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Zinc is essential not just for the surgery but for the periods before and after surgery

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Abstract

Zinc deficiency is associated with delayed bone healing, skin fragility, and susceptibility to infection due to immunodepression, therefore it has a significant impact on surgical outcomes. The author first became interested in the mechanism of bone healing in a case where an ankle fracture in a dialysis patient did not heal after three operations, and a zinc wave was later found in electron microscopy and electron probe X-ray microanalysis of frozen sections of the ossified area of the yellow ligament. Subsequently, shoulder injections to a rheumatoid arthritis patient caused pyogenic arthritis, suggesting that low zinc levels in rheumatoid arthritis patients resulted in weak skin and a low skin tenderness threshold. Later analysis showed that patients with zinc levels below 50 μg/dL died early due to infections, suggesting that low zinc levels are also related to poor immunity.

Two groups were compared after 2 months and after 6 months of supplementation with 34 mg/day of zinc to examine how much zinc should be supplemented by the time of joint replacement surgery. There was no significant difference in zinc levels in the two groups at 1 month before surgery, but at 7 days before surgery and 3 days after surgery, in the first group zinc levels were significantly lower, skin necrosis occurred in three cases, and skin healing was delayed in four cases.

If there is concern about the patient's preoperative condition, it is recommended that zinc levels be measured and that adequate zinc supplementation be performed before surgery.

Key words: zinc, immunity, arthroplasty, objective face scale, rheumatoid arthritis, nutritional support team

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1. Introduction

The human body contains about 2 grams of zinc, an essential trace metal, and the hippocampus and cerebral cortex in the brain contain high concentrations of nearly 100 ppm. Other organs in the human body that contain large amounts of zinc are bones (about 60%) and muscles (about 30%). Therefore, zinc seems to be an important element for orthopedic surgeons who deal with bones and muscles. Furthermore, since there is a negative correlation between grip strength and the ratio of copper to zinc levels [1], the need to maintain high zinc levels to prevent skeletal muscle weakness is now well known to many doctors.

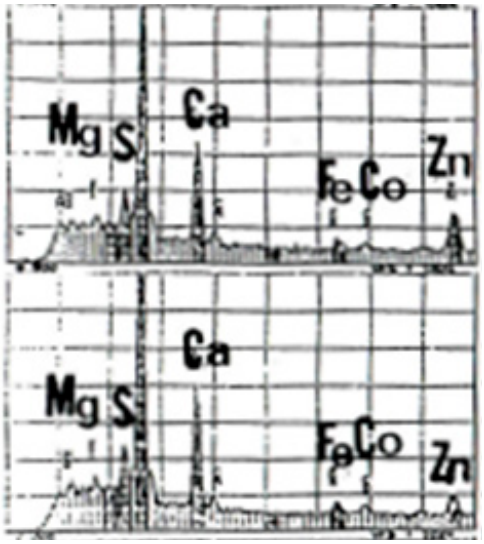

Fig. 1. Electron microscopic micro-Xray analysis of frozen sections of lumbar ligamentum flavum to detect zinc waves.

Recently, it has become clear that zinc is also involved in immunity to prevent infections [2-5]. Since bones are intractable when infected, zinc is an important element. Zinc levels in preoperative patients are important for orthopedic surgeons, but I will discuss why other surgeons should also pay attention to preoperative and postoperative zinc levels.

2. Zinc and Ossification

The ossification and bone repair mechanisms are important in orthopedic surgery. Early in my career I saw another doctor operate three times on a dialysis patient with an ankle joint fracture. The third operation included bone grafting from the pelvis and plate fixation, but the bone did not heal. This is the reason why I became interested in the ossification mechanism. It is now clear that in patients with severe renal failure, such as those on dialysis, intestinal absorption of zinc is poor and serum zinc levels are low [6], and that low serum zinc levels worsen osteoblast function [7].

In 1993, Nakamura reported that serum osteocalcin level significantly increased from 15.3±2.2 to 24.2±2.3 (p<0.01) after 6 months of zinc administration [8]. The increase in serum zinc levels increases ALP, IGF, and osteocalcin, which are favorable for bone formation.

In the 1980s, research on ossification of the posterior longitudinal ligament and yellow ligament of the spine began. I was also interested in the microstructure of endochondral ossification because of the poor bone healing in dialysis patients, and began to examine the ossified area of the end of the bone stem in mice and the ossified area of the lumbar yellow ligament in humans using an electron microscope [9]. In 1991, when frozen sections of human yellow ligament ossification were placed on a carbon grid and subjected to electron microscopy and electron probe X-ray microanalysis, zinc waves were detected (**Fig. 1**). Zinc waves were found in the tide mark of the ossification of the ligamentum flavum in the area of the mesenchymal cell osteoblasts. At that time, zinc in the ligamentous ossification area coexisted with calcium, magnesium, iron, and cobalt, and was thought to be derived from matrix vesicles.

According to Arizumi, in osteoblasts on a high-zinc diet, the Golgi and endoplasmic reticulum around the nucleus are well developed, as seen electron microscopically [10]. This is consistent with an increase in zinc in this region. The involvement of zinc in ossification is evident from the fact that Xia in 2002 found by atom microscopy many osteoblasts in the tibial metaphysis of rats on a high-zinc diet [11].

3. Skin fragility, immunocompromise and serum zinc level in rheumatoid arthritis patients

Working at a hospital in Nagano Prefecture, I have had the opportunity to see many patients with rheumatoid arthritis. For the first time in my career as a doctor I saw a case of a hospitalized rheumatoid arthritis patient, Case I, who developed pyogenic arthritis, even though my supervisor asked me to give him a shoulder joint injection and I did so with care. When I went to apologize to my supervisor, he said, “Oh, it happens all the time.” When I paid attention to the patient's general condition to find

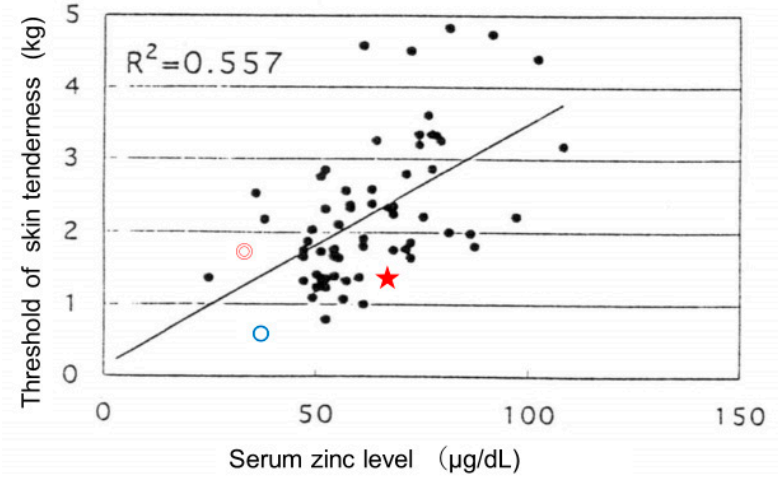

Fig. 2. Relationship between serum zinc level and mean skin tenderness threshold of both lower legs in rheumatoid arthritis patients. "red double circle": case 4; "blue circle": case 2; "red star": rheumatoid arthritis patient with diabetes between left TKA and right TKA

out what was causing the frequent infections in rheumatoid arthritis, I noticed that the patient's skin was as thin as cellophane. Furthermore, the epidermis sometimes peeled off easily with minor external force, and the patient's arms and lower legs were sometimes wrapped in cotton bandages to protect the skin. Based on my clinical experience of using zinc oxide ointment to treat dermatitis in babies with weak skin and rashes, I wondered if serum zinc levels were low in patients with fragile skin. First, I measured the zinc level of the patient with pyogenic shoulder arthritis. The zinc level was 33 μg/dL, which is very low ("red double circle" in **Fig. 2**: case 2 in **Table 1**) [12].

Thinking that the zinc levels of other rheumatoid arthritis patients with fragile skin might also be low, I measured the zinc levels of 66 patients (as volunteers) during the period from March 1998 to August 1999. The mean value was 63 μg/dL, which is a similar level to the mean value of 66 μg/dL (54-86 μg/dL) [13] in RA patients published by Kawate (2018) and much lower than the mean serum zinc level of 86 μg/dL found in 113 RA patients in 1975 by Kennedy et al. [14] The 26 patients with low serum zinc levels are shown in **Table 1**.

Reasons for the low zinc levels in Japanese rheumatoid arthritis patients may be that the zinc content in Japanese food is decreasing, and the absorption in the small intestine is impaired as a result of the shortening of intestinal villi due to heavy medicine use. A third possible cause is the increased use of electronic devices, less sleep time, and a stressed society, which is thought to have increased wear and tear on the liver, brain, and other parts of the body.

