance, ID, using the databases of the Consumer Affairs Agency (Consumer Affairs Agency 2018b) (as of October 10, 2017).

Differences between efficacy evaluation endpoints of clinical trials related to the "reduction of post-prandial glycemic responses" for Japan and the EU

We examined differences in efficacy evaluation endpoints of clinical trials that are specified in Japanese (Consumer Affairs Agency 2018a) and EU guidelines (Pravst et al. 2018; EFSA 2012).

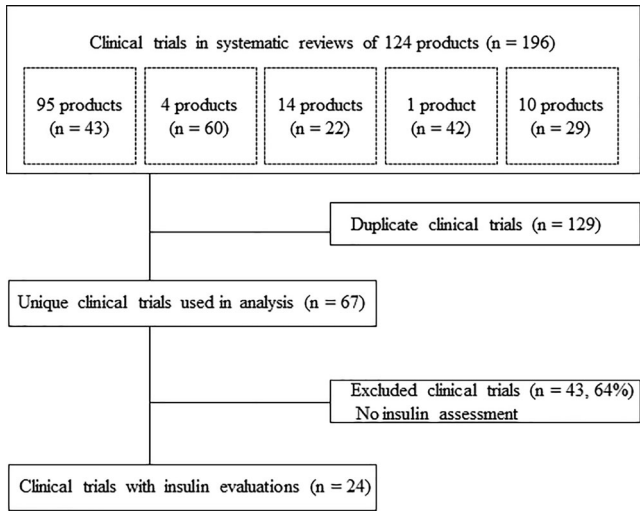

Figure 1. Flow of selection of clinical trials cited in systematic reviews of notified food with function claims for indigestible dextrin that involved evaluation of insulin level as an efficacy evaluation endpoint.

Analysis

We calculated the proportion of clinical trials cited for SRs of FFCs, which conformed to Japanese guidelines but lacked efficacy evaluation endpoints required by the EU to substantiate health claims of "reduction of post-prandial glycemic responses".

Results

Analysis set

A total of 124 FFCs that contained ID and were labeled with the claim of reducing post-prandial glycemic responses were selected for this study. Of these, a total of 196 clinical trials were cited for SRs in the application dossiers. After excluding 129 duplicate clinical trials, 67 unique clinical trials were identified and investigated (Figure 1) (Supplementary information). The Japanese FFC evaluation system requires that the efficacy of functional substances be proven using not only clinical trials but also SRs. Therefore, both the results and selected clinical trials of SRs tend to be similar among the same functional substance, even if each product was produced by a different food developer. For this reason, the results of SRs for ID among the investigated products had five patterns: 95 products were substantiated using 43 unique articles of clinical trials included in the SRs used for health claim applications; 4 products were substantiated using 60 unique articles; 14 products were substantiated using 22 unique articles; 1 product was substantiated using 42 unique articles; and 10 products were substantiated using 29 unique articles. These pattern groups were based on differences in search criteria in SRs used by food developers in Japan.

Table 1. Differences in endpoints in efficacy evaluation of clinical trials as supporting scientific evidence for "reduction of post-prandial glycemic responses" specified between Japanese and EU guidelines.

	Endpoints in efficacy evaluation	
	Japan*	EU**
Blood glucose	Post-prandial blood glucose level and AUC	Studies showing a decrease in blood glucose concentrations
Insulin level	None	No increase in insulin concentration in comparison to the reference food

*"FOSHU guideline" (Consumer Affairs Agency 2018b).
**"Guidance on the scientific requirements for health claims related to appetite ratings, weight management, and blood glucose concentrations" (European Food Safety Authority 2012).

Usage of insulin levels as an efficacy evaluation endpoint of clinical trials differs between Japan and the EU

Regarding the efficacy evaluation of a functional substance to reduce post-prandial glycemic responses, there are two evaluation endpoints: 1) blood glucose and 2) insulin level. Japanese guidelines state that only post-prandial blood glucose is required. However, to substantiate this health claim, the EU guidelines require the evaluation of insulin levels in comparison to a reference food. We therefore investigated the use of "insulin level" as an efficacy endpoint in the clinical trials cited for SRs in the submitted dossiers of FFCs (Table 1).

Number of clinical trials that does not substantiate the health claim "reduction of post-prandial glycemic responses" by EU standards

We calculated the proportion of clinical trials that did not examine insulin level. Of the 67 clinical trials for ID, 43 (64%) did not evaluate insulin levels as one of the efficacy evaluation endpoints in clinical trials, but 24 did (Figure 1).

