Low serum zinc concentration is associated with low serum testosterone but not erectile function

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Abstract

Objective: To investigate the relation between serum zinc concentration and several factors, including serum testosterone concentration and the score of questionnaires on sexual function in patients with sexual problems.

Methods: This study comprised 720 men (age, 46.3 [21-83] years) with some kind of sexual problem. Age, scores of the Sexual Health Inventory for Men and the Erection Hardness Score, and endocrinologic data including serum concentrations of testosterone, prostate-specific antigen, and zinc were included in this study. After serum zinc concentration of the men was classified into 5 groups (<70, 70≤ <80, 80≤ <90, 90≤ <100, ≤100 μg/dL), the relation of each parameter with serum zinc concentration was assessed for a trend analysis. Finally, the relation between serum concentrations of zinc and testosterone as well sexual function evaluated by the scores of the questionnaires was investigated.

Results: Only serum testosterone concentration (Ptrend = 0.028) and serum cortisol concentration (Ptrend = 0.003) showed a statistically significant relation to serum zinc concentration by trend analysis. Interestingly, trend analysis between serum concentrations of testosterone and zinc still showed a significant association after adjustment for serum cortisol concentration (Ptrend = 0.032). However, no significant association was found in the relation between serum zinc concentration and the scores of the questionnaires after adjustment for serum concentrations of testosterone and cortisol.

Conclusion: We clearly showed that after adjustment for serum cortisol concentration by trend analysis, serum testosterone concentration decreased as serum zinc concentration decreased, although sexual symptoms were not associated with this

decrease.

Key words: serum cortisol concentration, serum testosterone concentration, serum zinc concentration, sexual dysfunction

Abbreviations & Acronyms

ED = erectile dysfunction

EHS = Erection Hardness Score

LOH = late-onset hypogonadism

PSA = prostate-specific antigen

SHIM = Sexual Health Inventory for Men

Introduction

There is no doubt that testosterone has been considered a key molecule not only in the male reproductive system but also in the anti-aging process of men because it plays many physiological roles in various organs and tissues such as skin, muscle, liver, bone and bone marrow, brain, and sexual organs. It is well known that serum testosterone decreases with aging. Thus, late-onset hypogonadism (LOH), defined as "a clinical and biochemical syndrome associated with advancing age and characterized by typical symptoms and a deficiency in serum testosterone levels," has gained increased attention in the field of public health. Indeed, low serum testosterone levels are known to be associated with increased mortality in male veterans.[1] Various symptoms of LOH are known such as diminished sexual desire and sexual dysfunction, depression, anxiety, anger and mood changes, decreases in intellectual activity and spatial orientation, fatigue, decreases in lean body mass and muscle volume, decrease in body hair and skin alterations, and decreased bone mineral density.[2,3] Among several symptoms, a large survey with a random population sample of 3369 men between the ages of 40 and 79 years showed only the three sexual symptoms of poor morning erection, low sexual desire, and erectile dysfunction (ED) to have a syndromic association with decreased testosterone levels.[4] Thus, it is no exaggeration to say that sexual function may be the key symptom of LOH. Furthermore, according to the report of World Health Statistics in 2021, Japan is the country with the longest life expectancy, which is 84.3 years. Although it is welcome news from the point of view of public health in Japan, we have, as a result, faced the national issue of an aging society that requires care and treatment for aging people, and which is also influenced by a low birth rate. Thus, the attempt to struggle against the aging process including sexual dysfunction is important and

meaningful in this aging society.

In Japan, zinc, one of the popular antioxidant elements, has been increasingly highlighted because of a fitness boom. In general, zinc is essential for physiological functions of the whole body, such as normal growth, DNA synthesis, cell division, gene expression, photochemical processes of vision, wound healing, ossification, and the immune system.[5] It is well known that zinc in seminal plasma is associated with the male reproductive system, especially sperm motility.[6-8] We also have recently reported that serum, but not seminal, zinc concentration is an independent factor for categorizing men with poor semen quality and seminal zinc.[9] However, the relation between serum zinc concentration and endocrinological factors, especially testosterone, has not been fully investigated yet. As zinc supplementation has gained more attention, the relation of the serum concentration of zinc with testosterone and sexual function has become more interesting and important.