At the same time as measuring zinc levels in rheumatoid arthritis patients, I measured the mean skin tenderness thresholds of both forearms and both lower legs as criteria for skin fragility. The mean values of the skin tenderness thresholds of both lower legs were more strongly correlated to serum zinc levels, so they were graphed, and it was found that the patients whose lower leg skin was more vulnerable to pain had lower zinc levels (**Fig. 2**).

Table 2 sorts patients into Group A with zinc levels of less than 70 and Group B with zinc levels of 70 or more, based on Harrison's Internal Medicine, 17th edition [18] which defines zinc levels of less than 70 μg/dL (12 μmol/L) as zinc deficiency. The zinc level in group A was 52.5±9.3 μg/dL and that in group B was 81.0±10.6 μg/dL.

In the case of a 65-year-old woman, Case II (Case 4 in **Table 1**, indicated by a blue circle in the graph in **Fig. 2**), MRSA and Streptococcus pneumoniae were detected in her sputum and pharynx while she was waiting for artificial joint surgery. In April 1999, she developed skin fragility and skin rash on her thighs and lower legs. The serum zinc level was 37 μg/dL. She had an objective face scale of 17. Serum copper level was 91 μg/dL. The mean skin tenderness threshold on both lower legs was 0.63 kg, much lower than 4.02±1.84 kg in 62 healthy subjects. She was treated with oral polaprezinc (34 mg of zinc per day), but died of hematemesis caused by gastric ulcer 4 months after the zinc level was tested.

Case I (Case 2 in **Table 1**, indicated with a red double circle in **Fig. 2**), the 71-year-old patient [15] who had pyogenic shoulder arthritis, and the first patient I measured zinc levels for, was cured of the infection with intravenous antibiotics. The objective face scale was 18. Eventually, after 3 months of polaprezinc (34 mg of zinc per day) and 2 consecutive weeks of intravenous

Table 1. | Subjective face scale in rheumatoid arthritis patients with low serum zinc levels and cause of death in 13 patients

case	serum zinc	age	sex	face scale	cause of death	case	serum zinc	age	sex	face scale	alive or dead
	(μg/dL)						(μg/dL)				10 years later
1	25	64	F	17	pneumoia	14	51	49	F	10	alive
2	33	71	F	18	rupture of intestinse	15	51	76	F	13	alive
3	36	62	F	16	pneumonia	16	52	76	F	12	alive
4	37	65	F	17	bleeding from a stomach ulcer	17	52	69	F	10	alive
5	38	56	F	16	pneumoia	18	52	58	F	10	alive
6	47	50	F	12	pyelonephritis	19	52	68	F	11	alive
7	47	71	F	13	pneumonia	20	52	78	M	15	alive
8	47	56	F	14	pneumonia	21	54	72	F	11	alive
9	48	69	F	14	pneumonia	22	54	69	F	10	alive
10	49	59	F	13	pneumonia	23	54	63	F	10	alive
11	49	72	F	14	pneumonia	24	55	43	F	8	alive
12	50	51	F	13	pneumonia	25	55	61	F	10	alive
13	50	68	F	11	sepsis due to diabetes	26	56	78	F	9	alive
Avg.	42.8	63		14.5		Adv.	53.1	66		10.7	
SD	8	7.3		2.1		SD	1.7	11		1.8	

Table 2. | Skin tenderness threshold of group A with serum zinc level less than 70 and group B with serum zinc level more than 70 μg/dL

	Group A	Group B	Mann Whiteney U test
Zinc (μg/dL)	52.3 ± 9.3	81.0 ± 10.6	$p < 0.001$
GOT (IU/L)	20.2 ± 7.5	22.7 ± 10.6	N.S.
LDH (IU/L)	223 ± 54	210 ± 48	N.S.
CRP (mg/dL)	1.80 ± 1.80	2.00 ± 2.23	N.S.
Threshold for tenderness			
of forearm skin (kg)	1.68 ± 0.67	2.50 ± 0.96	$p < 0.01$
Threshold for tenderness			
of lower leg skin (kg)	1.75 ± 0.67	2.75 ± 0.98	$p < 0.001$

Aminofluid®, the zinc level did not increase. The patient had no appetite and chronic diarrhea, but neither upper nor lower gastrointestinal fibers revealed any abnormality, and during hospitalization, the gastrointestinal tract ruptured. She suffered three ruptures of the digestive tract within one year (four in total) and died.

The pathological findings were not severe inflammation, just perforation, similar to a leaky gut [16]. The inability in this patient to increase the zinc level from 33 μg/dL with a dose of 34 mg of polaprezinc led me to believe that a higher amount than 34 mg of zinc per day is a minimum dose necessary to increase low zinc levels.

Zinc deficiency is associated with an increased risk of gastrointestinal infections, adverse effects on the structure and function of the gastrointestinal tract, and impaired immune function [17,18,19].

As for the function and development of Paneth cells, which have a great influence on the formation of the intestinal microbiota, it has become clear that if zinc, especially ZIP7, does not work, intestinal stem cells are lost in the intestinal crypt and Paneth cell development is impaired. Even if there are no major findings on endoscopies [20], it is essential to measure zinc levels in patients with chronic diarrhea.

In 1998, the effects of zinc had not yet become widely known, and with my desperate guidance, I managed to convince the patient to take 34 mg of zinc in the morning and evening. In spite of taking 34 mg daily, four patients died within one year of taking zinc (cases 1, 2, 4, and 13 in **Table 1**). The number of patients who died 1 to 10 years after treatment and whose zinc level was less than 50 μg/dL at the time of initial diagnosis was 9 (cases 3, 5-12 in **Table 1**).

The causes of death in the 13 cases of rheumatoid arthritis with serum zinc levels below 50 μg/dL who died within 10 years were pneumonia in 9 patients, intestinal rupture in 1 patient, hematemesis of gastric ulcer in 1 patient, sepsis after diabetic foot necrosis in 1 patient, and pyelonephritis in 1 patient. There were 10 deaths due to infections out of 13 patients even after 34 mg of zinc was administered, and this was a time when many medical professionals protested that zinc administration was ineffective. Nevertheless, I did not want to lose the ability to administer zinc under the health insurance, so since 1998 I continued to submit the detailed descriptions of symptoms to the social insurance organization, stating the necessity of testing zinc levels and the necessity of sufficient zinc administration. Finally, in September 2011, it became possible to administer Promac® to patients with zinc deficiency in Nagano Prefecture.

All 13 patients with zinc levels below 50 μg/dL in **Table 1** were mentally depressed and had a mean objective face scale of 14.5 ± 2.1 [21,22]. The 13 patients with zinc levels of 51 μg/dL or higher had a mean of 10.7±1.8. Zinc is an antagonist of the N-methyl-D-aspartate (NMDA) glutamate receptor and exhibits antidepressant-like activity in rodent tests and models of depression. In a random sample of 100 female high school students, for every 10 μg/dL increase in serum zinc level, Beck's depression inventory (BDI) and hospital anxiety depression scale (HADS) decreased by 0.3 and 0.01 respectively ($p < 0.05$) [23]. These results suggest that serum zinc levels were associated with the Objective Face Scale.

From the physician's point of view, the five patients with zinc levels below 40 μg/dL (cases 1 to 5 in **Table 1**) gave the impression of being grumpy all the time, no matter when they were visited. Those with zinc levels below 50 μg/dL seemed not to be listening to me seriously, no matter how much I talked about the importance of zinc. I wondered if this was due to a decrease in zinc and an AGE (advanced glycation end-products) accumulation in the brain [24]. It could also be due to decreased microglial function.

The reason why I am describing an objective face scale is as follows. Before the consultation, I ask the patient to fill out the face scale questionnaire. Even if the physician thinks that the symptoms have improved and the patient's facial expression has improved, many patients continue to insist that the current situation is unsatisfactory and that the symptoms are still bad, so there is no change in the face scale. Since then, I have been using the face scale from the time the patient enters the examination room to the time they sit down as an objective face scale in their chart. This is because I believe that if there is "white-coat hypertension," there should be a "white-coat face scale," and that it is important to get a sense of the patient's true facial condition before they face the doctor.

Of the 53 patients with rheumatoid arthritis whose serum zinc levels were 50 μg/dL or higher who were tested between March 1998 and August 1999, only one died within 10 years despite continued zinc administration (Promac®: 32 mg of zinc per day).

