Title: Effects of Long-term Administration of Indigestible Dextrin on Visceral Fat Accumulation
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[Abstract]
We conducted a clinical trial in order to evaluate the effects of continual ingestion of indigestible dextrin on both glucose and lipid metabolism, and fat accumulation and its distribution in human subjects. There were twelve male subjects with either serum total cholesterol level more than 220 mg/dl or triacylglycerol level more than 150 mg/dl. Subjects were concurrently ingested 10g of indigestible dextrin with meal (3 times/day) for three month. Each was subjected to a glucose tolerance test and CT scan at umbilical level, and also taken blood sample to measure the clinical laboratory data before and after the test period. Compared to the starting levels, percent body fat in all the subjects and the area of visceral fat in subjects with obesity were significantly decreased. Although the average peak level of serum glucose was more than 200 mg/dl at 60 min after 75 g glucose administration, glucose tolerance was improved and the average levels of serum glucose at 30, 60, and 120 min were significantly reduced after the test period. Likewise, serum total-cholesterol and triacylglycerol levels were significantly reduced. No adverse event such as diarrhea was observed through the test period. In conclusion, continual ingestion of indigestible dextrin is useful for reducing the body fat accumulation, especially visceral fat.

Key words : indigestible dextrin, visceral fat, obesity, glucose tolerance, lipid

The prevalence of diabetes, hyperlipidemia, hypertension and other lifestyle-related diseases have recently been growing steadily. These diseases underlie ischemic heart and cerebrovascular diseases, from which death rate ranks high, following cancer.1) Obesity and relevant changes in sugar and lipid metabolism cause a cluster of symptoms and disorders that is called syndrome X, 2) deadly quartet, 3) or visceral fat accumulation syndrome. 4-8) Today these changes are regarded as originating from obesity or visceral fat accumulation rather than accompanying life-related diseases.7) In other words, obesity prevention is believed to be critical in lifestyle-related disease prevention. Relieving obesity can delay progression of these diseases and be effective in relieving or treating symptoms. Various attempts have been made for primary prevention of lifestyle-related disease defined as a cluster of disorders that develop and progress in association with life habits, such as diet, exercise, relaxation, smoking, and drinking. For instance, the Ministry of Health, Labor and Welfare has started the “Kenko Nippon 21” project, in which specific goals have been set for modification of living habits, as part of efforts to prevent lifestyle-related diseases.6)

Dietetically, active use of foods for specified health use is one approach. Of relevant ingredients in the so far approved foods, indigestible dextrin, a water-soluble dietary fiber the authors developed, has effects of regulating intestinal functions, 9,10) suppressing postprandial blood glucose elevation, 11,12) and reducing serum lipids (total cholesterol and triglyceride) levels.13,14) When ingested repeatedly, it prevents postprandial hyperglycemia and excessive insulin secretion, therefore improving sugar and lipid metabolism and suppressing body fat accumulation.16-18) Thus, indigestible dextrin is highly likely to help the above-described primary prevention of lifestyle-related diseases greatly. Although its reducing effect on body fat accumulation has been shown in rats,15,16) dogs, cats,17) and poultry,18) no study has investigated its remedial effect on obesity in humans. The present study then investigated changes in body fat accumulation amount and distribution as well as those in sugar and lipid metabolism by repeated ingestion of
Table 1. Somatometry of subjects before/after administration of indigestible dextrin

<table>
<thead>
<tr>
<th></th>
<th>Before Intake (start)</th>
<th>3-month Intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years old)</td>
<td>46.1 ± 3.0</td>
<td>46.1 ± 3.0</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>168.8 ± 1.3</td>
<td>168.8 ± 1.3</td>
</tr>
<tr>
<td>Body Weight (kg)</td>
<td>73.7 ± 3.4</td>
<td>73.0 ± 3.3</td>
</tr>
<tr>
<td>BMI</td>
<td>25.8 ± 0.9</td>
<td>25.6 ± 0.9</td>
</tr>
<tr>
<td>Body Fat (%)</td>
<td>27.7 ± 0.9</td>
<td>25.9 ± 1.0*</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>90.8 ± 2.4</td>
<td>89.5 ± 2.3</td>
</tr>
<tr>
<td>Hip (cm)</td>
<td>98.8 ± 2.1</td>
<td>98.3 ± 2.1</td>
</tr>
<tr>
<td>W/H</td>
<td>0.91 ± 0.01</td>
<td>0.91 ± 0.01</td>
</tr>
<tr>
<td>V: Area for Visceral Fat (cm²)</td>
<td>108.0 ± 13.7</td>
<td>101.9 ± 11.6</td>
</tr>
<tr>
<td>S: Area for Subcutaneous Fat (cm²)</td>
<td>175.2 ± 25.2</td>
<td>163.9 ± 19.9</td>
</tr>
<tr>
<td>V/S</td>
<td>0.70 ± 0.1</td>
<td>0.64 ± 0.07</td>
</tr>
</tbody>
</table>

"n=12, average ± SEM"
"n=9, only for V, S, V/S values"
*: Pair-matching t-test, significantly different from initial values at p<0.05.