In the present study, we investigated the relation between serum zinc concentration and several factors including serum testosterone concentration and the scores of questionnaires on sexual function in patients with sexual problems, such as ED, ejaculatory disorder, and decreased libido.

Methods

This study comprised 720 men who visited our hospital or affiliated clinic with some kind of sexual problem such as poor morning erection, low sexual desire, ED, or ejaculatory disorder between November 2014 and April 2018. Age and sexual symptoms assessed as scores evaluated by the Sexual Health Inventory for Men (SHIM) and the Erection Hardness Score (EHS) were included in this clinical study.

Endocrinologic data included total testosterone, dehydroepiandrosterone sulfate, cortisol, insulin-like growth factor 1, luteinizing hormone, follicle-stimulating hormone, and prolactin. Total testosterone, cortisol, insulin-like growth factor 1, and prolactin were measured by electrochemiluminescence immunoassay, whereas luteinizing hormone, follicle-stimulating hormone, and dehydroepiandrosterone sulfate were measured by chemiluminescent immunoassay. The serum concentrations of prostate-specific antigen (PSA) measured by electrochemiluminescence immunoassay and zinc measured by the colorimetric method were also assessed. All blood samples were collected between 09:00 and 11:00 to monitor endocrinological variables.

After classifying the men into five groups of serum zinc concentration (<70, $70 \leq <80$, $80 \leq <90$, $90 \leq <100$, ≤ 100 μg/dL), the relation of each parameter with serum zinc concentration was assessed by trend analysis. Finally, the relation between serum zinc concentration and serum testosterone concentration and sexual function as evaluated by the scores of the questionnaires was investigated.

This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines, and written informed consent was obtained from all subjects. The procedures were approved by the Regional Ethics Committee of Juntendo Urayasu Hospital, Urayasu, Japan (approval numbers: 2018-029 and 033) and D Clinic Tokyo.

Statistical analysis

Continuous variables and scores of the questionnaires are expressed as mean ± SD. The stepwise association between serum zinc concentration and each parameter was assessed using a trend analysis. Finally, a trend analysis between serum zinc

concentration and serum testosterone concentration was performed after adjustment for statistically significant factors identified by the previous trend analysis. A trend analysis between serum zinc concentration and the scores of the SHIM and EHS was also performed after adjustment for statistically significant factors identified by the original trend analysis. Statistical significance was set at $p < 0.05$. Statistical analyses were performed with SPSS version 24.0 (SPSS Inc., Chicago, IL, USA).

Results

The characteristics of the subjects are summarized in **Table 1**. Their mean age was 46.3 years (range, 21–83 years). On the basis of each patient's medical record entries, we excluded patients who had taken phosphodiesterase type 5 inhibitors, any kind of testosterone, 5-alpha reductase for benign prostatic hyperplasia or androgenetic alopecia, and zinc supplements. The mean scores of the SHIM and EHS questionnaires were 14.1 and 2.9, respectively. Based on the scores of the SHIM questionnaire, 275 patients (38.2%) corresponded to having mild (17–21), 158 patients (21.9%) to mild-to-moderate (12–16), 120 patients (16.7%) to moderate (8–11), and 167 patients (23.2%) to severe ED (1–7). None of the endocrinologic test values deviated from the reference values. The mean PSA concentration was 1.1 ng/mL, and the mean serum concentration of zinc was 90.1 μg/dL, which is within normal limits (80–130 μg/dL). Clinical characteristics of the association between serum concentration of zinc and age, questionnaire scores, endocrinological profiles, and PSA are shown in **Table 2**. Only serum concentrations of testosterone (Ptrend = 0.028) and cortisol (Ptrend = 0.003) were statistically significantly related to serum zinc concentration. This indicates that the serum concentration of testosterone decreased as the serum zinc concentration

decreased. Interestingly, a trend analysis between these factors after adjustment for serum cortisol concentration still showed a significant association (Ptrend = 0.032, **Figure 1**). However, no significant association was found in the relation between serum zinc concentration and the SHIM and EHS scores after adjustment for serum concentration of testosterone and cortisol (**Figure 2**).

