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Amelioration of abdominal obesity by low-molecular-weight polyphenol (Oligonol) from lychee

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ABSTRACT

The effect of low-molecular-weight polyphenols extracted from lychee (Oligonol) on metabolic syndrome characterized by abdominal obesity was examined. We performed a clinical trial for Oligonol conducted by randomized double-blind, placebo-controlled study. Eighteen (male, 14; female, 4) adult volunteers with abdominal circumference over 85 cm were enrolled and divided into two groups, Oligonol and placebo groups. All subjects took two capsules of Oligonol (50 mg/capsule) or placebo twice a day for 10 weeks. Physical and haematological examinations as well as a CT scan of the abdomen were carried out, before (control) and 10 weeks after Oligonol intake. Clinical parameters of body weight, abdominal circumference and visceral fat volume were significantly decreased in the Oligonol group compared to the control. Insulin resistance was improved by Oligonol in conjunction with elevation of serum adiponectin. These results suggest that Oligonol ameliorates metabolic syndrome by reducing visceral fat obesity.

1. Introduction

Polyphenols are categorized by the presence of phenolic acid derivatives, flavonoids, stilbenes, or ligands in their chemical structure (Harborne, 1988; Soobrattee et al., 2005). Fruits and leafy vegetables are rich sources of phenolic compounds such as flavonoids, and their extracts have been recognized to contain various kinds of functional elements having antioxidant, antibacterial, anti-inflammatory, anti-allergic, hepatoprotective, vasodilatory and neuroprotective actions (Middleton et al., 2000; Scalbert et al., 2005; Soobrattee et al., 2005, 2006). Polyphenols constitute a vital component of the plant defense system, protecting them from ultraviolet rays (Grace and Logan, 2000) and pathogens (Duzan et al., 2005). Polyphenol oligomers, which constitute a small portion of the total polyphenols in the plant, are responsible for these activities. However, as the fruit grows and ripens, the effective concentrations of their monomeric and oligomeric bioactive components eventually diminish to the point where only polymers with high molecular weights accumulate in the plant.

Recently, Oligonol, a unique low-molecular-weight polyphenol, was developed to enhance absorption of polyphenols from the intestines (Fujii et al., 2007). The low-molecular-weight polyphenol is a novel technological product derived from the oligomerization of polyphenols obtained from lychees. The patented process of oligomerization enables

Abbreviations: AC, abdominal circumference; BMI, body mass index; HOMA-IR, homeostasis model assessment insulin resistance; LPO, lipid peroxide; ROS, reactive oxygen species; SFA, subcutaneous fat area; SNP, single nucleotide polymorphism; TEAC, trolox equivalent antioxidant capacity; VFA, visceral fat area; WC, waist circumference.

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the production of Olignol, which is abundant with low-molecular-weight oligomers (Aruoma et al., 2006). Oligonol was approved as a new dietary ingredient by Food and Drug Administration (USA) in July, 2007 and is likely to be applied in a broad range of products, including pharmaceuticals, functional foods, and food and beverage supplements.

It has been reported that adipocytes generate reactive oxygen species (ROS), and that the increased oxidative stress in adipocytes might be a cause of obesity-associated metabolic syndrome (Furukawa et al., 2004). In fact, there are several reports which have shown evidence that polyphenols could improve obesity, lipid metabolism and glucose metabolism (Mohamed-Ali et al., 1998). (−)-Epigallocatechin-3-gallate (EGCG) treatment decreased visceral fat weight and attenuated insulin resistance in high-fat-fed mice (Bose et al., 2008), while cinnamon polyphenol extract was shown to regulate anti-inflammatory cytokine expression and glucose-transporter gene expression (Cao et al., 2008). Accordingly, it is conceivable that polyphenol intake could ameliorate lifestyle diseases exacerbated by dysregulation of glucose and lipid metabolism.

In this study, the potential effect of Oligonol for improvement of metabolic syndrome characterized by visceral fat obesity in conjunction with hypertension, dyslipidemia, and type-2 diabetes was assessed. The potential of this oligomerized polyphenol is also discussed.

2. Methods

2.1. Study subjects

Eligibility criteria included age 20 years or older, a determination of good health based on laboratory results, medical history and examination by a physician, and a body mass index (BMI) of 18–30 kg/m^2. Subjects were excluded from the study based on the following criteria: history of significant illness, recent gastrointestinal illness (e.g., diarrhea or other gastrointestinal tract illness within the last month), pregnancy, current use of any prescribed medication, use of any other supplements during the study, any diagnosed medical condition which might confound the evaluation of safety, and a history of severe allergic reactions to food. An adverse event was defined as any undesirable event that occurred to a subject during the course of the intervention.