The only deceased case was a 62-year-old female patient, Case III, ("red star" in **Fig. 2**) who had bilateral arthroplasties within one year; she had a 1999 zinc level of 64 μg/dL and a mean bilateral lower leg tenderness threshold of 1.42 kg. It was lower than the mean value of 2.50±0.96 kg in group B (serum zinc level >70) and lower than the mean value of 1.75±0.67 kg in group A (serum zinc level <70) (**Table 2**). I thought this was a great risk for surgery and at the pre-surgical meeting, I insisted that the zinc level be raised to 70 μg/dL or higher before surgery, but this was rejected, and the left knee joint arthroplasty was performed. Immediately after that, diabetes developed. According to the preliminary plan, the right arthroplasty, on the opposite side of the body, was scheduled one month after the surgery, but it was postponed to three months later due to the treatment of diabetes. The serum zinc level before the second surgery decreased to 32 μg/dL, and I rated the objective face scale as 16. The right knee arthroplasty was performed as usual and the surgery went well, but she had a stroke two days after the surgery and eventually died one month later.

By this time zinc administration was beginning to be shown to be effective in children with respiratory tract infections in double-blind, controlled trials [25]. The relationship between zinc and cerebral infarction is not clear, but the relationship between zinc and blood vessels, PPARγ, and PPARα has been reported [26], so it seems necessary to pay attention to zinc levels in patients who are prone to cerebral infarction. It has also been found that zinc inhibits phosphate-induced vascular calcification via TNF-α-induced protein 3-mediated inhibition of NF-κB [27]. Also, with regard to diabetes mellitus, it was clear in 2015 that zinc levels were low [28,29], but the pre-surgical meeting at the time dismissed my insistence on waiting until we increased

the zinc level to 70 μg/dL.

Since insulin granules of pancreatic β-cells decrease in zinc-deficient states [30] and zinc has actually been observed in insulin-containing granules of pancreatic β-cells [31], I believe that surgery should be postponed until zinc levels recover, if zinc levels are low in patients with diabetes mellitus.

In 2006, Kurasawa reported the results of zinc level measurement in local residents in Nagano Prefecture. The mean serum zinc level of 341 adults (mean age 54.8 years) was 78.9±11.6 μg/dL [32].

In 2007, a double-blind study of elderly patients in 33 nursing homes in Boston reported a significant reduction in pneumonia infection rate (about half), fewer days of illness, fewer days of antibiotic use, and lower all-cause mortality [33] in elderly patients with serum zinc levels in the normal range.

After three years of experience at the Marunouchi Hospital, I became convinced that patients with 1) weak skin, 2) poor objective face scale, 3) chronic diarrhea, and 4) diabetes mellitus should be tested and low zinc levels should be improved to at least 70 μg/dL before surgery. Therefore, I conducted a study between 2006 and 2008 at Shinonoi General Hospital, Minami-Nagano Medical Center, my next place of work, to determine 1) what symptoms would improve if the patient's zinc level was raised to 70 μg/dL and 2) what amount of zinc would be needed to raise the serum zinc level to 70 μg/dL.

4. Improvement in clinical symptoms by zinc administration

Serum zinc levels were measured in 312 patients with rheumatoid arthritis who visited the Minami Nagano Medical Center between April 2001 and October 2004. Fluctuations in serum zinc levels, the presence or absence of improvement in 21 subjective symptoms, and a disease activity index of 28 were investigated. The results showed that 228 patients (73.1%) had levels below 70 μg/dL. Of the 228 cases, 90 were treated with 34 mg of polaprezinc daily zinc dose [34]. Of these, 81 patients had been on the medication for more than 6 months, and during that period they took the same prescription of the drug used to treat rheumatoid arthritis.

For comparative purposes, the patients were divided into three groups: Group 1: those whose serum zinc levels increased after 6 months of polaprezinc, Group 2: those whose serum zinc levels did not change after 6 months of polaprezinc, and Group 3: those who did not receive polaprezinc. As a statistical check, a paired test was performed for each item before and after polaprezinc administration. There were 64 cases in group 1; 17 cases in group 2; and 19 cases in group 3.

In group 1, the average zinc serum level increased from 56.1 μg/dL to 86.3 μg/dL during the first 6 months of zinc administration. In group 2, zinc serum levels had decreased from 59.5 μg/dL to 56.1 μg/dL. The ratio of males to females was approximately 1:3 in each group. In terms of age, there was little difference among the three groups. There was also little difference in the duration of the disease.

In the first group with increased serum levels of zinc, the CRP level significantly improved from 1.82 mg/dL to 1.22 mg/dL. The total cholesterol level also increased significantly from 189 mg/dL to 198 mg/dL. In the second group where there was no change in serum levels of zinc, there was also no change in values other than zinc. In the third group, which did not receive polaprezinc medication, no changes were observed in any values (**Fig. 3**).

The main subjective symptoms of the first group were significantly better than those of the second group, including swollen joints (39.3%>20.0%), pale complexion (41.2%>14.3%), susceptibility to colds (66.7%>50%), mental instability (100%>33.3%), and dermal abscess (63.6%>50%). In the Zinc non-medication group no subjective symptoms improved.

DAS28 (Disease Activity Score 28) was calculated using four factors: A. Number of painful joints, B. Number of swollen joints, D. Visual analog scale, and E. CRP, which was used instead of erythrocyte sedimentation rate (C). By comparing the DAS28 of each patient at two different time points, improvement or response can be defined.

In the first group, 28.1% had "good" DAS28 and 29.7% were "moderate". In group 2, there were no cases judged to be "good" and 29.4% were "moderate". In group 3, where polaprezinc was not administered, only 5.6% were "moderate", and 94.4% had "no symptom improvement". In other words, DAS28 was improved by administration of zinc and increase in serum zinc level (**Fig. 4**).

However, the zinc levels of about 20% of the patients did not increase even after zinc administration, and it was necessary to examine whether a dosage of 68 mg or more, instead of 34 mg, was necessary to improve symptoms within 6 months in the rheumatoid arthritis patients with zinc deficiency. However, due to insurance reasons and drug costs, we could not perform a significant difference test between zinc doses of 34 mg, 68 mg, and 100 mg.