Discussion

Zinc, which is the second most abundant trace element in humans, plays important physiological roles as a cofactor for many metalloenzymes contributing to DNA transcription and protein synthesis[10] and is also involved in immune function and cell division.[11,12] The relation between serum zinc concentration and endocrinological factors, especially testosterone, has been focused on for some time. It was first reported that a statistically significant positive correlation was found between serum zinc concentration and serum testosterone concentration in 25 men aged 36–60 years, although that positive correlation was not found in 15 men aged 28–35 years.[13] Another study with 4 normal young men aged 27.5 ± 0.5 years showed that dietary zinc restriction was significantly associated with a decrease in serum testosterone concentration after 8 and 20 weeks of zinc restriction.[14] A similar study reported that 11 volunteers who were fed a basal diet supplemented with zinc sulfate solution to supply a mean total of either 1.4 or 4.4 mg of zinc per day exhibited decreased serum testosterone concentration compared with when they were consuming 10.4 mg of zinc per day.[15] Conversely, the serum testosterone concentration increased after administration of zinc supplement for 3 months in 8 elderly men in that study.[14] The findings of these previous decades-old studies seem to indicate a close relation between

serum concentrations of zinc and testosterone, although the number of men included in the studies was very small. A recent randomized controlled study has already shown a significant increase in serum testosterone concentration by zinc supplementation compared to the control group with placebo, even though this study was performed only in postmenopausal women.[16] However, it was conversely reported that no relationship existed between serum testosterone concentration and the concentrations of metals, including zinc, in 313 men aged 50–75 years.[17] Thus, the relationship between serum zinc and testosterone remains inconclusive.

In the present study, we clearly showed a close relation between the serum concentrations of zinc and testosterone in this cross-sectional study with a large number of subjects. Indeed, after adjustment for serum cortisol concentration by a trend analysis it is apparent that serum testosterone concentration decreased as serum zinc concentration decreased. Several previous studies have shown that zinc deficiency is associated with hypogonadism in animals[18] and humans.[19] The mechanism behind why low serum zinc concentration induces decreased serum testosterone concentration is not fully apparent. A previous basic study with electron microscopy showed that zinc deficiency caused Leydig cells to become smaller and induced abnormalities in endoplasmic reticulum.[20] It was also found that zinc-deficient Leydig cells can take up cholesterol and neutral lipids but cannot convert them into sex steroids such as testosterone. Recently, it was reported that the zinc transporter family plays an important role in the maintenance of zinc homeostasis and in mediating intracellular signaling events. Among this family, it was reported in a mouse model that zinc transporter 7 was expressed and colocalized with steroidogenic acute regular protein in Leydig cells.[21] In that study, zinc transporter 7 expression was downregulated by a zinc-

deficient diet, which led to decreases in the expression of enzymes related to testosterone synthesis and decreased serum testosterone level.[21] Furthermore, it was clearly shown that gene silencing of zinc transporter 7 in Leydig cells downregulated the expression of steroidogenic acute regular protein and the enzymes related to testosterone synthesis.[21] Recently, a similar study reported on zinc transporter 8, which is located in Leydig cells and is upregulated by human chorionic gonadotropin administration, causing zinc accumulation in mitochondria.[22] In addition, gene silencing of zinc transporter 8 in the Leydig cells also inhibited testosterone production, reduced zinc accumulation, and downregulated the expression of steroidogenic acute regular protein.[22] Thus, the decreased function of this zinc transporter protein by a zinc-deficient diet would appear to be one of the mechanisms behind the correlation between the serum concentrations of zinc and testosterone.

