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【 CASE REPORT 】

Secondary Hypogonadism due to Excessive Ingestion of Isoflavone in a Man

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Abstract:
A 54-year-old man had been drinking approximately 1.2 L of soy milk (equivalent to approximately 310 mg of isoflavones) per day for the previous 3 years. He then developed erectile dysfunction and gynecomastia. On an examination in our department in May, blood tests showed low gonadotropin and testosterone levels, indicative of secondary hypogonadism. He stopped drinking soy milk on his own in June of that year. When he was admitted in August, blood tests showed an improved gonadal function. Secondary hypogonadism caused by the excessive intake of isoflavones in soy milk was diagnosed. In men, an excessive intake of isoflavones may cause feminization and secondary hypogonadism.

Key words: male hypogonadism, feminizing effects, isoflavone, soy milk, endocrine disruptors

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Introduction

According to epidemiological studies, the consumption of soy isoflavones reduces the risk of a range of lifestyle-related diseases (1). Soy isoflavones increase insulin sensitivity and suppress the development of diabetes mellitus in postmenopausal women (2). Soy protein consumption is associated with reduced serum cholesterol levels (3). The long-term consumption of soy and soy products has been found to decrease the incidence of cardiovascular disease (4). In Asian women, soy isoflavone intake also reduces the risk of breast cancer (5).

Soy isoflavones are a type of flavonoids found in soy, particularly soy germ, and their forms include the three aglycones genistein, daidzein, and glycitein and their three respective glycosides genistin, daidzin, and glycitin, as well as the acetyl and malonyl forms of these glycosides (6). The isoflavones genistein and daidzein resemble 17-β-estradiol both structurally and functionally. Although they are less physiologically active than estradiol, they bind to estrogen receptor-α to exert an estrogen-like effect (7, 8). In men, the consumption of soy products causes a moderate decrease in serum testosterone levels (9), and gynecomastia and other manifestations of feminization as well as hypogonadism, associated with their excessive intake, have been reported in a few cases (10, 11).

However, in their literature review, Messina et al. concluded that feminizing effects are not observed in men who consume even a much larger amount of soy isoflavones than normal (12). Another meta-analysis similarly concluded that soy protein and isoflavone intake does not affect serum testosterone levels in men (13). The effect of excessive isoflavone intake in men is thus controversial.

In previous case reports, it was postulated that excessive intake of isoflavones may cause hypogonadism by affecting the metabolism of dehydroepiandrosterone or estrogen (10, 11), but the exact mechanisms, including the role of gonadotropins, are unclear. We herein report an adult man who developed secondary hypogonadism as a result of excessive isoflavone intake.

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Table 1. General and Endocrinological Laboratory Findings at Initial Visit to Our Hospital (May at Initial Visit).

WBC	5,220 /μL	Alb	3.8 g/dL	ACTH	7.3 pg/mL	[7.2-63.3]
RBC	418 $\times 10^4$/μL	Cre	0.81 mg/dL	Cortisol	17.6 μg/dL	[4.5-21.1]
Hb	12.6 g/dL	Na	139 mmol/L	TSH	2.710 μIU/mL	[0.50-5.0]
Ht	37.0 %	Cl	104 mmol/L	Free T3	2.84 pg/mL	[2.3-4.0]
Plt	25.0 $\times 10^4$/μL	K	4.4 mmol/L	Free T4	1.23 ng/dL	[0.9-1.7]
T-bil	0.4 mg/dL	Ca	9.1 mg/dL	GH	0.66 ng/mL	[<2.47]
AST	15 IU/L	Glucose	92 mg/dL	IGF-1	106 ng/mL	[84-239]
ALT	7 IU/L	T-chol	180 mg/dL	PRL	15.9 ng/mL	[3.6-12.8]
ALP	133 IU/L	HDL-chol	69 mg/dL	LH	<0.1 mIU/mL	[2.2-8.4]
LDH	140 IU/L	TG	134 mg/dL	FSH	0.1 mIU/mL	[2.0-8.3]
				DHEA-S	482 ng/mL	[480-2,860]
				Testosterone	12.6 ng/dL	[142.4-923.1]
				Free testosterone	1.0 pg/mL	[6.9-18.4]

ACTH: adrenocorticotropic hormone, TSH: thyroid stimulating hormone, GH: growth hormone, IGF-1: insulin-like growth factor-1, PRL: prolactin, LH: luteinizing hormone, FSH: follicle stimulating hormone, DHEA-S: dehydroepiandrosterone sulfate, [ ]: normal reference ranges