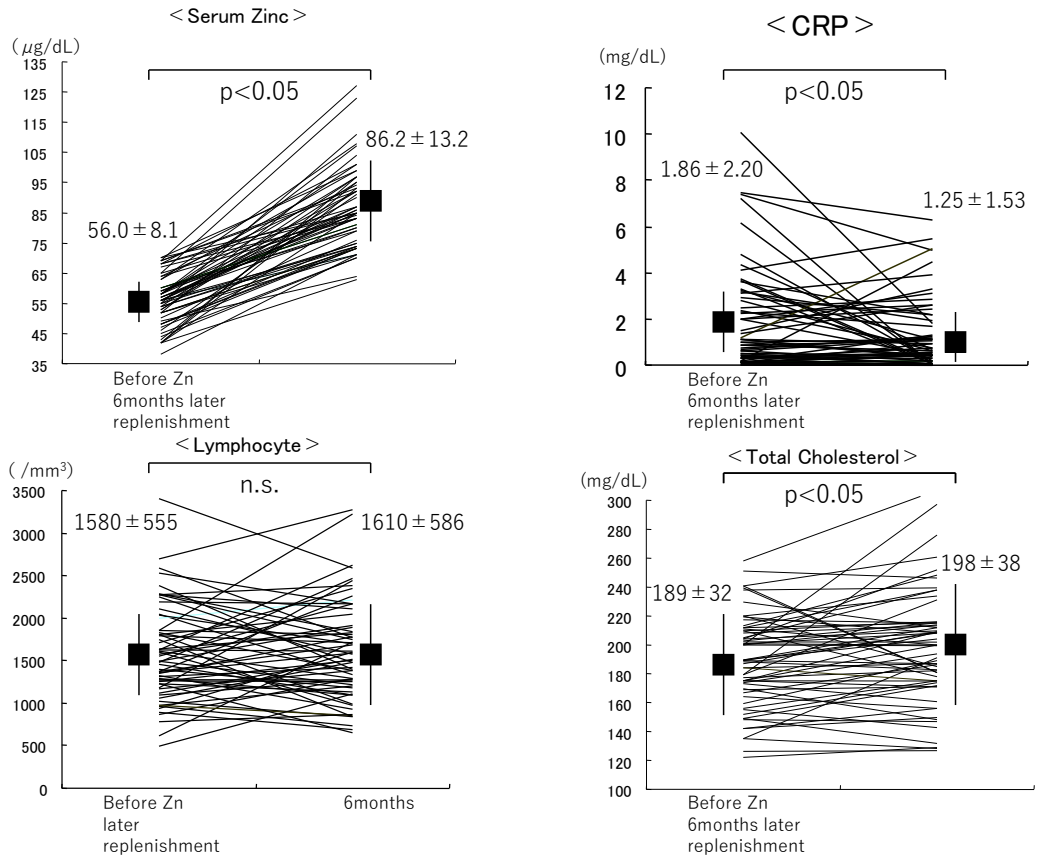

Fig. 3. | Change in CRP and cholesterol level in increased zinc group

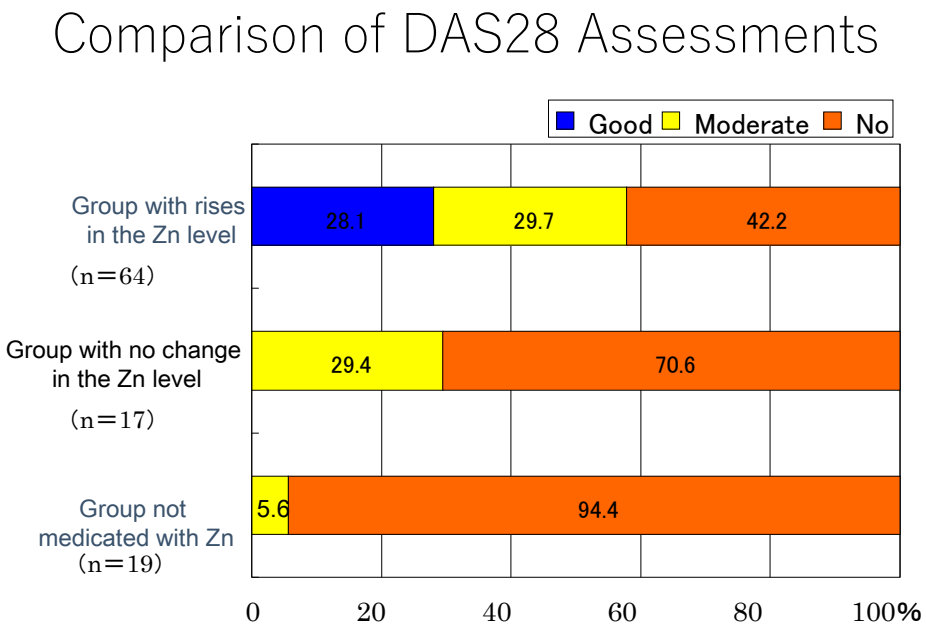

Fig. 4. | DAS28 is more likely to be improved in the group with increased zinc level

Later, in 2019, we reported that we were able to improve the sense of smell in patients with olfactory deafferentation after 2 years and 8 months of treatment with 34 mg of zinc followed by 3 months of treatment with 68 mg of zinc. There were three cases of olfactory disorders treated [35].

In addition, patients with neuropathic pain experienced relief after 9 months, 4 months, 3 months, 8 months, and 1 month of treatment with zinc doses of 100 mg or more per day. Since patients cannot tolerate their own neuropathic pain for a long period of time, I would argue that the attending physician should increase the zinc dose to the required amount needed by the patient.

Unless patients are on dialysis, the zinc dose should be increased so that the patient can reach a zinc level of 100 μg/dL to improve the symptoms quickly. I believe that the saving of a near-infected prosthesis was the result of raising the serum level to 108 μg/dL, and I attribute the case of a widespread pressure ulcer where Pseudomonas aeruginosa was detected all the time in local culture but the wound closed to increasing the serum level to 110 μg/dL. A case of sleepless neuropathic pain that improved from a VAS of 98 to 6 resulted from an increase in serum zinc levels from 61 μg/dL to 106 μg/dL. I aim to achieve a zinc level of 100 μg/dL or higher in cases that I judge to be difficult to treat.

5. Preoperative zinc administration and postoperative course

In 2002, I experienced a case of a patient who was referred from another physician to our department. The patient was treated with zinc only for a few days before surgery and did not have a good postoperative course.

The patient, Case IV, was diagnosed with rheumatoid arthritis in 1996 and had been treated with methotrexate 4 mg/week, and was first seen by a doctor in our department in August 2001, diagnosed as Steinbrocker stage IV class III. Because of the presence of a large geode (cystic bone destruction) and the side effects of 10 different medications, we offered to measure her zinc level and bone mass at the preoperative meeting. The zinc level was 55 μg/dl just before the surgery, so we suggested postponing the procedure until the zinc level increased, but the patient did not want to postpone. I performed the left knee arthroplasty with only 5 days of Promac® (34 mg zinc/day) supplementation; bone grafting and arthroplasty was performed on the geode, but immediately after, the patient developed left peroneal nerve palsy(**Fig.5**). She had a loss of muscle strength in the left tibialis anterior, left extensor hallucis longus, and left extensor digitorum longus muscles (manual muscle test was 0), and painful sensory loss between the first and second toes was observed, but tactile sensation was maintained. After 3 weeks of treatment with 2 tablets of Promac® (daily zinc dose 34 mg: the amount allowed by insurance), Tinel's sign was observed at the neck of the fibula.

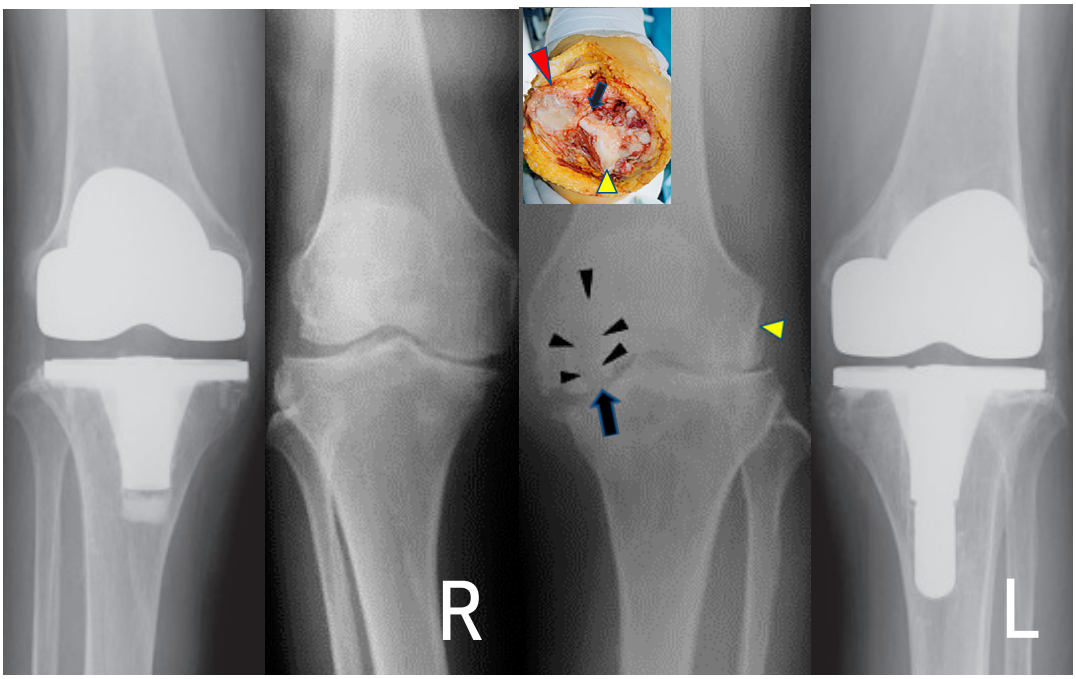

Fig. 5. Comparison of radiographs taken before and 10 years after surgery. Arrow heads: geode of left femur; arrows: hole leading from the cartilage of the femur to the geode; yellow arrow: left femur; red arrow: left patella

Postoperatively, there was skin fusion failure, and it was possible to remove stitches after 21 days. Three Promac® tablets (51 mg zinc/day) were continued, and muscle strength was completely restored after four months [36]. Since it usually takes about 6 months, we thought that zinc supplementation might have some effect on the peripheral nerves. Zinc was also observed in the synaptic vesicles of neurons in 1999 [37]. It is possible that the zinc worked to improve the damaged nerves.

In 2016, it was found that the expression of RANKL in synovial fibroblasts is mainly involved in the formation of osteoclasts and erosions in inflammatory arthritis [38], so the large femoral defect and the bone erosion on the tibial side in this case seemed to be caused by the action of RANKL in fibroblasts.

In this case with low zinc levels and poor osteoimmunity [39], I believe that excessive activation of the immune system inhibited bone formation and promoted bone resorption, resulting in disruption of bone homeostasis and inflammatory bone destruction.

Five months after zinc supplementation, she reported that the taste of cola improved. In other words, the patient had not been aware of any preoperative taste disturbance, despite a serum zinc level of 55 μg/dl.

Thereafter, zinc supplementation was continued and the right knee arthroplasty was successfully completed without peroneal nerve palsy or delayed skin fusion. After the right hip replacement autologous bone graft was performed. The left hip replacement was also successfully performed.