Materials and Methods

1. Test substances

Indigestible dextrin (Fibersol-2™, cornstarch-based granules in 10 g packs, Matsutani Chemical Industry Co.) was used as the test substance. The product had a dietary fiber content of 90%, as determined by the enzyme-HPLC method, and a solubility of 70%. It dissolved in both cold and hot water, producing a transparent solution. It was one-tenth less sweet than sucrose (sweetness intensity 10%).

2. Subjects

Those who had a total serum cholesterol level of 220 mg/dl or above or a triglyceride level of 150 mg/dl or above in the examination before study were first recruited. Among them, twelve adult men who voluntarily expressed their intention to participate in the study after receiving adequate explanation on nutritional physiological actions and anticipated adverse effects of indigestible dextrin as well as the purpose of the study, and understanding all the issues. The present study was conducted in conformity to the Declaration of Helsinki, after approved by both the Ethical Review Board of Matsutani Chemical Industry Co., (Approve No. 98-2) and Itami City Hospital.

3. Administration and measurement parameters

The subjects ingested 10 g of indigestible dextrin after each meal daily (30 g/day) for three months. They could ingest the test substance in any way they liked, although some ways allowing agreeable complete ingestion with meal were recommended, such as addition to beverages and foods, such as water, tea, coffee, miso soup, and soup, or sprinkling on or dissolution in dishes, if possible. In the early morning before and three months after the start of the study, physical examination, sugar challenge test and blood collection were conducted. Nine of twelve subjects, who gave their consent, were also examined by abdominal CT around the umbilicus at the same time. The parameters investigated are as follows:

Physical examinations:
- body height, body weight, waist size, hip size,
- percent body fat, and blood pressure

CT:
- visceral fat area and subcutaneous fat area

Sugar tolerance:
- blood glucose and insulin

Biochemical examinations:
- serum total cholesterol, HDL-cholesterol, triglyceride, fasting blood glucose, Na, K, Cl, total protein, albumin, bilirubin, direct bilirubin, uric acid, creatinine, GOT, GPT, ALP, LDH, γ-GTP, CK, cholinesterase, LAP

Blood chemical test:
- white blood cell count, red blood cell count, hemoglobin, hematocrit, and platelet count in blood chemical test

Accompanying symptoms were also investigated by asking the subjects to report any extraordinary condition or symptom in a questionnaire on physical conditions, gastrointestinal and subjective symptoms.

The subjects were instructed to maintain their
Start 3-month Start 3-month administration

Average ± SEM
*: Pair-matching t-test, significantly different from initial values at $p<0.05$.

Figure 1. Changes in area for visceral fat before/after administration of indigestible dextrin

living habits, without modifying exercise intensity, drinking amount, dietary habit and so on during the study. They had to report any extra exercise or food ingestion.

4. Statistical analysis
Experimental data were all presented as the mean±standard error. Significance of difference was tested by paired Student’s t-test at a significance level of 5%.

Results
Table 1 shows subject characteristics and physical examination results. The waist size, hip size and blood pressure after three-month administration of indigestible dextrin were lower than those before administration, with no significant difference. The percent body fat after the study was significantly lower than that before administration ($p<0.05$); especially, this tendency was more marked in ten subjects who were determined as obesity according to the criteria of the impedance-based body fat measurement device (28.6±0.7% before study vs. 26.6±1.0% after three months, $p<0.01$). CT-measured visceral and subcutaneous fat areas after three-month administration were both lower than those before administration, with no significant difference. Fig. 1a shows individual changes in visceral fat area. Fig. 1b shows the mean change over all subjects and that over five visceral obesity subjects having a ratio of visceral fat area to subcutaneous fat area (V/S ratio) of 0.4 or above and a visceral fat area of 100 cm$^2$ or above. For the individual changes, a decrease was found in seven of nine subjects, whereas an increase was found in two. For the mean changes, no significant change was found, although a significant decrease in visceral fat area was found in the visceral obesity subjects (118.2±13.3 cm$^2$ after three months vs. 139.0±16.7 cm$^2$ before administration). Fig. 2 shows a typical CT image from one of the aforementioned five subjects. The visceral and subcutaneous fat areas decreased from 196 cm$^2$ and 384 cm$^2$, respectively, before study to 149 cm$^2$ and 332 cm$^2$, respectively, after three months.