There have also been several studies regarding the effect of zinc intake on testosterone production. One study with goats showed that serum testosterone concentration was increased by zinc intake in the goats' diet for 90 days, and the testosterone concentration was higher in the goats fed the diet supplemented with zinc compared with those fed a basal diet.[23] In humans, a study of hemodialyzed men with low serum zinc concentration and low sexual function showed dialytic administration of zinc increased serum testosterone concentration.[24] A double-blind study with hemodialyzed men also showed that intake of 50 mg of zinc per day for 6 months significantly increased serum concentrations of both testosterone and zinc in men in the zinc-treated group but not in those receiving a placebo.[25] A study with elite athletes showed that both resting and exhaustion testosterone levels were significantly increased by zinc supplementation (3 mg/kg/day) in addition to their normal diet for 4 weeks,

compared to the level measured before zinc supplementation.[26] Another study with cyclists supplemented with oral zinc for 4 weeks revealed that zinc supplementation with exercise may be effective to increase free testosterone.[27] Although we do not have data regarding the alteration of serum testosterone concentration by zinc intake, these previous studies encourage us to let patients with low serum testosterone concentration and low serum zinc concentration take zinc supplements. Our cross-sectional analysis of the relation between the serum concentration of testosterone and zinc has become the groundwork behind this theory. Furthermore, it is also clear that there was not much change in serum testosterone concentrations in the group with serum zinc concentrations above 100 μg/dL compared to the group with serum zinc concentrations above 90 μg/dL and below 100 μg/dL (Figure 1). Although it is unclear whether this is a threshold, these data would indicate at the very least that higher serum zinc concentrations do not necessarily lead to higher serum testosterone concentrations.

The present study also clearly showed that sexual symptoms evaluated by SHIM and EHS were not associated with serum zinc concentration. The study with hemodialyzed men showing increased serum testosterone concentration by dialytic administration of zinc also revealed striking improvement of erectile function in all patients.[24] Furthermore, a double-blind study with hemodialyzed men showing increased serum testosterone concentration by zinc intake also revealed an improvement in erectile function, libido, and frequency of intercourse in the patients receiving zinc, whereas no improvement was found in the placebo group.[25] Conversely, there is also a study showing no benefit from zinc intake compared with placebo in the treatment of uremic patients with ED.[28] Although it is well known that the pathogenesis of sexual function, especially ED, is multifactorial, it remains unclear which and how many

factors contribute the most to the severity of ED. Our findings indicate only that low serum zinc concentration was not directly associated with erectile function, even though the serum concentration of testosterone decreased.

The present study has some limitations. First, as mentioned, the pathogenesis of ED is multifactorial. Thus, several kinds of patients with ED might be included in the present study. Therefore, other factors such as obesity, biochemical profiles, blood pressure, diabetic factors, atherosclerotic factors, mental status, and the effects of drugs for other diseases and foods may have affected the results of our study. Second, low sexual desire must also influence the SHIM score, regardless of the serum zinc concentration. However, we did not determine the percentage of such patients. This patient population bias might have affected the outcome. Third, we did not include healthy volunteers without sexual symptoms. If we had included them in this study, the association between serum zinc concentration and the scores related to sexual symptoms might have changed. However, we could not include them because this was a clinical study performed with our outpatients in the real world. Fourth, we do not have data regarding the efficacy of zinc intake on testosterone production. Furthermore, conversely, we did not check whether testosterone replacement treatment can increase serum zinc concentration. Fifth, blood examination was conducted only once, although all blood samples were collected between 09:00 and 11:00. The serum concentrations of testosterone and zinc may depend on the physical condition of the patient at the time of examination. Despite these limitations, we believe that our finding that the serum concentration of testosterone decreases as that of zinc decreases should be valuable.

Disclosure

Conflict of interest

The authors declare no conflict of interest.