Fifteen male (24–59 y.o.) and 4 female (40–59 y.o.) adult volunteers with abdominal circumferences (AC) over 85 cm were enrolled in this randomized double-blind, placebo-controlled study. At randomization, the 19 eligible subjects were randomly and blindly assigned to one of two treatment groups, Oligonol or placebo. All subjects took four Oligonol or starch-only placebo capsules (50 mg/capsule) daily for 10 weeks. Physical and haematological examinations as well as abdominal computer tomography (CT) scan were performed at baseline (0 week), and 5 weeks and 10 weeks after supplementation began.

All subjects were fully informed about this intervention study, and a written consent was obtained from each individual at the screening visit prior to any study-related activities. This study was approved by the local research ethics committee of the non-profit organization Tactics (Sapporo, Japan), and was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki.

2.2. Oligonol

Oligonol was obtained from Amino Up Chemical Co. Ltd. (Sapporo, Japan). Oligonol was prepared by oligomerizing the polyphenol polymers in lychee fruit-derived polyphenol. It contains 15.7% polyphenol monomer ((+)-catechin and (−)-epicatechin etc.) and 13.3% polyphenol dimer (procyanidin B2 ect.), while lychee fruit-derived polyphenol contains 6.4% polyphenol monomer and 9.9% polyphenol dimer. The process of Oligonol involves the extraction of powdered dried lychee fruit except seed with 80% (v/v) ethanol, subjecting the filtrate to a DIAION HP-20 column (Mitsubishi Chemical Holdings, Tokyo, Japan), washing the elute with H_2O, and evaporating to dryness yielding a dark brown powder consisting of a mixture of procyanidins. The mixture is combined with tea extract and citric acid in H_2O and heated at 60 °C for 48 h. The reaction mixture is filtered through a DIAION HP-20 column, washed with H_2O and eluted with 40% (v/v) ethanol. Evaporation of the elute yielded a reddish power, the oligomeric proanthocyanidin.

Supplementation of Oligonol for healthy human volunteers was carried out at doses of 100 mg/day and 400 mg/day for 92 days (Unpublished data). The data showed good bioavailability, and all the biochemical parameters were within the normal range, proving that Oligonol is safe for humans at more than 200 mg/day.

2.3. CT scan examination

For measurement of abdominal fat areas, skin fat and visceral fat at the navel level was measured by CT scan (Astein TSX-021B; Toshiba, Tokyo, Japan). Areas were analyzed by the computer software program, SlimVision (KGT, Tokyo, Japan).

2.4. Analysis of serum contents

Subjects fasted overnight, and blood samples were drawn before breakfast on days 0, 35, and 70 for haematological analysis, liver function, and renal function. The samples were separated immediately by centrifugation (1000*g*, 10 min) and were stored at −80 °C until use. Clinical diagnostics tests for alanine aminotransferase, cholesterol, blood urea nitrogen, and other biomarkers were carried out using a Roche/Hitachi 912 Chemistry Analyser (Roche Diagnostics, Mannheim, Germany).

2.5. Blood polyphenol concentration and antioxidant capacity

Bioavailability as well as antioxidant ability of Oligonol were assessed by methods described elsewhere (Thoss et al., 2002). In detail, the polyphenol content was measured on the basis of an oxidation-based assay (Prussian Blue assay). For deproteinization, 120 μl of serum were mixed with 40 μl of 60% perchloric acid, and extracted with 600 μl of *n*-buta-

nol for 10 s. After centrifugation at 15,000*g* for 10 min at 4 °C, a 200-μl aliquot of supernatant was dried up under a nitrogen gas purge for 15 min at 40 °C. Then, 1 ml of 0.1 M $FeCl_3$ was added, and the reaction was initiated by adding 80 μl of 10 mM $K_3[Fe(CN)_6]$. After incubation for 20 min at room temperature, the colour intensity was measured at 720 nm. Blood polyphenol concentration was calculated from a calibration curve prepared using catechin as a standard compound.

The TEAC assay was performed on the basis of the method described by Miller et al. (1993) with some modifications. In brief, 300 μl of 500 μM 2,2′-azinobis-(3-ethylbenzothiazoline-6-sulphonic acid) (ABTS), 36 μl of 70 μM metmyoglobin and 487 μl of 5 mM phosphate buffer (pH 7.4) were mixed before adding 10 μl of serum. The reaction was initiated by the addition of 167 μl of 450 μM hydrogen peroxide. The absorbance at 734 nm was measured following incubation for 15 min at room temperature (approximately 22 °C). Serum lipid peroxide (LPO) was evaluated using an LPO-Testwako assay kit (Wako Pure Chemical, Tokyo, Japan).

