

Transition of Intervention of Clinical Trials for Obesity

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Abstract

Objectives: Earlier studies have revealed that modification of lifestyle habits from the aspects of nutrition and exercise is the most effective measure to control metabolic syndrome, and this finding may be reflected in the number of registered clinical trials. This paper aims to test this assumption and conduct exploratory analysis of the recent trends in clinical trials related to obesity.

Design and methods: Of the clinical trial data registered with the International Clinical Trial Registry Platform (ICTRP), we used 1,478 data sets of obese patients for analysis (available as of August 2016).

This study is exploratory analysis, aiming to test some hypotheses and identify the overall tendency. The target hypotheses are as follows. Among clinical trials targeting obese patients, the number of those intended to verify the effect of lifestyle modification has been increasing year by year.

Results: The percentage of clinical trials targeting obesity has been increasing year by year. We clearly found that the number of clinical trials using lifestyle intervention has been increasing ($p < 0.05$). We conducted a chi-squared test to examine whether there is any difference in terms of interventions among countries, and found that while clinical trials targeting obese patients were relatively more frequently conducted in the United States, France, and the Netherlands, these clinical trials were relatively less frequent in Japan, China, India, and Australia/New Zealand. The coefficient of correlation between the ratio of people with BMI 25 or higher and the percentage of clinical trials targeting obese patients is 0.55, suggesting a moderate correlation.

Conclusion: In this study, we found that clinical trials conducted targeting obesity have led to the accumulation on a yearly basis of study results showing that lifestyle modification is the most effective way to control obesity, and that these clinical trials have been relatively more frequently conducted than other clinical trials. In the future, once a more effective method is discovered, it will be more frequently used in other clinical trials as well. According to the analysis results by country, we found that countries where obesity exists as a more serious health problem tend to conduct more clinical trials targeting obesity.

Keywords: Obesity; Metabolic syndrome; Clinical trials

Background

In the study conducted by Knowler [1] in 2002, the research team divided obese patients with BMI 25 or higher into three groups, i.e., those given a placebo, those treated with metformin, and those instructed to modify their lifestyle, and observed their conditions over four years. The research team found that the cumulative incidence of diabetes was statistically significantly lower among the lifestyle modification group than among the metformin group. Following a number of similar study results, more importance has been given to lifestyle modification than to treatment with medication as a strategy to control obesity, or metabolic syndrome. Leading the world in this area, Japan introduced a system of specified medical checkups and specified medical guidance in 2008. Under this system, people receiving medical checkups undergo measurement of their waist circumference, BMI, and so forth. The system is designed to thereby find people who are at risk of lifestyle-related diseases due to high blood sugar, high blood pressure, and lipid abnormality, from among those whose measurement results exceed the standard ranges. These people are given health guidance to modify their lifestyle habits.

Other countries followed Japan, starting to implement government-led measures to modify people's lifestyle habits including diet and exercise. Backed up by a number of study results such as those obtained by Sacks [2] and Eyles [3], the first bill in the United States to levy tax on soda and other sugar-sweetened beverages was passed by the council of the City of Berkeley, California [4]. A similar soda tax is also scheduled to be introduced in the City of Philadelphia [5]. This trend has the potential of spreading across the United States.

France also introduced the soda tax in January 2012, and the United Kingdom is planning to introduce it in 2018. A similar tax has already been introduced in Romania and Hungary. These tax policies may be based on the implication in some study results that consumption of soda and other sugary drinks is strongly related to childhood obesity [6].

Thus, earlier studies have revealed that modification of lifestyle habits from the aspects of nutrition and exercise is the most effective measure to control metabolic syndrome, and this finding may be reflected in the number of registered clinical trials. Presumably, among clinical trials targeting obese patients, while the number of trials using surgery and medication has been relatively decreasing year by year, the number of those intended to verify the effect of lifestyle modification has been relatively increasing year by year. This paper aims to test this assumption and conduct exploratory analysis of the recent trends in clinical trials related to obesity.