The patient was tranfered to another doctor, she stopped taking zinc and the serum level dropped to 58 μg/dL. Six months later, she suffered a fragile pubic fracture and was hospitalized; her osteocalcin level reached 6. A dosage of 34mg intake zinc had allowed completion of four arthroplasties (**Fig.6**), hand surgery and brain surgery [40]. The patient is still able to walk 19 years after the first surgery, keeping zinc levels above 80 μg/dl, and has not had a fragility fracture since 2010. The objective face scale improved from 14 at the initial visit to 3 after the final surgery. There is a striking contrast with Case III which I believe is due to osteoimmunity resulting from zinc treatment.

Based on the post-operative experience of the first prosthesis in this case, we reviewed the case zinc values of patients with rheumatoid arthritis who had prosthesis surgery over the period 2003-2010. Patients who were referred from other doctors and supplemented with 34 mg of zinc per day for 2 months prior to surgery were group 1, and patients who were treated at our hospital and supplemented with 34 mg of zinc per day for 6 months prior to surgery were group 2. The first group consisted of 67 patients with a mean age of 65.7±8.9 years, and the second group consisted of 24 patients with a mean age of 68.3±7.7 years, so there was no significant difference in age.

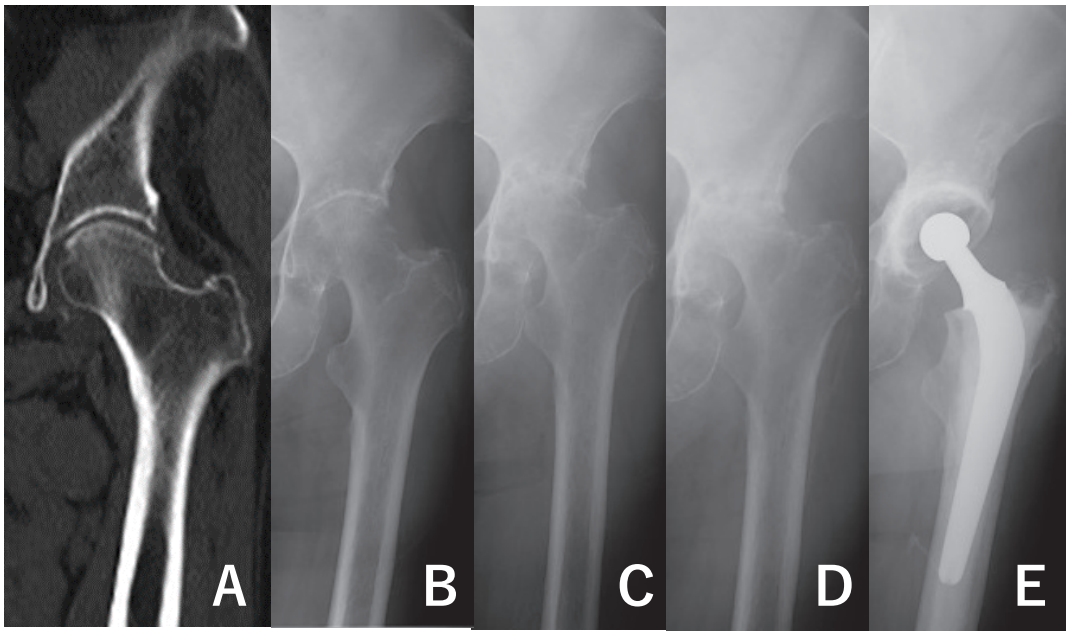

Fig. 6. The last arthroplasty of left hip joint. Preoperative CT, preoperative radiographs and postoperative radiographs of the left hip joint
A: CT of the right hip joint in December 2004; B: X-P in August 2005; C: X-P in June 2006; D: X-P in August 2006; E: Postoperative X-P in October 2006
As can be seen in A, B, C, and D, the joint gap narrowed as the years progressed

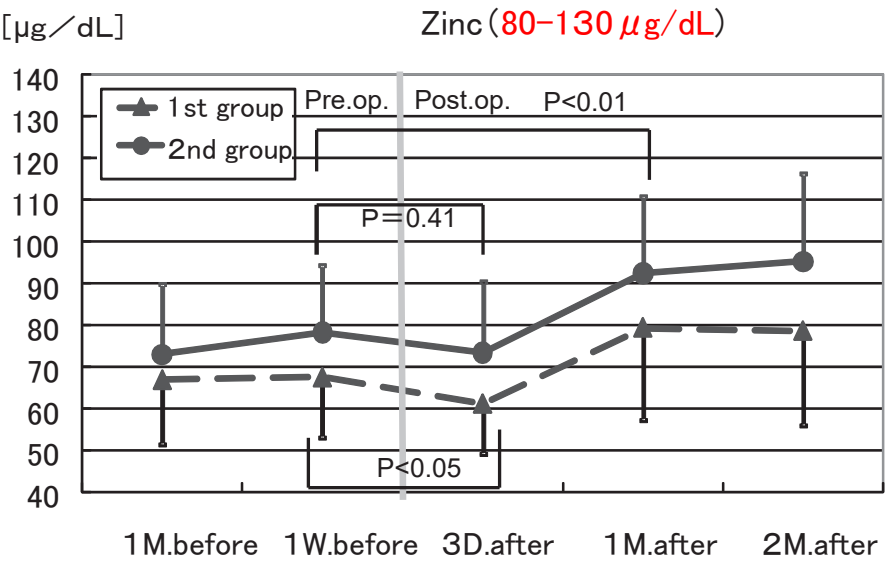

Fig. 7. Postoperative zinc levels were more stable in the 6-month preoperative zinc supplementation group than in the 2-month preoperative zinc supplementation group

One month before the surgery, the mean zinc level was slightly higher in the second group, but the difference was not significant at p=0.12. However, one week before the surgery, the level was higher in group 2 with p<0.01 (**Fig. 7**). One month after the decision to have surgery, patients are anxious. In the first group, there were four cases in which zinc levels dropped by more than 10 μg/dL just before the surgery compared to one month before, despite zinc supplementation. The range of decline was 22, 15, 14, and 13 μg/dL. In the second group, there was only one case that dropped 14 μg/dL from one month to one week before. The reason for this was thought to be that the patients were able to endure mental stress after 6 months of medication, as considered from the results of the previous study [23,41].

The postoperative wound condition was as follows: 3 cases of skin necrosis and 4 cases of delayed skin healing among 67 patients in the first group. In group 2, there were no cases of skin necrosis or delayed skin healing. Nishida showed that zinc released by mast cells is involved in the production of IL-6 during the inflammatory phase of wound healing [42]. It can be said that high serum zinc levels were effective for wound healing.

Considering the fact that the copper level did not drop below the reference level in any of the cases with a high dose of zinc, the safety margin of zinc in the preoperative and postoperative periods is much wider than expected.

The following are cases from the first group of patients who received zinc supplementation for two months.

Case V: The patient had severe signs of infection from 3 days after surgery, and in order to eliminate the risk, she was forced to use double the amount of zinc, 64 mg, until 2 weeks after surgery, when she had to use Aminofluid®, and then 34 mg of zinc per day, so she was placed in Group 1.

The patient was a 74-year-old woman with a history of ovarian cyst and intestinal obstruction; she had a history of pus from the toe two months after left toeplasty in 1993, and pus from the right upper arm and right sternoclavicular joint in the same year, both of which were detected to be Staphylococcus aureus; she underwent right knee arthroplasty by another doctor in 1993, which resulted in yellow exudate and delayed healing. In 1994, she had another abscess from the left fifth toe, and Staphylococcus aureus was detected by bacterial culture.

In 2007, she wanted to have left knee arthroplasty, so zinc supplementation was started 2 months before, and her serum zinc level was 75 μg/dL 1 month before. The zinc test was outsourced to SRL, and the report came back two days before the surgery that the zinc level had been 137 μg/dL one week before the surgery. I expected the zinc level to be 80 μg/dL, but the level was so much higher that I suspected contamination, but I gave up on retesting because the results would not be available until after the surgery. Therefore, the data of zinc level one week before the surgery was left blank. The preoperative VAS of pain was 64. The preoperative objective face scale was 14, which was a matter of concern.

The surgery was performed as usual, and the zinc level 3 days after surgery was 58 μg/dL, although the result came to us 10 days after surgery as reported by SRL. Five days after surgery, the blisters broke and the CRP was 7.61 (**Fig. 8A**). Thereafter, the skin rapidly became necrotic, and 8 days after surgery, the patient had a fever of 38.2°C. The zinc level 8 days postoperatively was 108 μg/dL (**Fig. 8B**). Pus from the ulcer area was submitted for bacterial culture on three occasions, but no bacteria were detected. During the course of the disease, the patient was treated according to the postoperative infection of the prosthesis [43,44].