2.6. *Determination of serum cytokine levels*

Quantitative 'sandwich' enzyme-linked immunosorbent assays (ELISA) were performed for adiponectin, leptin, and resistin according to the manufacturer's protocol (Abnova, Taipei, Taiwan). Briefly, 100 μl of sample or standard solutions provided with the kit were added in duplicate to respective adipokine-antibody-coated wells. Then 50 μl of biotinylated antibody for each adipokine were added and incubated for 2 h at 25 °C. After the samples were washed, 100 μl of streptavidin-horseradish peroxidase working solution was added to each well and incubated for 30 min. The reaction was terminated with 100 μl of stop solution (1 M H_2SO_4). The absorbance at 450 nm was measured using an AutoReader (Snako, Model ER-8000, Tokyo, Japan).

We also measured serum levels of insulin, plaminogen activator inhibitor (PAI)-1, interleukin (IL)-6, and tumor necrosis factor (TNF)-α were measured by the Luminex 200 system (Luminex, Austin, TX) and analyzed by DNASIS Plex version 2 (Hitachi soft, Tokyo, Japan) according to the manufacturer's protocol.

2.7. *SNPs of adiponectin*

Adiponectin is the product of the ADIPOQ gene (Accession No. NT005612.15), which spans approximately 15.8 kB and three exons. The gene is considered to be profoundly involved in susceptibility for metabolic syndrome, particularly type-2 diabetes (Vionnet et al., 2000). In brief, the protein is secreted by adipocytes that regulate glucose and lipid metabolism. Adiponectin expression is regulated by a gene structure for which 12 SNPs (single nucleotide polymorphisms) have been identified. In particular, the exon 2-synonymous SNP45T/G and SNP276G/T in intron 2 have been identified to be associated with serum adiponectin levels (Menzaghi et al., 2002).

Genomic DNA extraction was performed from buccal epithelial cells using BuccalAmp DNA extraction kit (Epicentre Biotechnologies, Madison, WI). All subjects voluntarily agreed to undergo genotyping. Briefly, after rinsing out the subject's mouth twice with water, we collected tissue by rolling the collection swab firmly on the inside of the cheek. DNA was extracted according to the manufacturer's protocol, and the region harboring an SNP of interest was amplified by polymerase chain reaction (PCR) using each specific primer. Oligonucleotide sequences for detection of adiponectin gene SNPs for 45 were 5′-GTCTCTCCATGGCTGACAGT-3′ (forward), 5′-CGTGGTTTCCTGGTCATGAC-3′ (reverse 45T), and 5′-CGTGGTTTCCTGGTCATGCC-3′ (reverse 45G). The sequences for 276 were 5′-GTCTCTCCATGGCTGACAGT-3′ (forward), 5′-GGCCTTAGTTAATAATGAATGCC-3′ (reverse 276G) and 5′-GGCCTTAGTTAATAATGAATGAC-3′ (reverse 276T). The PCR product was directly sequenced with ABI310 DNA sequencer (Applied Biosystems, Darmstadt, Germany).

2.8. *Homa-IR*

Homeostasis model assessment insulin resistance (HOMA-IR) is a parameter for insulin resistance obtained by the equation HOMA-IR = Insulin (μU/ml) × fasting plasma glucose (FPG) (mg/dl)/405. Values below 1.6, from 1.6 to 2.5, and above 2.5 are defined as normal, marginal, and abnormal, respectively. We calculated HOMA-IR for each volunteer to assess the effect of Oligonol with respect to insulin resistance. The value was excluded when FPG was more than 140 mg/dl.

2.9. *Statistical analysis*

Averages and standard deviations of body weight and other parameters were calculated for each group. Statistical analyses were performed using Dr. SPSS II package software (SPSS Inc., Chicago, IL). Paired *t*-test was performed for the data with or without Oligonol intake. On the other hand, Mann–Whitney test or Student's *t*-test was individually conducted for pairwise comparisons between Oligonol group and control group, depending on heterogeneity or homogeneity in variance, respectively.

3. Results

3.1. *Effect of Oligonol on WC, SFA, and VFA*

Eighteen subjects (14 male, 4 female) completed the study except one female volunteer who complained of minor diarrhea. First, we found that waist circumference (WC) was significantly reduced, from 93.5 ± 11.0 cm to 90.7 ± 9.8 cm, by 10-week Oligonol intake ($P < 0.01$), whereas no significant change was found by placebo intake (Fig. 1A and B). In addition, subcutaneous fat area (SFA) and visceral fat area (VFA) were reduced from 169.3 ± 72.8 to 158.6 ± 65.9 cm^2 ($P < 0.05$), and from 80.5 ± 45.8 to 68.6 ± 36.5 cm^2 ($P < 0.05$), respectively, before and after Oligonol intake.