For the biochemical test parameters, a significant decrease was found in total cholesterol and triglyceride levels at a significance level of 1% (Table 2). A significant change was also found in albumin, ALP, and cholinesterase, although the levels were within the normal range. No clinically significant observations were obtained for electrolyte, protein, and parameters for renal, pancreatic, and hepatic functions. No significant change was found in any of white blood cell, red blood cell and platelet counts.
Table 2. Changes in blood pressure, serum fat, and blood glucose before/after administration of indigestible dextrin

<table>
<thead>
<tr>
<th></th>
<th>Before Intake</th>
<th>3-month Intake</th>
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<tbody>
<tr>
<td>Systolic Blood Pressure (mmHg)</td>
<td>141.2 ± 1.8</td>
<td>135.7 ± 3.5</td>
</tr>
<tr>
<td>Diastolic Blood Pressure (mmHg)</td>
<td>85.8 ± 1.3</td>
<td>81.4 ± 2.3</td>
</tr>
<tr>
<td>Total-Cholesterol (mg/dl)</td>
<td>232.0 ± 10.8</td>
<td>201.3 ± 7.8**</td>
</tr>
<tr>
<td>HDL-Cholesterol (mg/dl)</td>
<td>47.8 ± 3.2</td>
<td>44.4 ± 3.0</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>344.7 ± 63.8</td>
<td>192.9 ± 28.2**</td>
</tr>
<tr>
<td>Fasting blood glucose (mg/dl)</td>
<td>105.8 ± 6.5</td>
<td>104.3 ± 4.5</td>
</tr>
</tbody>
</table>

"n=12, average ± SEM"
*: Pair-matching t-test, significantly different from initial values at $p<0.05$.
**: Significantly different from initial values at $p<0.01$.

Fig. 3 shows mean blood glucose and insulin levels determined in sugar challenge tests before and after study. Before administration, the blood glucose level increased from the baseline fasting level (106.8±7.8 mg/dl) to a peak level 60 minutes after sugar challenge, and then decreased. After three-month administration, the blood glucose level changed in the same pattern, although the levels 30, 60 and 120 minutes after sugar challenge were significantly lower than those before study (179.7±10.7 mg/dl vs. 159.0±10.7 mg/dl after 30 minutes; 212.1±19.1 mg/dl vs. 183.7±15.0 mg/dl after 60 minutes; and 178.3±18.5 mg/dl vs. 154.7±19.4 mg/dl after 120 minutes). The area under curve (AUC) after three months was also significantly lower than that before study (121.0±21.4 mg2h/dl vs. 151.2±18.8 mg2h/dl) as calculated by the trapezoid method. The insulin level increased steadily within 120 minutes after sugar challenge before study, whereas it reached a peak 60 minutes after sugar challenge and then decreased after three-month administration. Although there was no significant difference, the insulin secretion was improved, corresponding to changes in the blood glucose curve.

No accompanying symptoms were found, including digestive tract symptoms, such as diarrhea, during the study.

**Discussion**

It is widely recognized that obesity underlies lifestyle-related diseases, such as diabetes, hyperlipidemia, hypertension, and arteriosclerosis. Obesity has been believed to result from energy intake surpassing energy consumption. Positive correlation of fat intake with fat accumulation has been indicated on one hand, one study has shown...
Figure 3. Results of sugar loading tests conducted before/after administration of indigestible dextrin

lack of tendency supporting correlation between dietary fat and frequency of obesity on the other. Moreover, the US prevalence of obesity, Type 2 diabetes, and related diseases has been increasing since the 1960s in spite of decrease in the ratio of energy intake from total fat and saturated fatty acids to total dietary energy intake, suggesting other causal factors than fat or excessive energy intake.

Recent progress of CT technology has made it possible to investigate where fat accumulates in obesity in a precise manner. Consequently, visceral fat accumulation has been found to be closely associated with development and progression of lifestyle-related diseases. A study by Keno et al. using a high-sucrose diet found that saccharide ingestion facilitated visceral fat accumulation more greatly than fat ingestion, indicating that postprandial blood glucose control and insulin secretion may be associated with visceral fat accumulation and lifestyle-related disease development.