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Method

In the Advanced search of ICTRP [7], when inputting the disease name in the condition column, data of the corresponding clinical trial is output. In this study, we entered “obesity” in the condition field of Advanced search and analyzed the data of all clinical trials output. Of the clinical trial data registered with the International Clinical Trial Registry Platform (ICTRP) [8], we used 1,478 data sets of obese patients for analysis (all from database inception to August 19, 2016) (Figure 1).

The main analysis of this study excluded observational studies (except for Table 1). Also, because there was a change in the ICTRP search system in 2016, we analyzed the data until 2015.

This study is exploratory analysis, aiming to test some hypotheses and identify the overall tendency. The target hypotheses are as follows.

1. Among clinical trials targeting obese patients, the number of

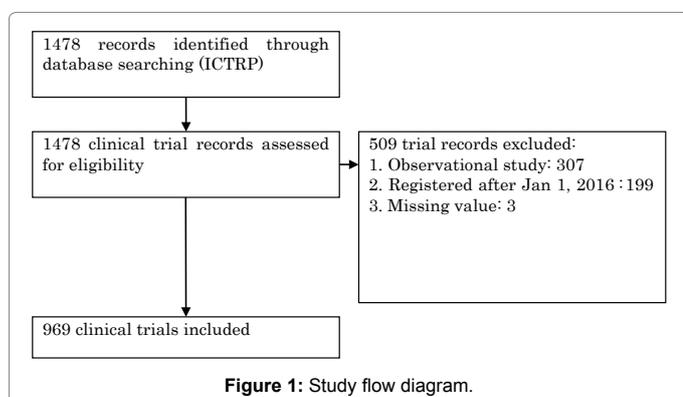


Figure 1: Study flow diagram.

Year	1. Obesity	2. Other	1/(1+2)
2005	18	19687	0.09%
2006	25	17320	0.14%
2007	46	20862	0.22%
2008	39	24517	0.16%
2009	57	26658	0.21%
2010	72	28903	0.25%
2011	96	30075	0.32%
2012	135	34132	0.40%
2013	167	34956	0.48%
2014	234	39430	0.59%
2015	336	42754	0.79%
Total	1225	319294	3.65%

*p<0.05 Mantel-Haenszel test for trend.

Table 1: Percentage of clinical trials targeting obesity.

Year	Life Style		Supplement		Drug/Device		Surgery		Others		Total	
2008	30	31.3%	5	5.2%	57	59.4%	1	1.0%	3	3.1%	96	100%
2009	14	31.1%	5	11.1%	16	35.6%	4	8.9%	6	13.3%	45	100%
2010	21	42.9%	5	10.2%	15	30.6%	6	12.2%	2	4.1%	49	100%
2011	27	39.1%	6	8.7%	24	34.8%	9	13%	3	4.3%	69	100%
2012	39	35.8%	13	11.9%	39	35.8%	8	7.3%	10	9.2%	109	100%
2013	59	42.4%	13	9.4%	42	30.2%	10	7.2%	15	10.8%	139	100%
2014	77	42.1%	26	14.2%	38	20.8%	16	8.7%	26	14.2%	183	100%
2015	125	44.8%	40	14.3%	65	23.3%	11	3.9%	38	13.6%	279	100%
Total	392	40.5%	113	11.7%	296	30.5%	65	6.7%	103	10.6%	969	100%

*p<0.05 Mantel-Haenszel test for trend concerning percentage of lifestyle modification.

Table 2: Interventions used in clinical trials targeting obese patients.

those intended to verify the effect of lifestyle modification has been increasing year by year.

2. The number of clinical trials targeting obese patients is relatively large in countries with a high degree of obesity.

3. Clinical trials targeting obesity differ from other clinical trials in terms of the type of study, target gender, target age, and trial phase.