Furthermore, we analyzed the data with respect to percent changes of body weight (BW), BMI, abdominal circumference (AC) and WC; for all of these parameters, 10-week Oligonol intake caused statistically significant reduction (Fig. 2A). VFA was also reduced by Oligonol intake, whereas no significant reduction of SFA was observed (Fig. 2B).

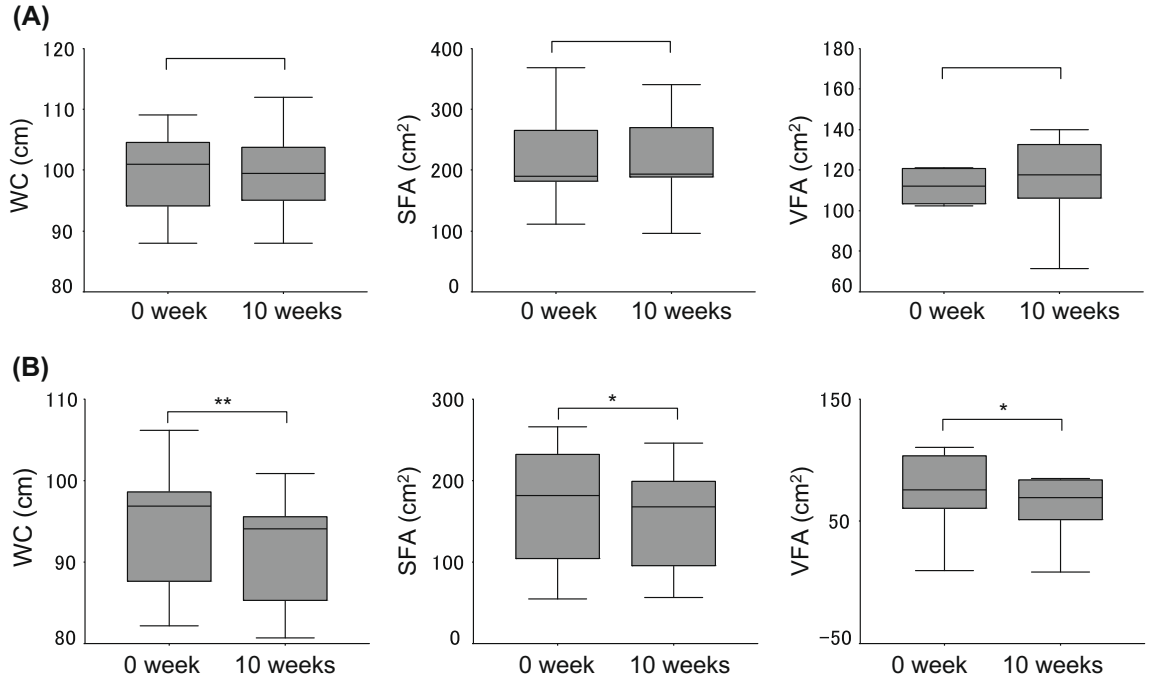

Fig. 1 – Effect of Oligonol on waist circumference, subcutaneous fat area, and visceral fat area. (A) Placebo (n = 8), (B) Oligonol (n = 10). WS, waist circumference: SFA, subcutaneous fat area: VFA, visceral fat area. Statistical analysis was performed by paired t-test. Data for 95th percentiles and median are shown. $^{**}P < 0.01$, $^{*}P < 0.05$ (0 week vs. 10 weeks).

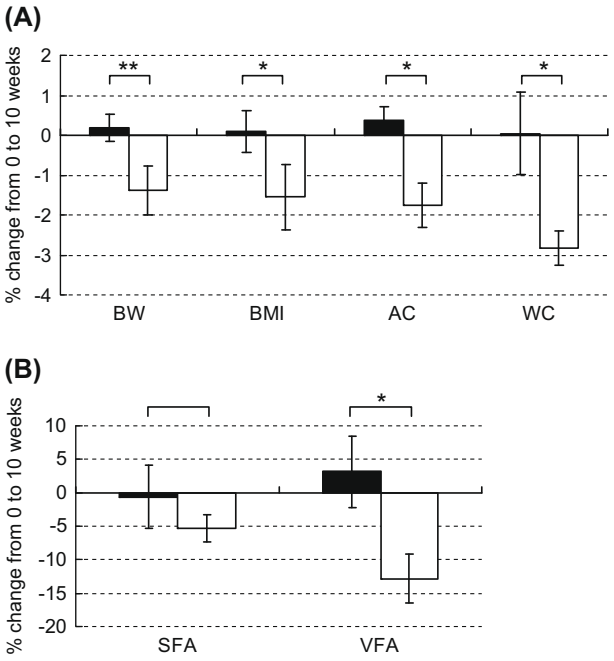

Fig. 2 – Percent change of parameters for obesity before and after 10-week Oligonol intake. (A) Body weight (BW), body mass index (BMI), abdominal circumference (AC), and waist circumference (WC). (B) Subcutaneous fat area (SFA) and visceral fat area (VFA). Closed column, placebo group (n = 8); open column, Oligonol group (n = 10). Values shown are mean ± SE. Statistical analysis was performed by unpaired t-test. $^{**}P < 0.01$, $^{*}P < 0.05$ (0 week vs. 10 weeks).

