Study on the Effect of Porcine Placental Extract Ingestion on Symptoms of Late-onset Hypogonadism Syndrome in Middle-aged and Elderly Men

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INTRODUCTION

Age-related male hypogonadism decreases androgen secretion, inducing nonspecific somatic, psychological, and sexual symptoms. These symptoms are collectively referred to as late-onset hypogonadism (LOH) syndrome, which is also called male climacteric and has gradually been recognized by the public1).
Androgens have a number of significant physiological functions that influence the muscles, bones, central nervous system, prostate gland, bone marrow, and sexual function. Most LOH syndrome cases are attributed to blood androgen deficiency. Therefore, androgen replacement therapy is considered effective for treating LOH syndrome.

Meanwhile, androgen replacement therapy, which may accelerate the progression of prostate cancer or enlarge the prostate, is contraindicated for patients with prostate cancer or moderate-to-severe prostatic hyperplasia. Given that prostate diseases are common among middle-aged and elderly men, it is clinically meaningful to develop useful materials for improving LOH syndrome symptoms without affecting the blood androgen level.

Under these circumstances, we focused on the placental extract. As shown in a report on its anti-inflammatory, analgesic, antioxidative, anti-allergic, cell proliferation, and fibroblast proliferation effects as well as hormone-like effects, placental extract has been drawing attention for its broad functionality. In Chinese herbal medicine, it is called "Shikasha" and has been valued since ancient times due to its analeptic and anti-aging effects. In recent years, placental extract has been used as an active ingredient of injectable drugs indicated for improvement in hepatic function or climacteric disturbance. Porcine placental extract (PPE) is suggested to contain substances that inhibit androgenicity based on the results of an experiment on the inhibition of prostatic hyperplasia caused by exogenous testosterone. PPE ingestion has been reported to be effective for improving menopausal symptoms such as hot flushes, insomnia, depression, and frustration. Regardless of sex, PPE is also effective for treating locomotive syndrome.

This clinical study was conducted to evaluate PPE functionality in males, with a focus on LOH syndrome. Using a test food containing PPE, produced by degrading the porcine placenta with enzymes, the effect of 8-week ingestion of PPE on LOH syndrome was evaluated in this study. Besides assessment based on Aging Males' Symptoms (AMS) scores, hematological tests and other examinations were conducted, and the safety of repeated PPE ingestion was also evaluated.

### MATERIAL AND METHODS

#### Test food

The test food was gelatinous; each pack contained 1 g of PPE (JBP Placenta Jelly Pure®, Japan Bio Products Co., Ltd.). Besides PPE, the test food contained reduced starch syrup, mango puree, palatinose, agar, trehalose, acidulant, gelator (polysaccharide thickener), sweeteners (acesulfame potassium, sucralose), and flavoring agent.

PPE was produced by degrading the porcine placenta with enzymes. PPE contains proteins and amino acids, and is also thought to contain various other bioactive ingredients, although their chemical species have not been identified.

#### Study design

This study was designed as a multicenter, open-label, single-arm study. The study was conducted in compliance with the Declaration of Helsinki (adopted in 1964 and revised in 2000) in 15 subjects who were assessed by sub-investigators as eligible for the study and who voluntarily provided written informed consent after receiving a thorough explanation of the study from sub-investigators.

These subjects were required to daily ingest three packs of the test food (3 g of PPE in total). The timing of test food ingestion was not specified, and the subjects were allowed to take it at their convenience.

#### Eligibility criteria

Those who met all the following inclusion criteria and who did not meet any of the exclusion criteria were considered eligible for the study.

**Inclusion criteria**

1. Healthy men aged 40–84 years, with no serious disease
2. AMS score of at least 27
3. Capable of providing written informed consent for study participation

All the inclusion criteria were established to evaluate the safety and functionality of the test food appropriately.
Exclusion criteria
1) Those who may be allergic to any component of the test food
2) Those who have renal or hepatic disorder, depression, cancer, or any other serious disease
3) Those who have been on any supplements containing placental extract, turmeric, ornithine, or soy isoflavone
4) Those who started to take any Chinese herbal medicine within 2 months before providing informed consent. However, those who have been taking any Chinese herbal medicine for more than 2 months before providing informed consent are eligible if they continue taking the same medicine during the study period.
5) Those who are considered by the sub-investigator to be unsuitable for study participation

All the exclusion criteria were established to evaluate the safety and functionality of the test food appropriately.

Endpoints
The following endpoints were measured before the test food ingestion period (hereinafter referred to as baseline), Week 4, and Week 8 to evaluate the functionality and usefulness of the test food.