In order to analyze these hypotheses, we extracted data regarding Date Registration, Study Type, Gender, Minimum Age, Maximum Age, and Phase, from the 1,478 data sets mentioned above. We also read data regarding interventions one by one and classified the data into five categories, i.e. Surgery, Device, Supplement, Lifestyle Habits, and Other. An intervention that may fall within more than one category, such as modification of lifestyle habits after surgery, is classified as “Surgery.” Other interventions that may fall within more than one category are classified into the category of more invasive intervention. “Device” covers a wide range, including implantable devices, communication devices for remote medical care, and even video games. “Supplement” mainly includes vitamin tablets and plant extracts. As “Lifestyle Habits,” we selected nutrition and exercise as well as education on these as the major types of interventions. Other interventions that cannot be assigned to one of these categories, such as acupuncture and moxibustion therapy, music therapy, and survey, are classified into “Other.”

We conducted a t-test regarding the age of the subjects to compare the mean value between the obesity clinical trial group and the other clinical trial group. For other items, we conducted a test of independence through cross tabulation to confirm the residuals adjusted for degrees of freedom.

Results

The percentage of clinical trials targeting obesity has been increasing year by year. This trend is clear from the residuals adjusted for degrees of freedom. While all residuals in clinical trials targeting obesity conducted years ago take negative values, all residuals in recent clinical trials take positive values.

Table 2 shows the yearly trends of interventions used in clinical trials targeting obese patients. Looking at the residuals adjusted for degrees of freedom after conducting a chi-squared test, we clearly found that the number of clinical trials using lifestyle intervention has been increasing (p<0.05). We further divided lifestyle modification into subcategories such as nutrition, exercise, and provision of information, and conducted a chi-squared test, but this time, we did not find a noticeable increase in the number of clinical trials regarding any of these interventions.

	Life Style		Supplement		Drug/Device		Surgery		Others		Total	
US	215	49.3%	36	8.3%	120	27.5%	21	4.8%	44	10.1%	436	100%
AU/NZ	4	25.0%	2	12.5%	10	62.5%	0	0%	0	0%	16	100%
UK	36	37.1%	7	7.2%	41	42.3%	5	5.2%	8	8.2%	97	100%
FR	17	18.3%	5	5.4%	34	36.6%	12	12.9%	25	26.9%	93	100%
IT	7	21.2%	4	12.1%	18	54.5%	2	6.1%	2	6.1%	33	100%
NE	44	39.6%	9	8.1%	36	32.4%	8	7.2%	14	12.6%	111	100%
DE	31	30.4%	4	3.9%	38	37.3%	11	10.8%	18	17.6%	102	100%
CH	9	25.7%	3	8.6%	13	37.1%	3	8.6%	7	20.0%	35	100%
JP	6	31.6%	4	21.1%	3	15.8%	5	26.3%	1	5.3%	19	100%
IN	5	45.5%	3	27.3%	2	18.2%	1	9.1%	0	0%	11	100%

*p<0.05 chi-squared test of independence; The countries are arranged in descending order in terms of the ratio of people with BMI 25 or higher.

Table 3: Interventions by country.

Table 3 shows interventions used in clinical trials in each country. We conducted a chi-squared test to examine whether there is any difference in terms of interventions among countries, and found that while clinical trials targeting obese patients were relatively more frequently conducted in the United States, France, and the Netherlands, these clinical trials were relatively less frequent in Japan, China, India, and Australia/New Zealand. The analysis revealed that the number of clinical trials targeting obesity is relatively smaller among countries where the ratio of obese people is relatively low.

Table 4 shows a country-by-country comparison of the percentage of clinical trials targeting obesity in the total number of clinical trials in each country based on the data retrieved from ICTRP, and the ratio of people with BMI 25 or higher in each country based on the data published by the WHO [9]. The coefficient of correlation between the ratio of people with BMI 25 or higher and the percentage of clinical trials targeting obese patients is 0.55, suggesting a moderate correlation. This result implies a positive correlation, although it is not statistically significant due to an insufficient number of samples.