3.2. *Biochemical profiles of sera after Oligonol intake*

The biomarker levels of haematological tests, liver function, diabetic index, fasting blood glucose, lipid index and renal function parameters were examined. Parameters for liver function, e.g., aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transpeptidase (γ-GTP), and for renal function, e.g., blood urea nitrogen (BUN) and creatinin, showed minimal change by Oligonol intake. In a similar manner, we found no significant changes in lipid parameters, e.g., cholesterol. This result indicates that Oligonol causes no short-term unfavourable effect on those systems at the dose of 200 mg/day.

3.3. *Serum content of polyphenol and antioxidant activities*

The serum contents of antioxidant parameters, polyphenol, TEAC, and LPO were measured. In the group treated with 200 mg/day of Oligonol, a gradual increase in concentrations of polyphenol was observed, but it was not statistically significant (Fig. 3). These data suggest that there is no cumulative effect of Oligonol by long-term intake. Similarly, only a minimal difference in contents of TEAC or LP was seen between samples of the Oligonol-treated and placebo groups.

3.4. *Change of adipokines in response to Oligonol intake*

Adipose tissue is the major depot for energy storage and is an active endocrine organ, secreting a variety of cytokines that

influence metabolism (Ahima and Flier, 2000). We assessed serum contents of three adipokines, adiponectin, leptin, and resistin, before and at the end of 10 weeks of Oligonol intake (Fig. 4). The data showed up-regulation of adiponectin from 11.7 ± 1.3 μg/ml to 13.1 ± 1.7 μg/ml ($P = 0.054$). This result indicates that Oligonol may have the potential to stimulate adiponectin secretion. There was no significant difference before and after Oligonol supplementation for leptin or resistin. In addition, we found that serum levels of PAI-1, TNF-α, and IL-6 were not significantly affected by Oligonol intake (data not shown).

3.5. *SNPs of adiponectin*

Adiponectin is considered an insulin-sensitive protein in the muscle, and low serum levels characterize obesity and insulin resistance. Expression of adiponectin is regulated by nucleotide polymorphisms SNP45 and SNP276 (SNPs). Among the 8 subjects in the Oligonol group, 7 voluntarily agreed to have gene analysis, and we analyzed them for these SNPs. Subjects were clearly divided into two types of SNP45, namely SNP45T/T and SNP45G/G, so we examined the relationship between serum adiponectin level and SNP45. We did not carry out statistical analysis on SNP276 because of the low frequency of homogeneous alleles. Subjects with SNP45T/T ($n = 3$) showed a significantly higher serum adiponectin level than those with SNP45G/G ($n = 4$) (Fig. 5A). The average of SNP45T/T and SNP45G/G were changed from 11.4 ± 2.9 (average ± SE) to 13.9 ± 2.8 μg/ml, and from 10.0 ± 1.4 to 9.7 ± 1.6 μg/ml, respectively. We further assessed percent change of adiponectin due to Oligonol treatment for the two SNP45 haplotypes. Percent change of adiponectin was significantly greater with SNP45T/T (26.3 ± 9.7%) than with SNP45G/G (−1.1 ± 9.6%) (Fig. 5B and C). Although decrease of VFA was also observed in all subjects with either SNP45T/T (−14.3 ± 5.5%) or SNP45G/G (−12.9 ± 8.8%) by Oligonol, it is conceivable that Oligonol would increase the serum adiponectin level in subjects with SNP45T/T much more than in those with SNP45G/G.