Primary endpoint
1) AMS score
   Heinemann’s AMS Questionnaire, translated into Japanese (tentatively translated by Sapporo Medical University), was used.

   The study used the AMS rating scale, which was developed by Heinemann et al., and is often used for the screening of LOH syndrome. The Heinemann Questionnaire, a self-administered questionnaire, consists of a total of 17 items: seven items of the somatic domain (items 1–5, 9, and 10); five items of the psychological domain (items 6–8, 11, and 13), and five items of the sexual domain (items 12 and 14–17) (Table 1). For each questionnaire item, subjects are required to rate the severity of an applicable symptom by choosing one of the following five options: “none,” “mild,” “moderate,” “severe,” and “extremely severe.” These options are scored 1–5, and a total AMS score is determined by summing up scores for the 17 questionnaire items. Based on the total AMS score, the severity of LOH syndrome in each subject is determined as “none” (17–26), “mild” (27–36), “moderate” (37–49), or “severe” (50–85). The Japanese

Table 1 Heinemann’s Questionnaire

| Somatic Score | 1 | Decline in your feeling of general well-being |
|---------------|---|---------------------------------------------|
|               | 2 | Joint pain and muscular ache                 |
|               | 3 | Excessive sweating                           |
|               | 4 | Sleep problems                               |
|               | 5 | Increased need for sleep, often feeling tired |
|               | 9 | Physical exhaustion / lacking vitality       |
|               | 10| Decrease in muscular strength                |
| Psychological Score | 6 | Irritability                                  |
|                   | 7 | Nervousness                                   |
|                   | 8 | Anxiety                                      |
|                   | 11| Depressive mood                              |
|                   | 13| Feeling burnt out, having hit rock-bottom    |
| Sexual Score     | 12| Feeling that you have passed your peak       |
|                   | 14| Decrease in beard growth                     |
|                   | 15| Decrease in ability/frequency to perform sexually |
|                   | 16| Decrease in the number of morning erections  |
|                   | 17| Decrease in sexual desire/libido             |
translation of the questionnaire is also available, and its reliability and validity have been evaluated 10.

Secondary endpoints
1) Vital signs (systolic blood pressure, diastolic blood pressure, and pulse rate)
2) Biochemistry tests (total testosterone, estradiol, aspartate aminotransferase [AST], alanine aminotransferase [ALT], urea nitrogen, creatinine, triglyceride, total cholesterol, LDL cholesterol, HDL cholesterol, casual blood glucose, hemoglobin A1c, high-sensitivity C-reactive protein [CRP])
3) Blood count (red blood cell, white blood cell, platelet, hematocrit, hemoglobin, hemoglobin concentration, mean corpuscular volume [MCV], mean corpuscular hemoglobin [MCH], mean cell hemoglobin concentration [MCHC])
4) Urinalysis (protein, glucose, occult blood, urobilinogen, bilirubin, ketone body)
5) Adverse events
6) PPE ingestion compliance

Ethics statement
The study protocol was reviewed and approved by the institutional review board of the Japanese Society for Complementary and Alternative Medicine on May 12, 2017 (Reg. No. 1704-01). Informed consent was submitted by all subjects when they were enrolled.

Statistical analysis
All data were expressed as mean ± standard error. A statistical analysis software, IBM SPSS Statistic Version 24, was used for statistical analysis, and significance was analyzed using Wilcoxon signed rank test for AMS scores and paired t-test for other endpoints. The significance level was set at 5% (two-sided). Multiplicity was not adjusted for time points. The significance level was not adjusted for multiple tests.

RESULTS

Subjects
Fifteen subjects were enrolled in the study and began ingesting the test food.

Fourteen subjects, excluding one subject who was withdrawn from the study due to surgery for acute cholecystitis caused by cholelithiasis, completed the study and were included in the analysis population.

The age and baseline AMS score of the analysis population were 62.6 ± 3.6 years (range, 40–84 years) and 44.0 ± 3.5 (range, 27–63), respectively.

AMS score
The AMS score was 44.0 ± 3.5 at baseline, 41.2 ± 2.5 (p = 0.451) at Week 4, and 34.6 ± 2.4 (p = 0.007) at Week 8 (Fig. 1). Although the AMS score at Week 4 was not significantly different from the baseline, the score at Week 8 was significantly lower than the baseline.