Discussion

Insulin level as an endpoint in efficacy evaluation for reduction of post-prandial glycemic responses

Type 2 diabetes is caused by insulin resistance and/or a disturbance of insulin secretion triggered by life-style factors, such as overeating, lack of physical activity, and obesity, in addition to intrinsic factors such as genetic predisposition. The main cause of type 2 diabetes in the western population is insulin resistance (Fukushima, Suzuki, and Seino 2004), whereas in Japan the main cause is a disturbance of insulin secretion because of the smaller number of obese people (Tripathy et al. 2000; Sone et al. 2004). However, obesity caused by increased dietary fat intake even in Japan after westernization of dietary habits leads to insulin resistance (Inagaki 2016). Therefore, it is clinically relevant to evaluate insulin levels to aid in the prevention of type 2 diabetes.

Of the clinical trials cited for SRs describing the efficacy of ID in Japan, 64% lacked evaluation of insulin response. In addition to blood glucose, the evaluation of insulin levels to establish whether FHCs effectively reduce post-prandial glycemic responses in asymptomatic healthy subjects will demonstrate the clinical significance and benefits of ID in the context of preventing progression to disease by inhibition of the flow of events and chain reactions associated with cardiovascular risk, called "metabolic domino" (Itoh 2006). If individuals without any perceivable signs and symptoms have their insulin levels evaluated, we may be able to prevent this flow.

Global standardization of efficacy evaluation endpoints to reduce global trade barriers

There are slight differences in efficacy evaluation endpoints in the guidelines of "reduction of post-prandial glycemic responses" for FHC in Japan and what is necessary to substantiate health claims in the EU. In Japan, efficacy evaluation guidelines for FHC are available for cholesterol, blood neutral fat, blood pressure, post-prandial hyperglycemia, body fat, and intestinal regulatory function. However, the EFSA, which provides assessment criteria for scientific opinions (de Boer, Vos, and Bast 2014), publishes guidelines on the scientific requirements for health claims in six areas: 1) functions of the nervous system, including psychological functions; 2) physical performance; 3) bone, joints, skin, and oral health; 4) appetite ratings, weight management, and blood glucose concentrations; 5) immune system, gastrointestinal tract, and defense against pathogenic microorganisms; and 6) antioxidants, oxidative damage, and cardiovascular health. The EFSA also publishes an assessment report in the EFSA Journal for each health claim application.

Our present findings may highlight the need for harmonization and re-evaluation of efficacy endpoints in clinical trials for health claims between Japan and the EU. For example, Pinefiber®, which was developed in Japan and for which insulin levels have not been evaluated in clinical trials, was not approved for that labeling in the EU as indicated in the EFSA report, which reported a lack of scientific evidence for post-prandial insulinemic responses (EFSA Panel on Dietetic Products, Nutrition and Allergies 2011) for this product. Thus, a health claim of FHC made legally in Japan cannot be used on a label in the EU. Consideration of efficacy evaluation criteria for the scientific basis of FHCs is important in the perspective of FHC development (Shimizu 2013). We previously showed that establishing global scientific requirements for FHCs promotes healthcare by promoting its free trade (Tanemura, Hamadate, and Urushihara 2017; Ministry of Health, Labor and Welfare 2018). We trust that this difference will be addressed by standardization of the regulatory system for evaluating efficacy endpoints of health claim.

Limitations

We only examined health claims regarding the reduction of post-prandial glycemic responses with ID. Other health claims should also be examined to further elucidate the status of gaps in efficacy evaluation and improve standardization. For example, probiotic products such as fermented milk and yoghurt have been produced in the Mediterranean region (Melendez-Illanes et al. 2015) and indeed account for the largest market of FOSHU in Japan (Japan Health and Nutrition Food Association 2017). Therefore, future studies should initially examine health claims for "intestinal regulatory function".

Conclusion

Sixty-four percent of clinical trials in Japan cited for SRs as the scientific evidence of ID did not evaluate insulin levels to support the health claim that ID reduces post-prandial glycemic responses. To standardize scientific regulatory systems at a global level in terms of clinical implications, it may be meaningful to have mutual communication in the world regarding the differences in efficacy evaluation endpoints of clinical trials.

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Abbreviations

FFC	food with function claims
FOSHU	food for specified health uses
FHC	foods with health claims
ID	indigestible dextrin

Declaration of conflicting interests

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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