3.6. *Homeostasis model assessment insulin resistance (HOMA-IR)*

HOMA-IR is a good clinical indicator to analyze insulin resistance. Thus, we examined the change of HOMA-IR before and

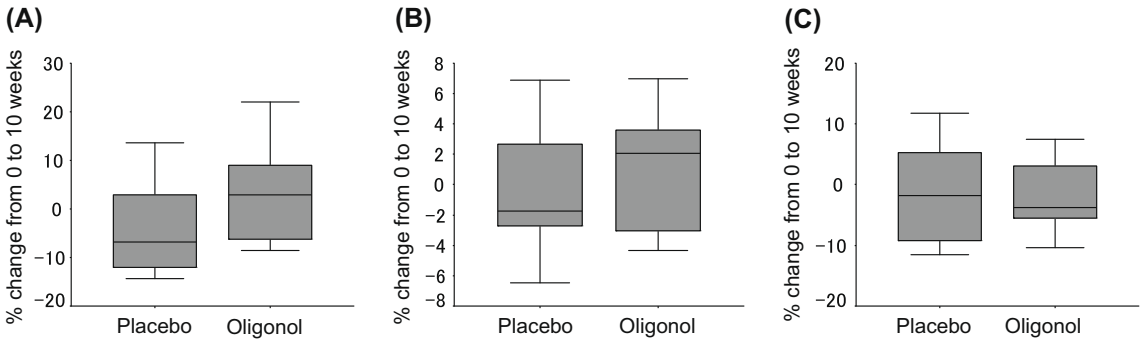

Fig. 3 – Effect of Oligonol on serum contents of polyphenol and antioxidant enzymes. Percent changes of polyphenol (A), TEAC (B), and LPO (C) after Oligonol intake are shown. Data for 95th percentiles and median are shown.

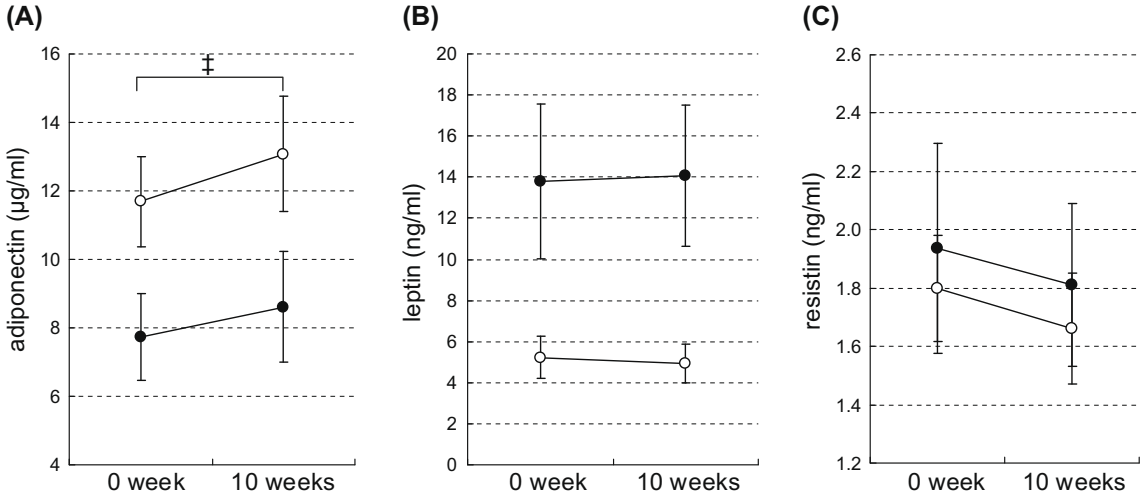

Fig. 4 – Change of adipokines in response to Oligonol intake. Values shown are mean ± SE. (A) Adiponectin, (B) leptin, and (C) resistin. Open circles, Oligonol group ($n = 8$); closed circles, placebo group ($n = 10$). Statistical analysis was carried out by paired *t*-test. ‡ $P = 0.052$.