Case Report

The patient was a 54-year-old man. His medical history was unremarkable, with no delayed development of secondary sexual characteristics or slow physical growth in childhood and no history of head injury. There was also no family history of hypogonadism or endocrine disorders. He was unmarried, with no children. From three years ago, he had started restricting his carbohydrate intake with the intention of losing weight, and he was drinking approximately 1.2 L of soy milk per day. His weight had been 85 kg at that time. He subsequently noticed erectile dysfunction, and starting two years ago, he became aware of gynecomastia. Malaise and muscle weakness appeared around January (54 years old), and he visited a local physician in April that year. Serum luteinizing hormone (LH) and free testosterone (FT) levels were both low, and he was referred to our hospital in May, at which point his weight was 60 kg. Table 1 shows the laboratory findings. Endocrinological tests showed low levels of LH, follicle-stimulating hormone (FSH), testosterone (T), and FT, and secondary hypogonadism was suspected. The serum dehydroepiandrosterone sulfate (DHEA-S) level was within the normal range. He stopped drinking soy milk and restricting his carbohydrate intake on his own in June that year. He was then admitted in August for a further investigation.

On admission, his physical examination findings were as follows: height 169 cm, weight 61.0 kg, body mass index 21.4 kg/m^2, temperature 35.8°C, blood pressure 114/72 mmHg, and pulse rate 62 beats/min. Gynecomastia was evident but with no galactorrhea. There was moderate loss of axillary and pubic hair. His testicular volume measured with an orchidometer was normal at 14 mL.

Table 2 shows the laboratory findings. Hematological and general biochemistry tests were all normal. Endocrinological tests showed that although the LH level was within the normal range at 5.5 mIU/mL, the FSH level was high, at 16.4 mIU/mL. The T level was within the normal range at 401.8 ng/dL. The FT level was low at 4.4 pg/mL, but it had increased compared with its level at the initial examination in May. The estradiol level was low. Prolactin (PRL) and DHEA-S levels were within the normal ranges. Magnetic resonance imaging (MRI) of the pituitary gland was unremarkable.

In a combined pituitary stimulation test, the responses of LH, FSH, adrenocorticotropic hormone (ACTH), cortisol, thyroid-stimulating hormone (TSH), and PRL were all normal (Table 3A). In an insulin tolerance test, the responses of ACTH, cortisol, and growth hormone were all normal (Table 3B). In a human chorionic gonadotrophin stimulation test, both the T and FT levels had increased appreciably (Table 3C).

Although LH, FSH, T, and FT levels had all been markedly low at the initial examination in May, by the time the patient was admitted (August), their levels had increased appreciably. The various challenge tests had ruled out hypothalamic, pituitary, and primary hypogonadism. The patient had been consuming approximately 1.2 L of soy milk per day for around 3 years until he had stopped June. The estimated isoflavone content of this amount of soy milk was 310 mg/day, according to the nutrition facts label. He continued to avoid soy milk consumption after discharge.

As shown in Table 4, his LH and FSH levels increased further, and the FT level improved to within the normal range. His malaise, gynecomastia, and loss of axillary hair improved gradually within about six months, but his erectile dysfunction did not improve completely.

Discussion

Congenital causes of hypogonadism were excluded in this patient. He had no history of head injury, and pituitary MRI did not show a tumor or signs of inflammation. Blood tests

Table 2. General and Endocrinological Laboratory Findings on Admission (August on Admission).

WBC	5,040 /μL	TP	6.8 g/dL	ACTH	9.2 pg/mL	[7.2-63.3]
RBC	404 ×10⁴/μL	Alb	3.8 g/dL	Cortisol	7.2 μg/dL	[4.5-21.1]
Hb	13.5 g/dL	BUN	14.5 mg/dL	TSH	3.400 μIU/mL	[0.50-5.0]
Ht	35.5 %	UA	4.3 mg/dL	Free T3	3.34 pg/mL	[2.3-4.0]
Plt	21.9 ×10⁴/μL	Cre	0.75 mg/dL	Free T4	1.16 ng/dL	[0.9-1.7]
T-bil	0.3 mg/dL	Na	139 mmol/L	GH	0.61 ng/mL	[<2.47]
AST	17 IU/L	Cl	107 mmol/L	IGF-1	138 ng/mL	[84-239]
ALT	8 IU/L	K	4.4 mmol/L	PRL	11.9 ng/mL	[3.6-12.8]
ALP	117 IU/L	Ca	8.8 mg/dL	LH	5.5 mIU/mL	[2.2-8.4]
LDH	132 IU/L	Glucose	92 mg/dL	FSH	16.4 mIU/mL	[2.0-8.3]
γ-GTP	9 IU/L	HbA1c	5.7 %	Estradiol	<10.0 pg/mL	[15-35]
ChE	291 IU/L	T-chol	167 mg/dL	DHEA-S	482 ng/mL	[480-2,860]
CRP	0.10 mg/dL	HDL-chol	58 mg/dL	hCG	0.5 mIU/mL	[<3.0]
		TG	90 mg/dL	Testosterone	401.8 ng/dL	[142.4-923.1]
				Free testosterone	4.4 pg/mL	[6.9-18.4]