Ethical Approval

The procedures were approved by the Regional Ethics Committee of Juntendo Urayasu Hospital, Urayasu, Japan (approval number: 2018-029 and 033) and D Clinic Tokyo.

Informed Consent

All human subjects provided written informed consent with guarantees of confidentiality.

Registry of the study

N/A.

Animal Studies

N/A.

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Figure Legends

Fig. 1 Trend analysis between the serum concentrations of testosterone and zinc after adjustment for serum cortisol concentration. (Ptrend = 0.032).

Fig. 2 No significant association was found in the relation between serum zinc concentration and (**a**) the score of the Sexual Health Inventory for Men (SHIM) and (**b**) the Erection Hardness Score after adjustment for serum concentrations of testosterone and cortisol.

TABLE 1 Clinical characteristics of 720 patients with sexual dysfunction

Age (y)	46.3 ± 11.6	(21-81)
SHIM	14.1 ± 6.9	(1-25)
Mild	275 cases	(38.2%)
Mild to moderate	158 cases	(21.9%)
Moderate	120 cases	(16.7%)
Severe	167 cases	(23.2%)
EHS	2.9 ± 1.0	(0-4)
Testosterone (ng/mL)	5.1 ± 2.1	(0.4-25.1)
DHEA-S (µg/dL)	246.4 ± 117.0	(27.0-751.0)
Cortisol (µg/dL)	8.2 ± 3.2	(0.4-22.2)
IGF-1 (ng/mL)	139.9 ± 36.7	(50.0-296.0)
LH (mIU/mL)	3.7 ± 2.9	(0.1-39.3)
FSH (mIU/mL)	5.8 ± 5.0	(0.0-42.3)
Prolactin (ng/mL)	12.4 ± 9.5	(0.3-91.1)
PSA (ng/mL)	1.1 ± 0.9	(0.01-10.2)
Zinc (µg/dL)	90.1 ± 14.3	(52.0-151.0)

DHEA-S: dehydroepiandrosterone sulfate; EHS: Erection Hardness Score; IGF-1: insulin-like growth factor 1; PSA: prostate-specific antigen; SHIM: Sexual Health Inventory for Men.

TABLE 2 Clinical characteristics of the association between serum zinc level and age, questionnaire scores, endocrinological profiles, and PSA.

Serum zinc level (μg/dL)	<70	70≤ <80	80≤ <90	90≤ <100	≤100	
N	42	119	202	205	152	Ptrend
Age (y)	46.2 ± 10.8	48.3 ± 12.9	46.4 ± 11.6	46.0 ± 11.3	45.1 ± 11.2	0.290
SHIM	14.5 ± 7.7	13.6 ± 7.4	14.3 ± 6.6	14.5 ± 6.9	13.7 ± 6.9	0.842
EHS	2.9 ± 0.9	2.8 ± 1.0	3.0 ± 0.9	3.0 ± 1.0	2.8 ± 1.0	0.846
Testosterone (ng/mL)	4.6 ± 1.9	4.9 ± 2.1	5.2 ± 1.8	5.3 ± 2.5	5.2 ± 2.0	0.028
DHEA-S (μg/dL)	237.9 ± 105.4	270.3 ± 243.7	243.7 ± 124.8	235.8 ± 100.3	248.3 ± 125.1	0.751
Cortisol (μg/dL)	7.1 ± 2.5	8.1 ± 3.4	8.2 ± 3.4	8.0 ± 2.9	8.9 ± 3.3	0.003
IGF-1 (ng/mL)	138.5 ± 34.8	137.4 ± 36.7	140.0 ± 38.0	141.5 ± 35.2	139.6 ± 37.7	0.640
LH (mIU/mL)	3.3 ± 2.0	3.5 ± 2.3	3.9 ± 3.6	3.8 ± 2.7	3.5 ± 3.0	0.473
FSH (mIU/mL)	5.0 ± 3.2	5.5 ± 4.3	6.0 ± 5.2	6.3 ± 6.0	5.2 ± 4.1	0.565
Prolactin (ng/mL)	11.1 ± 7.0	12.6 ± 12.1	12.1 ± 9.3	12.5 ± 11.6	13.1 ± 8.7	0.279
PSA (ng/mL)	1.1 ± 0.8	1.1 ± 1.0	1.1 ± 1.0	1.1 ± 0.9	1.1 ± 0.8	0.944

DHEA-S: dehydroepiandrosterone sulfate; EHS: Erection Hardness Score; IGF-1: insulin-like growth factor 1; LH: luteinizing hormone; PSA: prostate-specific antigen; SHIM: Sexual Health Inventory for Men.