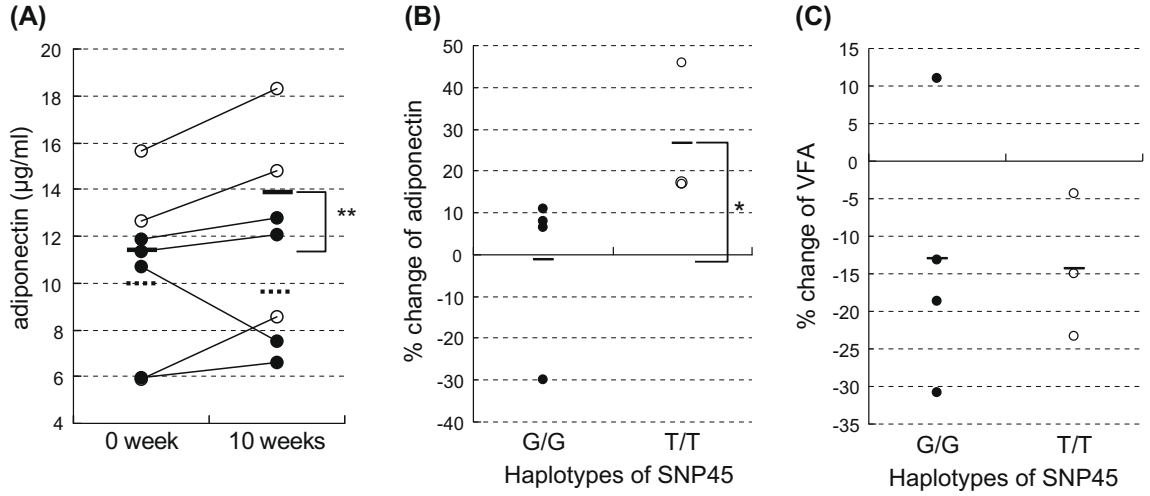

Fig. 5 – Serum adiponectin levels in response to Oligonol with regard to SNP45 (A). Open circles, levels for subjects with SNP45T/T alleles (n = 3); closed circles, those for subjects with SNP45G/G (n = 4). Horizontal and dot-horizontal bars indicate averages for SNP45T/T and SNP45G/G, respectively. Statistical analysis was performed by paired t-test. $^{**}P < 0.01$ (0 week vs. 10 weeks). Percent change of serum adiponectin (B) and VFA (C) in response to Oligonol with respect to SNP45. Horizontal bars indicate averages in each figure. Statistical analysis was performed by Mann–Whitney test. $^{*}P < 0.05$ (SNPS45G/G vs. SNPS45T/T).

after Oligonol intake to investigate its effect on insulin sensitivity. One subject was excluded because of a high FPG value. HOMA-IR was decreased from 2.4 ± 0.3 to 1.9 ± 0.2 ($P < 0.05$) in the Oliginol group, whereas the indicator in the placebo group was minimal (Fig. 6). These results suggest that Oligonol has the potential to improve insulin resistance.

4. Discussion

Dietary antioxidants and components of fruits and vegetables are suggested to have the capacity to modulate the pathogenic and clinical mechanisms of chronic diseases such as cardiovascular disease, diabetes, hypertension, immune disease, cancer and neurodegenerative disorders as well as the general aging process (Aruoma et al., 2005; Behl, 1999; Marchetti and Abbracchio, 2005; Soobrattee et al., 2005, 2006). Recently, Furuyashiki et al. (2004) reported that tea catechin and genistein, a soybean-derived polyphenol, inhibit adipocyte differentiation. This fact suggests that polyphenols can exert a regulatory effect on lipid metabolism. In this context, we examined the potential role of Oligonol, an antioxidant supplement, for the improvement of metabolic syndrome.

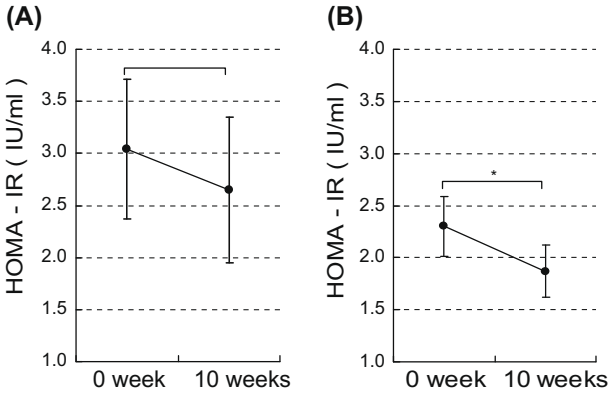

Fig. 6 – Changes of HOMA-IR before and after Oligonol intake. Homeostasis Model Assessment Insulin Resistance (HOMA-IR) was calculated using the equation described in Section 2. (A) Placebo (n = 8), (B) Oligonol (n = 10). Values shown are mean ± SE. Statistical analysis was performed by paired t-test. $^{*}P < 0.05$ (0 week vs. 10 weeks).

In this study, we demonstrated the effect of Oligonol on metabolic syndrome using clinical parameters characterized by abdominal visceral fat area and insulin resistance. We revealed that Oligonol reduced BMI and subcutaneous and visceral fat volumes, and improved insulin resistance. In particular, remarkable reduction of visceral fat areas was observed. These findings strongly indicate that Oligonol would be a beneficial supplement for prevention and improvement of metabolic syndrome, especially in the stage of hyperinsulinemia often seen during pre-diabetic conditions.

Oligonol is a lychee fruit-derived polyphenol converted into a low-molecular weight form by a novel manufacturing process (Fujii et al., 2007). It has been shown that Oligonol is readily absorbed from intestines, and has a strong antioxidative activity and ability to prevent photocarcinogenesis (Kundu et al., 2008). Regarding lipid metabolism and obesity, Oligonol promotes adiponectin production in rat visceral fat cells in conjunction with a reduction of triacylglycerol accumulation (Fujii et al., 2008).