Other trends

Table 5 shows target gender in clinical trials targeting obese patients. Table 3 is a cross table prepared based on close scrutiny of all data from 2012 to 2014, focusing on whether or not each clinical trial targets obesity and the gender targeted in the clinical trial. The result of a chi-squared test reveals that a larger part of clinical trials targeting obese patients chose women as the trial subject. We used the same data to prepare another cross table, focusing on whether or not each clinical trial targets obesity and the phase of the clinical trial, and conducted a chi-squared test. From this table, we found that a larger part of the clinical trials targeting obese patients were in phase 4 than among other clinical trials. On the other hand, we found no statistically significant difference between the results of chi-squared tests conducted focusing on whether or not each clinical trial targets obese patients and whether or not each clinical trial uses any intervention.

Discussion

In this study, we found that clinical trials conducted targeting obesity have led to the accumulation on a yearly basis of study results showing that lifestyle modification is the most effective way to control obesity, and that these clinical trials have been relatively more frequently conducted than other clinical trials. From some of the meta-analysis on clinical trials with obesity as the target disease, we can see that improving lifestyle is most effective in eliminating obesity. The meta-analysis of RCT with adolescent obesity as a target disease is listed below. Elles et al. analyzed the effect of surgery with target disease of obesity in adolescents [10]. According to this study, the weight loss of

Country	Ratio of people with BMI 25 or higher	Percentage of clinical trials targeting obese patients
United States of America	67.3	0.41%
Australia	64.0	0.08%
United Kingdom of Great Britain and Northern Ireland	63.4	0.30%
France	60.7	0.38%
Italy	58.8	0.16%
Netherlands	55.9	0.54%
Germany	54.8	0.30%
China	34.4	0.19%
Japan	24.2	0.06%
India	22.0	0.10%

*The ratio of people with BMI 25 or higher is based on the age-adjusted data published by the WHO (2014).

Table 4: Ratio of people with BMI 25 or higher and the percentage of clinical trials targeting obese patients, by country.

2012-2014	Obesity		Others	
Both	410	82.3%	82481	84.8%
Female	72	14.5%	9622	9.9%
Male	16	3.2%	5186	5.3%
Total	498	100%	97289	100%

Table 5: Target gender in clinical trials targeting obese patients.

Laparoscopic adjustable gastric banding surgery was greater than that of Multi component lifestyle program, but its quality of the evidence was low and adverse events occurred frequently. In the study of Mead et al., The effect of pharmacological intervention on obesity was analyzed. According to this study, Pharmacological intervention showed more significant weight loss compared to Comparator, but its quality of the evidence was low [11]. In addition, the comparator of this study may be only placebo, in some cases placebo and lifestyle modification, interpretation of the mean reduction in weight is difficult [12,13].

In the future, once a more effective method is discovered, it will be more frequently used in other clinical trials as well. In this regard, the rate of increase has been almost the same among specific means of lifestyle modification, namely, nutrition, exercise, and education (provision of information), which suggests that it is not that only one of them is outstandingly effective, but it is important to modify lifestyle habits from each of all of these aspects.

According to the analysis results by country, we found that countries where obesity exists as a more serious health problem tend to conduct more clinical trials targeting obesity. This finding may be valid, because state-sponsored research funds and research institutes

may reflect social needs to a certain extent, and also because private companies may reasonably expect to earn a greater profit by solving a more serious health problem.

According to Roderik's research, the major funder of public health research is a public or philanthropic organization, and it is natural that those organizations will focus on their main health problems [14].

The reason why clinical trials that chose women as the trial subjects account for a relatively large share of clinical trials targeting obese patients may be that interventions are mostly suitable for parents and nurses, and that women hold a larger proportion among parents who are mainly in charge of taking care of children and among people who work as nurses. Women's obesity may be one of the causes in countries where the number of registered clinical trials is increasing in recent years like China [15].

Meanwhile, a large part of clinical trials targeting obese patients were in phase 4, which is probably because interventions have shifted from medication to lifestyle modification.

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