ACTH: adrenocorticotropic hormone, TSH: thyroid stimulating hormone, GH: growth hormone, IGF-1: insulin-like growth factor-1, PRL: prolactin, LH: luteinizing hormone, FSH: follicle stimulating hormone, DHEA-S: dehydroepiandrosterone sulfate, hCG: human chorionic gonadotropin, [ ]: normal reference ranges

Table 3. Endocrinological Examinations (August on Admission).

A. Combined pituitary stimulation test (intravenous loading of CRH 100 μg, TRH 0.5 mg and LH-RH 0.1 mg)

	0 min	30 min	60 min	90 min	120 min
LH (mIU/mL)	5.5	23.7	24.5	19.8	18.5
FSH (mIU/mL)	16.4	23.6	27.2	26.0	25.7
ACTH (pg/mL)	9.2	32.4	30.1	22.5	10.2
Cortisol (μg/dL)	7.2	16.1	19.1	20.4	17.3
TSH (μIU/mL)	1.08	20.68	16.55	11.76	8.45
PRL (ng/mL)	11.9	158.8	109.2	75.7	45.8

B. Insulin tolerance test (intravenous loading of regular insulin 6 units)

	0 min	30 min	60 min	90 min
Glucose (mg/dL)	91	39	62	73
ACTH (pg/mL)	11.0	30.3	116.0	39.4
Cortisol (μg/dL)	8.2	10.7	20.5	23.4
GH (ng/mL)	0.41	0.23	11.6	7.65

C. Human chorionic gonadotrophin (hCG) stimulation test (intramuscular injection of hCG 5,000 U, three consecutive days)

	Day 0	Day 3
LH (mIU/mL)	5.5	8.7
FSH (mIU/mL)	16.4	21.1
Testosterone (ng/dL)	401.8	666.6
Free testosterone (pg/mL)	4.4	10.0

CRH: corticotropin-releasing hormone, TRH: thyrotropin-releasing hormone, LH-RH: luteinizing hormone-releasing hormone, LH: luteinizing hormone, FSH: follicle stimulating hormone, ACTH: adrenocorticotropic hormone, TSH: thyroid stimulating hormone, PRL: prolactin, GH: growth hormone

were negative for hyperprolactinemia and systemic diseases. Secondary hypogonadism due to weight loss was deemed unlikely because his weight on admission (August) was comparable to that at the initial visit to our hospital (May). During the medical interview, the patient stated that he had been drinking approximately 1.2 L of soy milk per day for the past 3 years and that he had subsequently noticed erectile dysfunction and gynecomastia.

Blood tests at the initial examination in May showed markedly low LH, FSH, T, and FT levels. He stopped drink-

Table 4. Sequential Data for LH, FSH, Testosterone, and Free Testosterone.

	May	August	November	Next January
LH (mIU/mL)	<0.1	5.7	18.9	22.1
FSH (mIU/mL)	0.1	20.3	34.2	46.7
Testosterone (ng/dL)	12.6	401.8	565.6	560.1
Free testosterone (pg/mL)	1.0	4.4	7.7	11.1

The patient had been drinking approximately 1.2 L of soy milk per day from three years ago. He stopped drinking soy milk in June, and was admitted in August.

LH: luteinizing hormone, FSH: follicle stimulating hormone

ing soy milk in June, and by August (when he was admitted), the levels of these hormones had increased appreciably. Based on the increases in hormone levels after the patient stopped consuming soy milk, secondary hypogonadism due to excessive intake of isoflavones in soy milk was diagnosed. The main new finding is that the hypogonadism in this case was likely due to a decreased gonadotropin secretion, possibly due to the estrogen-like effect of isoflavones (7, 8, 14).