The AMS scale was divided into three subscales (somatic, psychological, and sexual), and the AMS scores for the respective subscales were analyzed. The somatic score was 18.8 ± 1.3 at baseline, 17.9 ± 1.2 (p = 0.656) at Week 4, and 14.1 ± 1.0 (p = 0.002) at Week 8, showing a significant decrease at Week 8, similar to the total AMS score (Fig. 2). No significant decrease from baseline was detected in the psychological or sexual scores.

Sexual hormones
Following an 8-week PPE ingestion, no significant change from the baseline was observed in the levels of total testosterone or estradiol (Table 2).

Laboratory tests
Following an 8-week PPE ingestion, no significant change from baseline was observed in the levels of AST, ALT, urea nitrogen, hemoglobin A1c, casual blood glucose, total cholesterol, HDL cholesterol, or high-sensitivity CRP (Table 3).

![Fig. 1 Changes in AMS score after porcine placental extract ingestion.](image-url)
Fig. 2 Changes in subscales of AMS score after porcine placental extract ingestion. (A) Somatic Score, (B) Psychological Score, (C) Sexual Function Score are shown.

Data are expressed as the mean ± standard error. ** p < 0.01, † p < 0.1 vs. Baseline

Table 2 Effect of serum sexual hormones after porcine placental extract ingestion

|                  | n  | Baseline  | 4W         | 8W         | p value (8W vs. Baseline) |
|------------------|----|-----------|------------|------------|--------------------------|
| Total testosterone (ng/mL) | 14 | 4.69 ± 0.40 | 4.88 ± 0.50 | 4.59 ± 0.41 | 0.820                   |
| Estradiol (pg/mL)  | 14 | 31.2 ± 4.8 | 32.3 ± 5.5 | 29.5 ± 5.6 | 0.586                   |

Data are expressed as mean ± standard error.

Table 3 Changes in blood biochemical endpoints after porcine placental extract ingestion

|                  | N  | Baseline  | 4W         | 8W         | p-value (8W vs. baseline) |
|------------------|----|-----------|------------|------------|----------------------------|
| AST (U/L)        | 14 | 23.5 ± 1.4 | 22.8 ± 1.0 | 26.6 ± 2.0 | 0.212                      |
| ALT (U/L)        | 14 | 24.6 ± 2.7 | 22.6 ± 1.6 | 25.4 ± 2.1 | 0.707                      |
| Creatinine (mg/dL) | 14 | 0.95 ± 0.05 | 0.94 ± 0.06 | 0.90 ± 0.05 | 0.003 **                 |
| Blood urea nitrogen (mg/dL) | 14 | 15.5 ± 0.9 | 16.0 ± 1.2 | 15.1 ± 0.9 | 0.496                      |
| Hemoglobin A1c (%) | 14 | 5.52 ± 0.10 | 5.56 ± 0.10 | 5.55 ± 0.09 | 0.414                      |
| Casual blood glucose (mg/dL) | 14 | 103.9 ± 4.8 | 107.6 ± 4.2 | 109.1 ± 7.4 | 0.488                      |
| Triglyceride (mg/dL) | 14 | 133.6 ± 24.0 | 131.4 ± 13.9 | 293.7 ± 110.3 | 0.157                      |
| Total cholesterol (mg/dL) | 14 | 206.0 ± 8.5 | 205.1 ± 8.7 | 200.1 ± 10.6 | 0.468                      |
| HDL cholesterol (mg/dL) | 14 | 58.9 ± 5.0 | 57.3 ± 3.9 | 54.3 ± 4.8 | 0.067                      |
| LDL cholesterol (mg/dL) | 14 | 122.1 ± 7.4 | 122.4 ± 7.7 | 106.1 ± 6.2 | 0.014 *                   |
| hs-CRP (ng/mL)    | 14 | 678 ± 238  | 656 ± 168  | 750 ± 220  | 0.812                      |

AST: aspartic aminotransferase, ALT: alanine aminotransferase, HDL: high-density lipoprotein, LDL: low-density lipoprotein, hs-CRP: high sensitivity C-reactive protein

Data are expressed as mean ± standard error. * p < 0.05, ** p < 0.01 vs. baseline.
While creatinine and LDL cholesterol levels decreased significantly from baseline at Week 8, no clinically significant changes were noted.

The mean triglyceride level was 133.6 ± 24.0 mg/dL at baseline, which markedly increased to 293.7 ± 110.3 mg/dL at Week 8. However, because the data varied widely, no significant difference was detected (p = 0.157).

**Adverse events**

While one subject was withdrawn from the study due to surgery for acute cholecystitis caused by cholelithiasis, this event was assessed as unrelated to the test food. No test food-related adverse events occurred.