From 5 to 14 days after surgery, the patient was treated with a combination of polaprezinc (68 mg of zinc per day) and an intravenous infusion of a vitamin, sugar, electrolyte, and amino acid preparation (Bfluid®) containing 2.5 μmol (0.7 mg) zinc, followed by 34 mg of zinc per day, and the serum zinc level was maintained at 107 μg/dL after one month. The wound was completely closed at 83 days postoperatively (**Fig. 8H**) [45]. Two months after surgery, the patient's face scale improved to 2. Preoperatively, the patient was very anxious and refused to have her face photographed even though I wanted to do so. After the surgery, the patient was smiling so it was easy for me to take her picture. I would really like to have a comparison of the pre- and post-operative facial photos, but more than 90% of the patients refused to have their pre-operative photos taken, so there are no comparison photos.

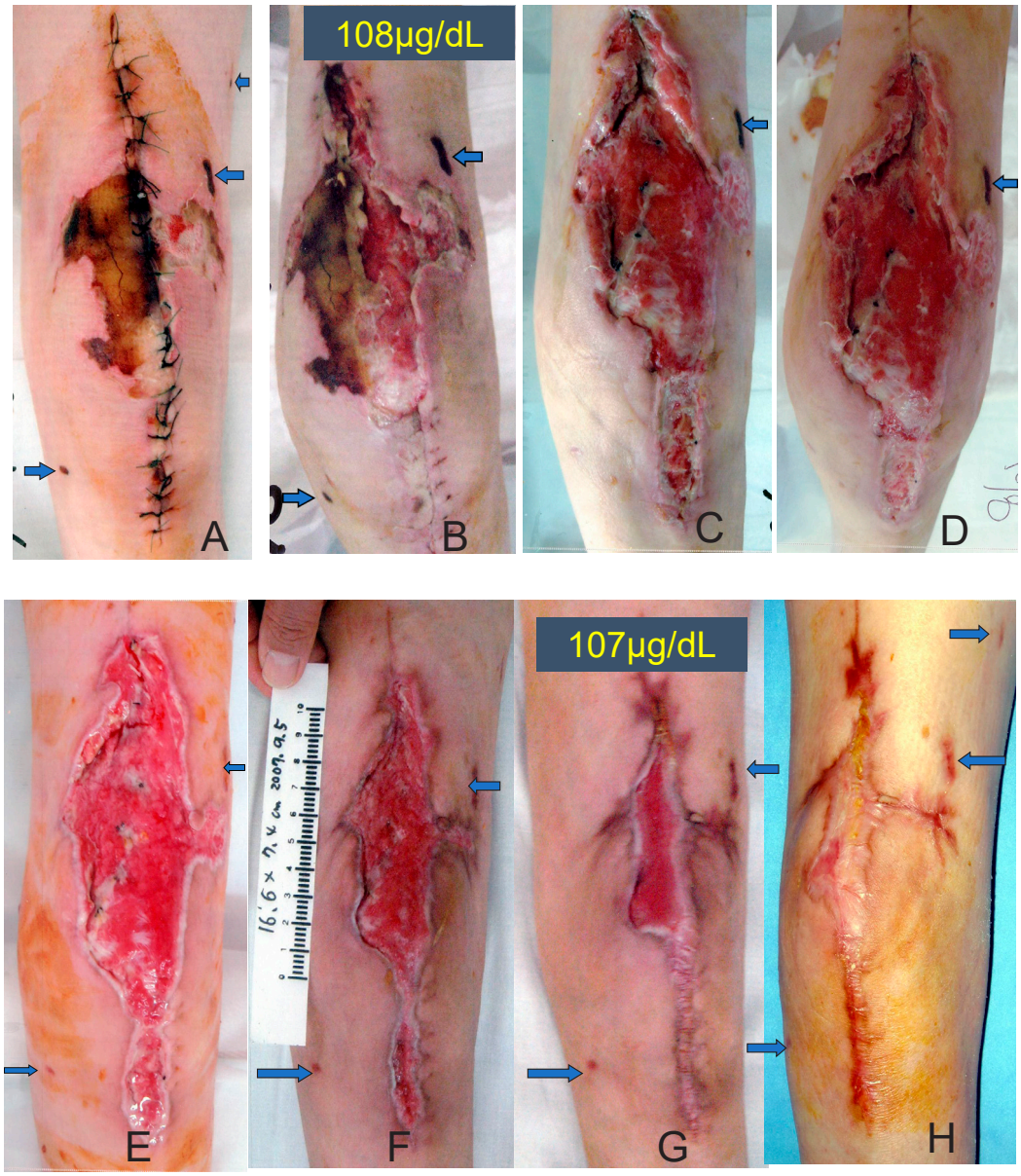

Fig. 8 A-H. Change in skin condition after knee replacement surgery. Arrows show skin necrosis site. A: 5d.aft.surg. B: 8d.aft.surg. H: Wound completely closed 83 days after surgery

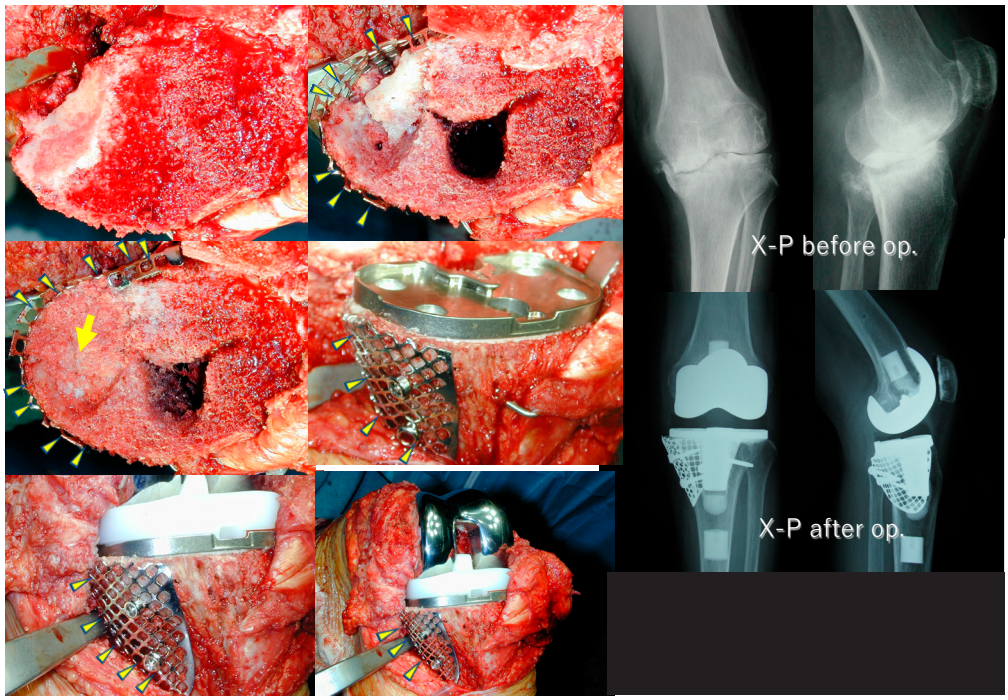

Fig. 9. | Knee joint prosthesis after impaction bone graft covered with mesh

The serum zinc level was 75 μg/dL one month before the surgery, so we were confident to start zinc supplementation two months before the surgery. However, considering the history of four Staphylococcus aureus infections, the preoperative objective face scale of 14, and the VAS of pain of 64, we thought that the patient was at significant risk and should have been treated with zinc for more than six months before the surgery. As a final result, the right knee was able to flex 100 degrees after surgery, and the patient and her family were grateful.

This case, which was very difficult to treat, made the hospital laboratory aware of the dangers that can occur if zinc testing is not performed in the hospital. Sinotest's Acuras Auto Zn® was introduced to the Minami-Nagano Medical Center in April 2008. Since then, it has been very useful for us to be able to immediately retest the zinc in case of any contamination such as red blood cell destruction.

It has long been known that zinc acts on skin metabolism and promotes wound repair [46,47]. We have continued to supplement 34 mg of zinc after surgery in all cases, and the patients have been followed for up to 18 years after joint replacement. In all postoperative patients, including those who had large bone blocks grafted, those who had impaction bone grafting with rim mesh (**Fig. 9**), [45] and dialysis patients, there were no patients with crushed bones or diabetes mellitus after 18 years. When postmenopausal osteoporosis was treated with zinc preparations, bone density was reported to be higher as serum zinc was satisfied [48]. There were no cases of skin necrosis. In cases of skin necrosis, the necrosis could spread and develop into pyogenic arthritis and pyogenic osteomyelitis of the bone joints. In orthopedic surgery, it is very important to prevent infection of bones and joints.

Vikbladh was the first to report a decrease in serum zinc levels in infectious diseases in 1951 [49], but when I became an orthopedic surgeon in 1983, the detailed mechanism was not yet known. Only a few surgeons recognized that zinc was related to infections. Therefore, no orthopedic surgeon would measure zinc levels before operating on a patient. Later papers advocating the importance of zinc levels in surgery were published by Shoji et al. [50], Ono [36], Kaido et al. [51], Yan et al. [52] and others.