To date, the mechanisms responsible for the biological activity of Oligonol have not been fully investigated. As for the intracellular mechanism, it was reported that transcriptional activity of NF-κβ and extracellular signal-regulated kinase (ERK1/2) were down-regulated (Furuyashiki et al., 2004). It is hypothesized that the monomeric catechin of Oligonol promotes energy consumption through direct interac-

tion with PPAR-α, which may lead to visceral fat loss. Although the mechanism of Oligonol's action needs to be investigated, it is evident that Oligonol acts on visceral fat cells and reduces fat volume.

It has been reported that reactive oxygen species produced by excessive amounts of adipose tissues cause up-regulation or down-regulation of a variety of adipokines (Mohamed-Ali et al., 1998). Dysregulation of adipokines may result in hypertension, dyslipidemia, and diabetes mellitus. We examined serum level of three adipokines, adiponectin, leptin, and resistin. As shown in Fig. 4, we found minimal changes in adipokine (leptin or resistin) levels; however, adiponectin appeared to be increased after Oligonol intake. It has been reported that adiponectin is inversely correlated with diabetic illness (Thompson et al., 1984). Adiponectin, the major adipocyte secretory protein, is one of several adipokines with roles in insulin sensitivity, suggesting the beneficial effect of Oligonol on insulin sensitivity.

Adiponectin levels have a strong genetic component, with heritability estimated to have between 30% and 50% influence with regard to obesity (Comussie et al., 2001). Adiponectin plays an important role in obesity, and this role has been frequently discussed in terms of specific SNP genotypes (Arita et al., 1999). Taking these reports into consideration, we examined the biological action of Oligonol with respect to the genotypes at the SNPs 45 and 276. Fig. 5 shows that our findings that Oligonol increased the serum content of adiponectin much more effectively for subjects possessing the T/T allele at SNP45. This fact suggests the possibility that there is a strong association of the 45 T/T allele with elevated adiponectin in response to Oligonol. It is of interest to investigate the mechanism by which Oligonol affects the circulating adiponectin at the molecular basis and thereby prevents the development of metabolic syndrome.

We here demonstrated that insulin resistance was improved by Oligonol intake as shown in Fig. 6. Dysregulated secretion of adipokines is considered to be a major factor in the development of metabolic syndrome. For example, TNF-α secretion in obese patients is increased (Kern et al., 2001), and increased secretion of TNF-α induces insulin resistance in adipocytes (Hotamisligil et al., 1993). Insulin resistance, which often precedes type-2 diabetes, is observed in metabolic syndrome. Several reports have shown that polyphenols are effective in improving insulin resistance. For example, polyphenol-rich extract from Aloe vera was shown to both decrease body weight and blood glucose levels in mice, and protect animals against unfavourable results of insulin resistance assessed by HOMA-IR (Perez et al., 2007).

It was reported that epigallocatechin gallate (EGCG), a bioactive polyphenol in green tea, augmented metabolic and vascular actions of insulin in a hypertensive rat model (SHR model) (Potenza et al., 2007). These facts suggest that polyphenols, including Oligonol, could improve metabolic syndrome by improving insulin sensitivity. The gene expression system associated with the insulin-signaling pathway, e.g. Ins1, Ins2, Irs1 and Irs2 needs to be searched in order to the molecular action of polyphenols for insulin resistance.

The antioxidant effects of Oligonol inhibited the increase of epididymal white adipose tissue mass induced by a high-fat diet and regulated the expression of genes for adipokines (Sakurai et al., 2008). Polyphenols restored dysregulated expression of adipokines in adipocytes, and that the absorption rate of polyphenol was important for their antioxidant effects in adipocytes. We observed little change in serum polyphenol levels even after intake of Oligonol. Although no significant difference in TEAC or LPO activity were observed in this study, Oligonol may work as an antioxidant supplement, even though its work is transient as demonstrated by the previous study in mice (Sakurai et al., 2008). It is assumed that polyphenols have preventative effects against obesity-induced metabolic syndrome, possibly through their antioxidant effects, even with only minimal changes of serum polyphenol levels or antioxidant activities.

Finally, polyphenol can be absorbed through the gastrointestinal tract. However, increases in serum concentrations of active metabolites of epicatechin achieved by dietary intake are slight due to rapid metabolism by enzymes from hosts and bacteria flora (communication with Dr. C. Keen, UC Davis). On the other hand, Oligonol is readily absorbed from the intestine without any serious side effects (Fujii et al., 2008), a promising characteristic for clinical use, especially for amelioration of visceral obesity. Taking all those facts into consideration, it is evident that the enhanced presence of oligomerized proanthocyanidins in Oligonol may offer a wide-range of benefits in pharmaceutical preparations, food products, and dietary supplements as well as in the development of functional beverages.

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