**Ingestion compliance**

The test food ingestion compliance among the analysis population (n = 14) was as high as 98.9%.

**DISCUSSION**

In this study, PPE ingestion significantly decreased the AMS score. This result demonstrated that PPE improves LOH syndrome symptoms. Although there was no significant change in the AMS score at Week 4, an improvement in the score was confirmed at Week 8. Therefore, PPE was likely to improve LOH syndrome symptoms in a gradual manner. There was no significant change in sexual hormones (total testosterone and estradiol levels), suggesting that PPE ingestion has little effect on sexual hormone secretion. Given that LOH syndrome is mainly induced by androgen deficiency, PPE may improve LOH syndrome symptoms independently of androgens. Data from the subscale analyses showed a significant improvement in somatic scores. This result demonstrated that PPE has an effect on somatic function, as presented in another report showing that PPE ingestion had a beneficial effect on patients with locomotive syndrome. PPE can even be used in patients with prostate cancer or prostate-specific antigen level of ≥2.0 ng/mL, for whom androgen replacement therapy is contraindicated or should be carefully used. Therefore, PPE is expected to serve as a new LOH syndrome treatment option for these patients.

The biochemistry test results confirmed improved renal function. The resulting improvement in renal function possibly contributed to an improvement in sleep or fatigue. Furthermore, an improvement in LDL cholesterol levels was confirmed. Human Placental Extract has been confirmed to be effective in improving hepatic function. PPE also improves hepatic function; therefore, it is suggested that this function improved LDL cholesterol levels in this study.

However, because this study was exploratory, there were limitations to the study, including the fact that the effect of PPE was not compared with that of any control, such as a placebo and androgen replacement therapy. Therefore, an additional study may be performed in the near future to verify the effect of PPE on LOH syndrome.

**CONCLUSION**

Following PPE ingestion, a significant improvement in the AMS score was confirmed in addition to improved renal function and LDL cholesterol levels. These results demonstrated that PPE is effective for improving LOH syndrome symptoms in healthy middle-aged and elderly men.

**CONFLICTS OF INTEREST**

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要  旨

男性更年期症状を有する中高年男性に対するブタプラセンタエキス経口摂取の有用性の検討

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【目的】加齢男性性腺機能低下症候群（LOH 症候群）に対するブタプラセンタエキスの機能性を探索することを目的に、ブタプラセンタエキスを含有する試験食（JBP プラセンタゼリーピュア®、日本生物製剤）を用いて、介入群のみの単群オープン試験を実施した。併せて血液学的検査などで継続摂取に対する安全性を評価したので報告する。

【方法】AMS スコアが 27 点以上の軽度以上の LOH 症候群と判定される健常男性 15 人に、ブタプラセンタエキス 3 g を含有する試験食を毎日経口摂取するよう指示した。摂取前、摂取 4 週後、摂取 8 週後に AMS スコア、性ホルモン、生化学検査、血算、一般尿検査を行った。併せて摂取期間に発生した有害事象を集積した。

【結果】試験食と因果関係なしと判定された 1 名の脱落があったため、14 名を解析対象集団とした。被験者の年齢は 62.6±3.6 歳（40 ～ 84 歳）であった。AMS スコアは摂取前 44.0±3.5 に対し、摂取 4 週後は 41.2±2.5 (p = 0.451)，摂取 8 週後は 34.6±2.4 (p = 0.007) であり、摂取 8 週後で有意に低下した。

AMS スコアを「心理的因子」「身体的因子」「性機能因子」の 3 つのサブスケールに分けて解析した。身体的因子は摂取前 18.8±1.3 に対し、摂取 8 週後 14.1±1.0 (p = 0.002) と、総スコア同様摂取 8 週後で有意にスコアの低下がみられた。心理的因子、性機能因子でのスコアの有意な低下は見られなかった。摂取による性ホルモンの有意な変動はみられなかった。クレアチニン、LDL コレステロールの有意な低下がみられたが、その他の生化学検査、血算、一般尿検査も有意な変動はみられなかった。試験食の摂取との因果関係が疑われる有害事象の発生はなかった。

【結論】中高年男性における 8 週間のブタプラセンタエキスの経口摂取は、AMS スコアを有意に低下させたことから、LOH 症候群の諸症状の改善に対する機能性を有している可能性が示唆された。摂取 4 週後で有意な変化は見られなかったことは、プレコンセプトは LOH 症候群の諸症状に対し期待に用作用することを示唆している可能性がある。

キーワード：ブタプラセンタエキス、胎盤抽出物、LOH 症候群、AMS スコア、性ホルモン