In 2006, a prospective study of 80 total hip arthroplasties was published, suggesting an association between delayed wound healing and preoperative serum zinc levels [53].

6. A study of patients from other departments who had problems before and after surgery

During my 11 years of experience as the chief of a nutrition support team (NST) in a 433-bed hospital from April 2005 to March 2016, I have had many problems with zinc levels among the 30 referrals per week. Among them, I would like to show you the patients who left a lasting impression on me after surgery.

Fig. 10. | Grade 3 oral mucosal disorder of tongue

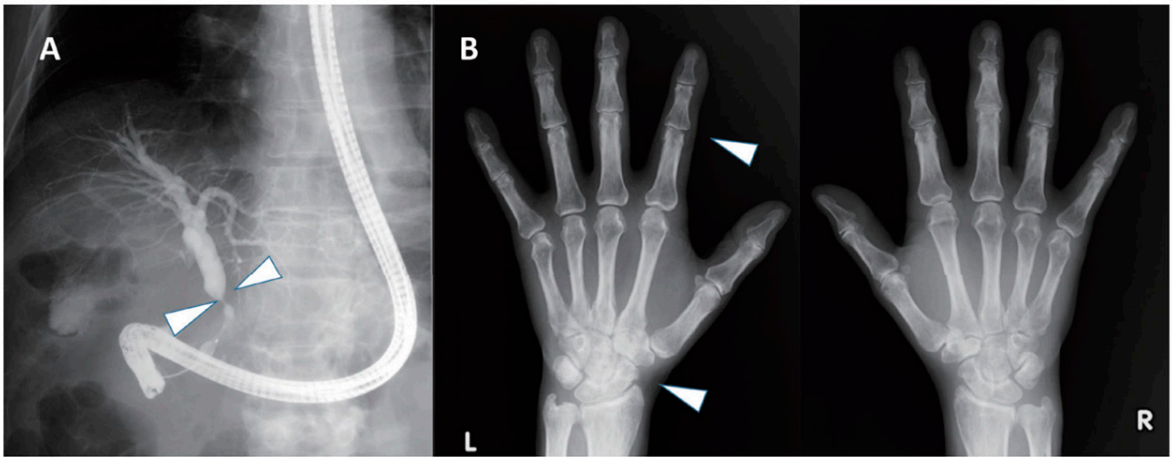

Fig. 11. | Hand pain after pancreatoduodenectomy, but no bone ulcer

The patient, Case VI, came to see me after thoracic surgery. The skin of the chest did not heal, the zinc level was 54 μg/dL, and the patient had grade 3 oral mucosal disorder (**Fig. 10**). She had an objective face scale of 12. After 58 days of treatment with 3 Promac® tablets (51 mg zinc), the sutures were closed and the moderate grade 3 oral mucosal ulcerations were healed when the zinc level reached 84 μg/dL. The objective face scale was 7. The patient was encouraged to swallow Promac® after keeping it in her mouth for about 1 minute so that it could spread to the oral mucosa.

A postoperative abdominal surgery patient also had problems.

Case VII: The patient was a 67-year-old male post-surgical patient. He underwent pancreaticoduodenectomy for cholangiocarcinoma, and anticancer drugs were used from the postoperative period until one year and two months after the surgery was completed. One year and eight months after surgery, CRP was 0.08 and CT and PET showed no metastasis. Immediately thereafter, the patient developed fever for 3 days, with swelling of the hands and wrist joint pain (**Fig. 11**).

The main complaint was stiffness of the hands. Other symptoms were severe general malaise, difficulty walking, decreased right grip strength, insomnia, and loss of appetite. The patient's right grip strength was 90 mmHg, which was very low. He could only complete the 30-second chair stand test [54,55] 3 times. The patient's first words were, “I'm going to die if you don't do something”. We suspected rheumatoid arthritis because of the RF quantification of 58 and CRP of 1.65, but the anti-CCP

antibody was 35.3 and MMP-3 was 65.5 at this point. Furthermore, joint echocardiography showed no synovitis, and radiographs showed no erosions, so rheumatoid arthritis was ruled out. The only abnormal value was the serum zinc level (21.3 μg/dL) [56], which was the lowest zinc level I had ever experienced.

Polaprezinc (51 mg of zinc per day) was started, and after 11 days, the patient's right grip strength recovered to 220 mmHg and CRP improved to 0.15. Thereafter, 68 mg of zinc daily was administered until 10 weeks later, and the patient recovered to CRP 0.06, right grip strength 280 mmHg, and zinc level increased to 70.1 μg/dL. The objective face scale was 11. This patient was very noncompliant. He stopped taking zinc after each symptom improvement, did not see the doctor for several months, and then only when the symptoms reappeared.

Three years and six months after surgery (September 2018), he was taking 100 mg of zinc (Nobelzin®: Zinc acetate hydrate preparation) daily and had a zinc level of 89.5 μg/dL, anti-CCP antibody of 33.8, and MMP-3 of 75.4, which was not bad. His grip strength improved to 300 mmHg on the right side. He had been insomniac, but now he could sleep well and his appetite was recovered. His fatigue and feeling of wanting to die disappeared.

On the day of his visit, I spent an hour explaining to him and his family that a decrease in zinc level would cause Th17 of T lymphocytes to function poorly, resulting in runaway immunity, but he did not understand it at all.

He did not take zinc internally for 8 months and was seen again 4 years and 4 months after surgery due to general fatigue. His serum zinc level had dropped to 47.2 μg/dL and his anti-CCP antibody had doubled to 184. His MMP-3 was 80.1, and joint echocardiography showed no synovitis, so no arthritis was occurring.

The patient's zinc level was originally low at 21.3 μg/dL, suggesting low intestinal absorption, but when the zinc level rose to 89.5 μg/dL and his symptoms improved, he stopped taking zinc. I showed him my book. After I explained it in detail, his understanding gradually deepened. From the time he entered the examination room to the time he sat down in the chair, his objective face scale was 10.

If the grip strength is less than 200 mmHg and the lower limb muscle strength is less than 20 times in the 30-second chair stand test, the preoperative zinc level should be measured, and if it is low, zinc supplementation is necessary.

Some urological postoperative patients also had problems.

An 81-year-old male patient, Case VIII, who had undergone left nephrostomy for left hydronephrosis was referred to NST 13 days after surgery. His medical history included retroperitoneal tumor, left hydronephrosis, left pyothorax, and sepsis. Thirteen days after surgery, the serum zinc level was 54 μg/dL as shown in the left picture. The objective face scale was 15. Polaprezinc 1.5 g (51 mg of zinc per day) was started, and the zinc level rose by 13 μg/dL to 67 μg/dL after 14 days (**Fig. 12**). At that point, the stomatitis and glossitis were cured. The face scale was 9, probably due to the absence of pain in the mouth. With zinc supplementation, the patient's main complaint of not being able to eat any food disappeared, and he was very happy to be able to eat eel.

At the same time, many patients in the cardiology department were also cured of post-catheterization stomatitis by zinc administration (34 mg of zinc per day). Furthermore, the Cu/Zn ratio increases with the progression of liver metastasis and gastric cancer, and is useful for estimating malignancy and prognosis [57]. Therefore, it is recommended that zinc levels be measured in patients with severe disease, even after surgery for cancer.