FIGURE 1

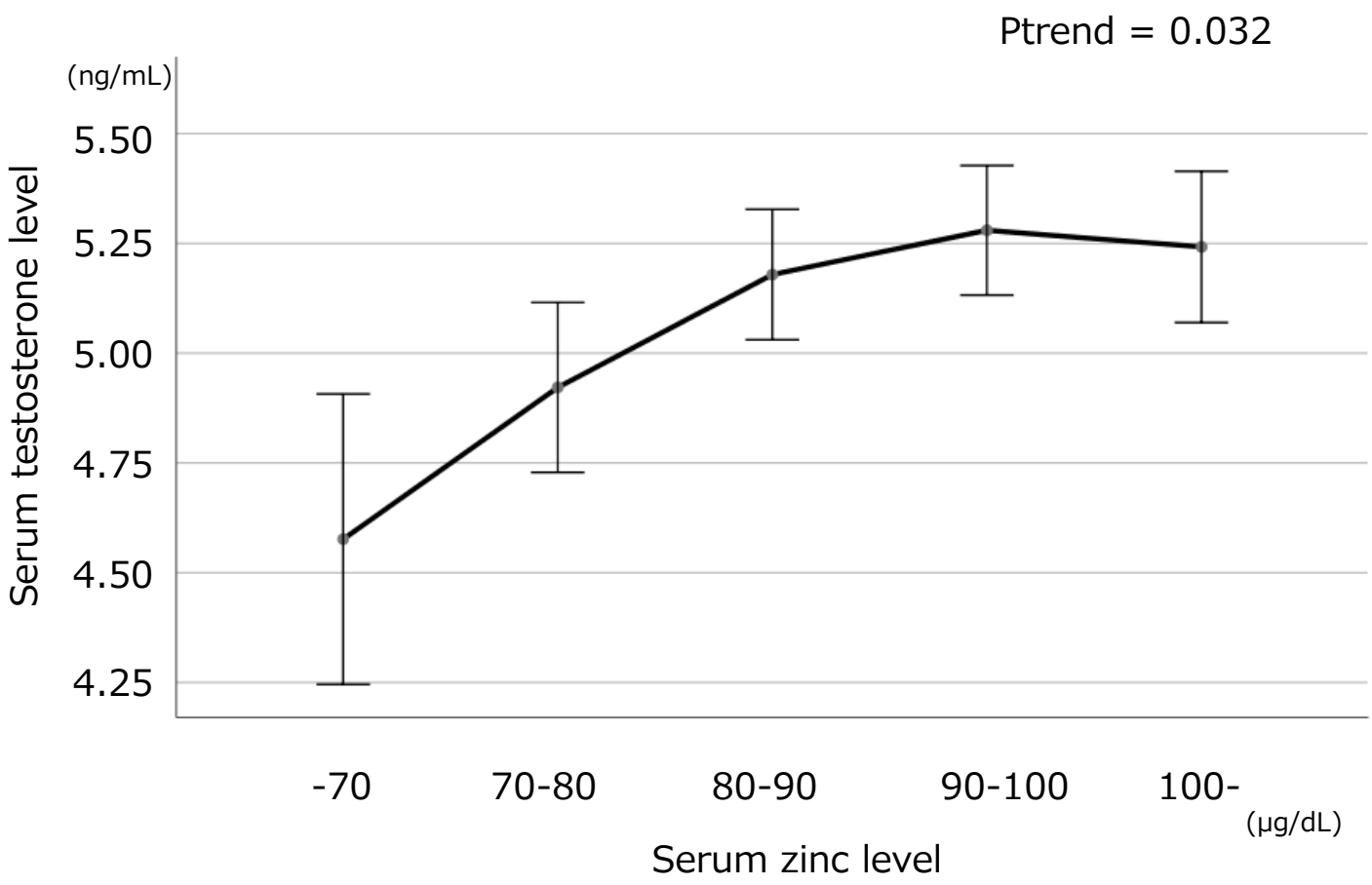
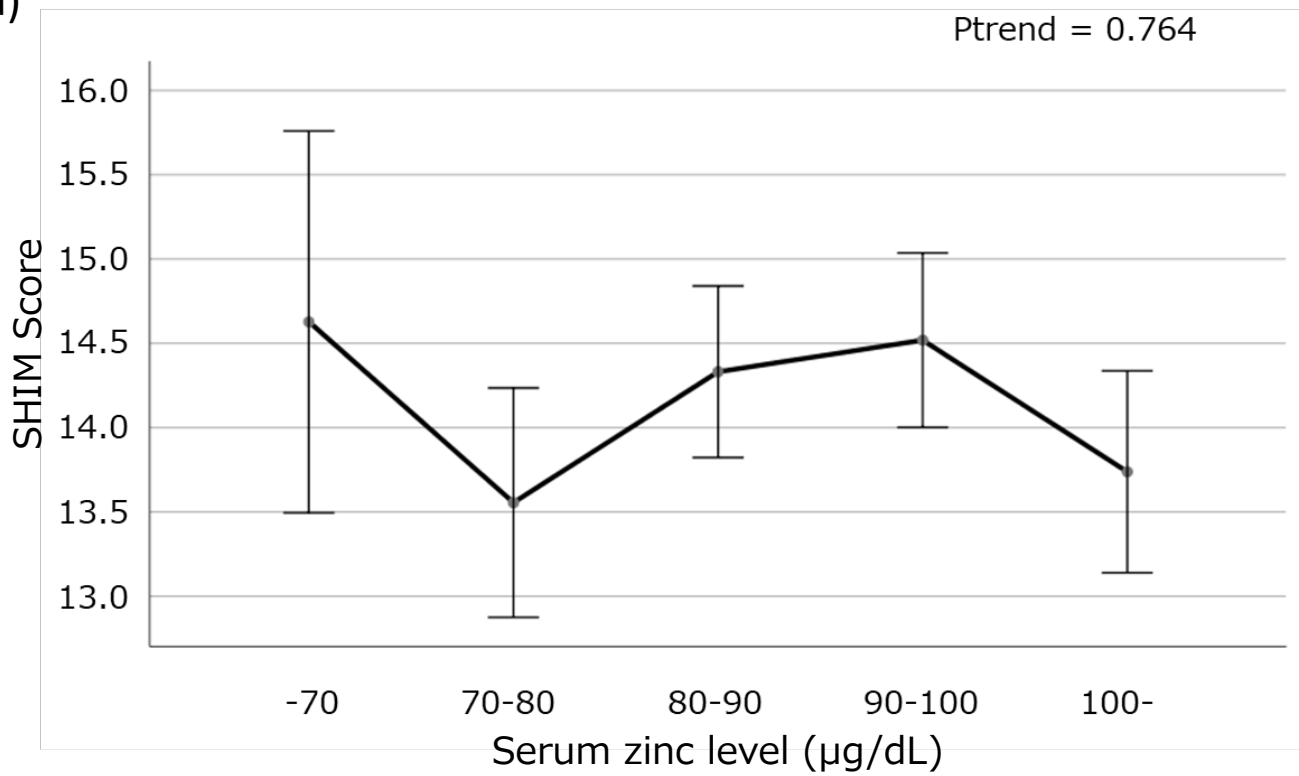
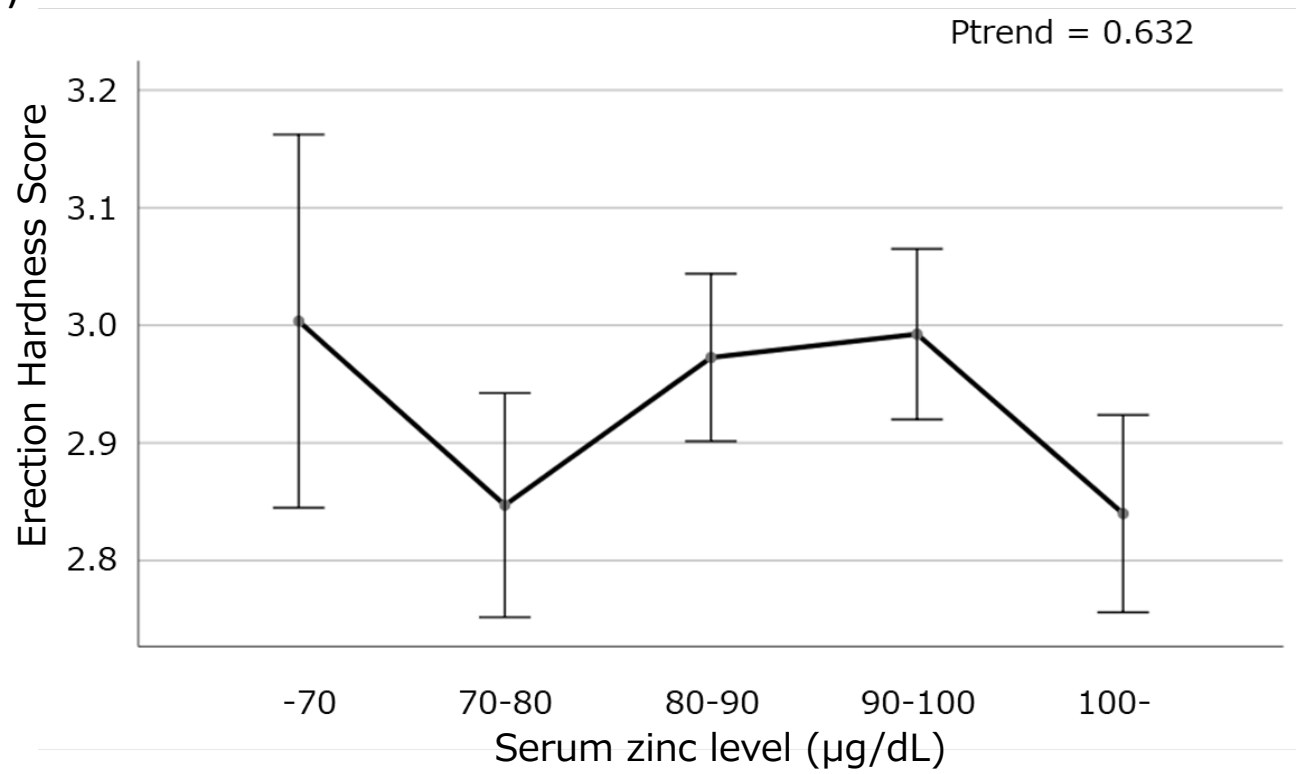

Ptrend = 0.032
(ng/mL)
5.50
5.25
5.00
4.75
4.50
4.25
Serum testosterone level
-70
70-80
80-90
90-100
100-
(μg/dL)
Serum zinc level

FIGURE 2

a)


Ptrend = 0.764
SHIM Score
16.0
15.5
15.0
14.5
14.0
13.5
13.0
-70
70-80
80-90
90-100
100-
Serum zinc level (μg/dL)

b)


Ptrend = 0.632
Erection Hardness Score
3.2
3.1
3.0
2.9
2.8
-70
70-80
80-90
90-100
100-
Serum zinc level (μg/dL)