Indigestible dextrin evaluated in the present study has been so far confirmed to retard absorption of carbohydrates in diet and suppress postprandial rapid blood glucose elevation in rats and humans. These effects are utilized in four food products for specified health use approved by the Ministry of Health, Labor and Welfare, with a statement that "the product suppresses sugar absorption and improves dietary habits of a person who is beginning to be concerned about blood glucose level." To control postprandial blood glucose levels is to control subsequent insulin secretion, which affects fat accumulation. This is critical in suppressing lipid release from the liver, facilitated lipid synthesis in adipose cells, and suppressed lipid decomposition, all of which are caused by excessive insulin secretion. Animal and clinical studies have confirmed that the effects of indigestible dextrin found in the single administration studies are exhibited repeatedly at each every meal in long-term continuous administration, resulting in improved glucose tolerance (sugar metabolism) and reduced serum cholesterol and triglyceride levels. The present study also reproduced the results of the previous clinical studies; three-month administration of indigestible dextrin reduced serum cholesterol and triglyceride levels significantly. Lack of change in HDL-cholesterol indicated that reduced total cholesterol levels could be attributed to reduced LDL- or VLDL-cholesterol levels. These results suggest that indigestible dextrin may suppress
insulin-related lipid release from the liver.

The present study included measurements of body weight, BMI, waist size, hip size, body fat percentage, and CT-measured subcutaneous and visceral fat area as measures for evaluating body type, body fat amount, and body fat distribution, and investigation on changes in these measures. As a result, a significant decrease in percent body fat was found in the whole population, with especially marked reduction in ten subjects who were determined as obesity based on percent body fat data before study. Fat accumulation is closely related with and insulin action, as described above; it is widely known that excessive fat accumulation causes adipose cell hypertrophy, then reducing the number of insulin receptors in adipose cells, inducing secretion of TNF-α, a cytokine that inhibits insulin, from the adipose cells, thus reducing the action of insulin markedly and eventually causing hyperinsulinemia. This condition is the very state of insulin resistance, which may trigger lifestyle-related diseases. In the present study, the sugar challenge tests before and after the test drink administration revealed that continuous administration of indigestible dextrin exhibited a significant improving effect on glucose tolerance in consistency with a study by Fujiwara et al. in patients with Type 2 diabetes. In the present study, ΣIRI (in μU/ml•2 hr) as an index of insulin resistance was 216.9±36.5 μU/ml•2 hr and 162.5±23.0 μU/ml•2 hr after three-month administration, a 25% decrease, with no significant difference. Similarly, the homeostasis model assessment (HOMA-r) value calculated from fasting blood glucose and insulin levels, another index of insulin resistance, was 2.09±0.50 before administration and 1.93±0.40 after three-month administration, again a decrease with no significant difference. These results suggest that improved glucose tolerance may reduce insulin secretion and thus visceral fat accumulation.

It has been reported that visceral fat accumulation is more likely to induce sugar and lipid metabolism modulation and greater insulin resistance than with subcutaneous fat accumulation. The possible mechanism of this may be that an increase in visceral fat creates greater flow of free fatty acids via portal system into the liver, which activates fat synthesis and induces insulin resistance. In light of this, the significant reduction in visceral fat accumulation by ingestion of indigestible dextrin can be beneficial to lifestyle-related disease prevention. It should also be noted that two of nine subjects showed an increase in visceral fat area, which was attributable to changes in dietary habits that were elucidated by a later interview. Although the present study without any strict diet survey could not identify the cause, dietary habits affect changes in body fat accumulation, whether positive or negative, and thus should be investigated adequately in further studies.

The present study used indigestible dextrin in 10 g packs as the test substance and left ingestion style to the individual subjects, so far as they ingested indigestible dextrin with each meal. The interview about usage showed that they dissolved the test substance in green tea and miso soup most often, and coffee or soup often; the majority of them selected what food they used for this purpose, depending on the cooking style (Japanese or Western). They individually did all things to ingest the test substance completely, for example, by sprinkling it on foods containing a large amount of water, such as stew and curry, and dissolving it in soup for udon, soba or Chinese noodles and eating the whole amount. The test substance, indigestible dextrin, is beneficial in that it is easy to add in various foods because of its high water solubility, ability to provide clear solution, and tastelessness. In the present study, these merits were used to the full, giving the subjects liberty to select the usage, which allowed them to continue to consume the test substance for three months without getting tired. This suggests that regardless of usage variation with the individual or day, the effectiveness of indigestible dextrin can be assured, if ingested with meal constantly. The indigestible dextrin used in the present study can be an essential adjuvant means for diet therapy for lifestyle-related disease prevention.

The authors will carry out investigation into effects of indigestible dextrin on lifestyle-related diseases, such as obesity, based on the findings of the present study.

References
1) Japanese
5) Nakamura T, Tokunaga K, Shimomura I,

6-18) Japanese


20) Japanese


24-26) Japanese


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