Fig. 12. | Postoperative tongue disorder in a patient with urological disease, healed after 14 days of zinc supplementation

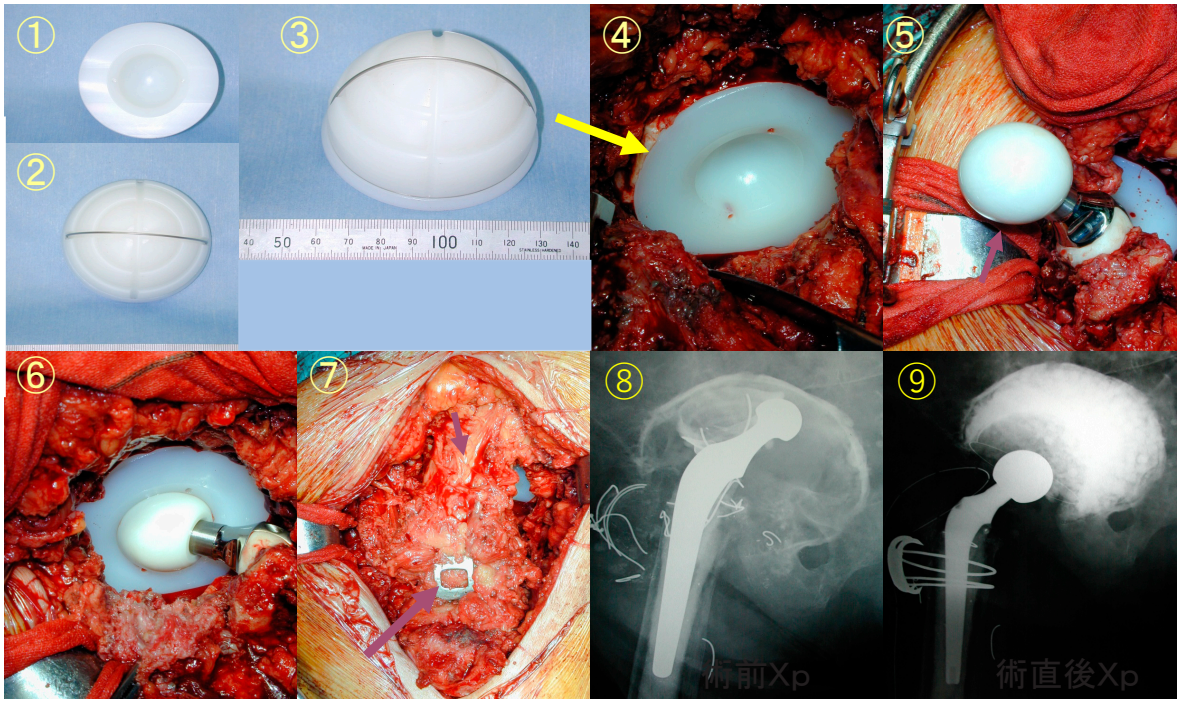

Fig. 13. Revision Total hip arthroplasty (THA) with large cup in a dialysis patient
1, 2, 3: Special order large socket (Φ73 X 68 mm) was fixed by 160g bone cementing. 4: Socket fixation
5: Zirconia ball diameter was 32 mm. 6: Stem was fixed by cement-in-cement. 7: Bone atrophy was marked.
8: Before revison THA 9: After revision THA

A patient, Case IX, 23 years after starting hemodialysis had continued shoulder edema, and the joint prosthesis operated by another orthopedic surgeon dislocated 20 years after surgery, rendering the patient unable to walk. She was scheduled for reoperation, but was referred to NST every two weeks because of shoulder edema and drainage of more than 100 cc. The zinc level was 58.1 μg/dL. She was always in a wheelchair. She had an objective face scale of 12. After 9 years of zinc supplementation, her zinc level reached 78 μg/dL and her shoulder joint edema disappeared. The objective face scale improved to 7. Our surgical team performed bone grafting using three cryopreserved femoral heads, followed by special order large socket (φ73 x 68 mm) hip replacement in 2009 (**Fig. 13**). The grafted bone was still attached two years later [58]. The patient recovered to be able to drive a car by herself.

Suzuki (2015) also reported that osteocalcin was decreased, serum Ca was decreased, and serum PTH was increased in the zinc-deficient diet group of rats, inducing bone fragility [59]. In the case of dialysis patients, it is important not to lower copper levels too much in order to maintain blood vessels, and the fact that zinc levels only increased from 58.1 μg/dL to 78.8 μg/dL in order not to lower copper levels too much by administering polaprezinc (34 mg of zinc per day) may have led to a favorable prognosis.

According to Nishime in 2020, it is safe to administer zinc to patients who are not on dialysis and raise their serum zinc level to 250 μg/dL, but copper is only calculated to drop to 75 μg/dL. However, if a patient on dialysis is given zinc to raise the zinc level to 100 μg/dL, the copper level will drop to 52 μg/dL, causing vascular fragility, which is dangerous [60]. For serum zinc levels in dialysis patients, it is preferable to use cocoa in combination with zinc tablets while measuring copper levels and reducing the amount of zinc tablets when copper levels become low. If the serum zinc level increases, ALP, IGF, and osteocalcin also increase, which is beneficial for bone formation.

There is a report from vascular surgeons on the surgical outcomes of the zinc level group above 60 μg/dL and the group below 60 μg/dL. In clinical outcomes after subungual bypass surgery for critical lower limb ischemia, hypozinchemia below 60 μg/dL worsened limb salvage rate, amputation-free survival rate, and wound healing rate [61]. It is gratifying to see increasing reports of the dangers of hypozinchemia in surgery at other institutions.

Another patient, Case X, is a 77-year-old with rheumatoid arthritis who had been experiencing joint edema and other doctors were thinking of performing arthroscopic surgery. The patient had been experiencing diarrhea for a long time, and the

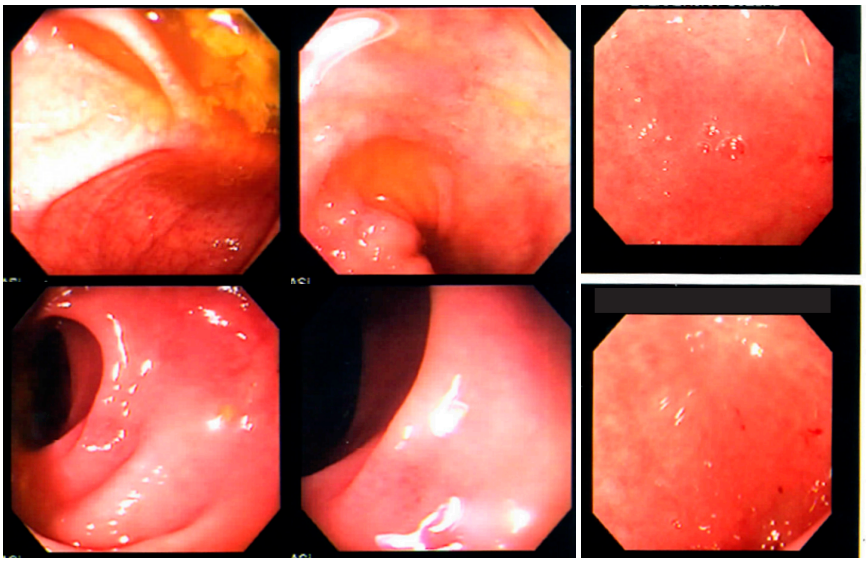

Fig. 14. Neither upper gastrointestinal endoscopy and colonfiberscopy, revealed any abnormal findings.

gastroenterologist performed both upper gastrointestinal endoscopy and colonfiberscopy, but found no abnormalities anywhere (**Fig. 14**). In our department, we found a zinc level of 36 μg/dL.

The patient was admitted to the hospital for 8 weeks and treated daily with 34 mg of polaprezinc and intravenous Aminofluid® to increase the zinc level to 53 μg/dL, and the diarrhea was cured. Finally, when the serum zinc level was raised to more than 70 μg/dL, the arthroedema healed and arthroscopy was not performed.

Zinc is clearly effective in the treatment of diarrhea in children [62,63,64]. Since even 5 mg zinc is effective in children after 30 days of administration, it seems that even a 77-year-old rheumatoid arthritis patient with a very poor absorption rate could be improved in 8 weeks.

Furthermore, in my personal experience, over the past 30 years from 1991 to 2021, there have been more than 1,000 patients with zinc levels below 78 μg/dL who have been treated with zinc doses. Of the zinc-treated patients, only one 79-year-old with liver cancer (who complained beer did not taste good any more) was found to have cancer after 3 years of zinc treatment. According to the National Cancer Institute, the probability of dying from cancer in the entire population was 26.7% for men and 17.8% for women in 2019 data. The cancer mortality rate of 0.1% in zinc-treated patients is clearly lower than this, so I would even say that it is beneficial rather than safe. According to Prasad et al. zinc supplementation should have beneficial effects on cancer by decreasing angiogenesis and the induction of inflammatory cytokines while increasing apoptosis in cancer cells [65], and these effects will need to be further investigated. I believe that zinc is safe as long as the patient is properly tested for copper at 6-month intervals.

These serum zinc level measurements and associated clinical studies were approved by the Ethics Committee and Clinical Research Review Committee in February 1998, March 2001, and July 2016. Furthermore, the study was approved by the Ethics Committee and Clinical Research Review Committee of the hospital in 2019 under approval number R-20.

Conclusion

Before any surgery, I recommend that patients with poor face scale, obvious skin fragility, chronic diarrhea, diabetes, or weakened immune system should have their zinc levels measured and raised before the surgery. However, in elderly patients aged 65 years or more with serum zinc levels below 60 μg/dL, even 3 months of supplementation with 30 mg/day of zinc failed to increase serum zinc levels above 70 μg/dL [66]. Therefore, if we want to raise the serum zinc level of preoperative patients from below 60 to above 80 μg/dL as soon as possible, we should consider administering 50, 75, or 100 mg of zinc per day using Nobelzin®.

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