Isoflavones are found mainly in beans, with soy beans having a particularly high isoflavone content (1). The consumption of soy beans and soy products varies in different countries, but in Asia, soy beans are a popular legume, and their intake there is higher than in the United States or Western Europe. In East and South Asian countries, the isoflavone intake is around 20-50 mg/day on average, compared with only around 0.15-0.3 mg in the United States (1). The chemical structure of soy isoflavones resembles that of estrogen, and they exert an estrogen-like effect by binding to estrogen receptors (7, 8, 14). Several animal experiments have shown that isoflavone exposure causes blood testosterone levels to decrease (15, 16). Pan et al. reported that excessive isoflavone exposure causes erectile dysfunction in rats (17). Isoflavones are therefore considered to be endocrine disruptors of the human reproductive system (18). According to the Japanese government's Food Safety Commission, the maximum safe daily isoflavone intake is 70-75 mg/day (6). The Agence Française de Sécurité Sanitaire des Aliments has indicated that the highest isoflavone (aglycone equivalent) intake that is not considered to have any health risk is 1 mg/kg body weight/day (19).

Although some studies have found that isoflavone intake has no effect on feminization or gonadal hormones despite its estrogen-like effect in men (12, 13), several interventional studies and case reports have described feminization and hypogonadism due to excessive isoflavone intake. Because interventional studies by excessive administration of isoflavones are impossible due to safety concerns, the accumulation of spontaneous case reports is important. Gardner-Thorpe et al. found that men who ate soya flour (containing isoflavones 120 mg/day) for 6 weeks showed a moderate decrease in serum testosterone levels (from 19.30 nmol/L to 18.20 nmol/L) (9). Martinez et al. reported that a 60-year-old man who drank 2.8 L of soy milk per day (isoflavones 361 mg/day) developed gynecomastia, erectile dysfunction, and a diminished libido (10). Siepmann et al. reported that a 19-year-old man eating a vegan diet exhibited erectile dysfunction, a diminished libido, and a low FT level as a result of consuming isoflavones 360 mg/day for 1 year (11). The present patient's estimated isoflavone intake was 310 mg/day.

The duration of excessive isoflavone intake is also considered to be an important factor in the development of hypogonadism. A meta-analysis conducted by Hamilton-Reeves et al. concluded that isoflavones do not affect testosterone and other reproductive hormone levels in men (13). However, that meta-analysis had the limitation that the studies included were of short duration, with a mean study length of around 74 days. Although the duration of soy milk consumption was not reported in one of the case reports mentioned above (10), in the other (11), it was one year, and the present patient's estimated isoflavone intake had been 310 mg/day for around 3 years. This suggests that excessive isoflavone intake for a long period (a year or more) may affect the gonadal function.

Individual differences in the effects of soy isoflavones on the body may be due to differences in absorption and metabolism. In particular, there may be differences in the ability to produce equol, a metabolite of soy isoflavones (13, 20). The gut microbiota is believed to be involved in the mechanism of equol production (21). Equol producers may be more susceptible to the physiological action of isoflavones than equol nonproducers (22). The proportion of equol-producing individuals varies among races, but it is believed to be approximately 30-60% (21). It is conceivable that the present patient may have been an equol producer, and that this may have contributed to his isoflavone-induced hypogonadism, but we were unable to explore this possibility.

In one of the case reports (10), after discontinuing soy milk, the patient's breast tenderness resolved (other symptoms were not reported) and estradiol concentration slowly returned to normal after about one year. In the other report (11), after discontinuing soy products, the patient noted

a gradual improvement in symptoms (loss of libido and erectile dysfunction) and normalization of FT and estradiol within 12 months. In the present case, malaise, gynecomastia, and the loss of axillary hair improved gradually within about six months, but the erectile dysfunction did not improve completely. The reason for the persistent erectile dysfunction was unclear, but it may have been due to his being older than the patient in the previous report (11). A much longer duration may be necessary for the improvement of erectile dysfunction in older individuals.

In conclusion, this case report clearly shows that excessive isoflavone intake causes male secondary hypogonadism due to low gonadotropin levels. The mechanism underlying isoflavone-induced secondary hypogonadism in this patient may have involved the estrogen-like effect of isoflavones acting on the pituitary gland to suppress gonadotropin secretion (7, 8, 23). We consider both the amount and duration of isoflavone intake to affect the development of male hypogonadism. Isoflavones have many beneficial effects, including the prevention of atherosclerosis, but caution is required, as their excessive intake may cause hypogonadism and associated symptoms in men.

The authors state that they have no Conflict of Interest (COI).

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