Iran. J. Radiat. Res., 2012; 9(4): 221-229

Study on effects of thoron and thermal treatment for aging-related diseases in humans

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Background: The aim of this study was to analyze the effects of thoron and thermal treatment for aging-related diseases in humans. ***Materials and Methods:*** All subjects inhaled thoron with a high concentration (about 4900 Bq/m^3) for 2 weeks. Blood pressures were measured and blood samples were collected after each treatment 1, 2 and 3 weeks after the first treatment. ***Results:*** The α-atrial natriuretic peptide level of the rheumatoid arthritis group was increased and the blood pressure was significantly decreased. Superoxide dismutase activity of rheumatoid arthritis group was significantly increased by treatment. In addition, thoron and thermal treatment significantly enhanced the concanavalin A-induced mitogen response and increased the level of CD4-positive cells; it decreased the level of CD8-positive cells. The results suggest that thoron and thermal treatment activates antioxidative function. Furthermore, these findings suggest that thoron and thermal treatment prevents diabetic ketoacidosis and contributes to the prevention of aging-related diseases. ***Conclusion:*** Thoron and thermal therapy may be part of the mechanism for the alleviation of diabetes mellitus and rheumatoid arthritis. **Iran. J. Radiat. Res., 2012; 9(4): 221-229**

Keywords: *Thoron and thermal treatment, health effect, diabetes mellitus, rheumatoid arthritis, antioxidant function.*

INTRODUCTION

Radon (^{222}Rn) is a radioactive gaseous element that mainly emits α-rays. The half-life of thoron (^{220}Rn, 55.6 sec), which is an isotope of radon, is shorter than that of radon (3.824 days), and the α-particle energy of thoron (6.288 MeV) is larger than that of radon (5.490 MeV).

Therapy using radon gas, which is volatilized from radon-enriched water and induces a small amount of active oxygen in the body, is performed for various diseases. A large number of patients are treated in countries with a tradition of spa therapy (i.e. Japan [1,2], central Europe [3] and Russia [4], but the mechanism of radon effects is almost unknown. Despite reports of a potentially increased risk of lung cancer development induced by radon inhalation [5, 6], radon treatment facilities have been established in many countries [3]. If radon is inhaled, the lungs will be subjected to the actions of free radicals created by radiation and may suffer inflammation. Although radon inhalation has been thought to be hazardous in general, radon hot-springs have been reported to have therapeutic effects on senile brain disorders and hypertension [7]. Radon inhalation promotes the effects of tissue perfusion agents such as adrenaline in plasma; that is, the level of plasma adrenaline is increased by radon inhalation [8, 9].

We previously reported that radon effects, such as antioxidative function, are

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twice as effective as thermal effects [10]. This suggests that antioxidative function was more enhanced by radon therapy than by thermal therapy. Furthermore, we have reported that thoron and thermal treatment was effective for the prevention of peroxidation reaction in hypertension [11]. So far, no epidemiologic data exist on the hazardous effects of radon [12].

In recent years, several attempts have been made to clarify the mechanism of radon effects [1, 2, 8], but there have been only a few studies on thoron effects in humans. As most diseases for which radon or thoron therapy and thermal therapy are applied are related to activate oxygen, it is important to clarify the radioactive effects of radon or thoron and thermal therapy under hot-spring conditions. Therefore, in this study, we examined the biochemical effects of thoron and thermal treatment of diabetes mellitus (DM) and rheumatoid arthritis (RA). We investigated several biochemical parameters, such as antioxidant-, diabetes mellitus- and rheumatoi arthritis-associated substances, which are causes of aging-related diseases, to clarify the mechanism of diseases for which thoron hot-spring therapy is used as a treatment, most of which are called activated oxygen-related diseases.

MATERIALS AND METHODS

Subjects

The subjects were 76 individuals (31 males and 45 females; mean age 62.7, range 31-83; Japanese) who were divided into 3 groups: normal, DM and RA. The normal group included 25 individuals (12 males and 13 females; mean age 55.1, range 31-78), the DM group 25 individuals (15 males and 10 females; mean age 66.4, range 44-83), and the RA group 26 individuals (4 males and 22 females; mean age 66.4, range 40-78). Informed consent was obtained from all subjects. The study protocol was approved by the ethics committee of Iwate Health Service Association (Iwate, Japan), and was executed by the Medical Association in Iwate Prefecture and Hanamaki city.

Thoron and thermal treatment

All subjects attended a Hanamaki spa (Iwate, Japan) with a high concentration of thoron. The room temperature was 39 °C, humidity 90 %, water 40 °C, and the air concentration in the thoron hot-spring was about 4900 Bq/m^3. All subjects stayed in the bathroom for 30 minutes a day under the following conditions. Furthermore, they bathed for more than five days a week and continued for 2 weeks.

Assays

Blood pressures (BP) and height and weight were measured before each thoron and thermal treatment and blood samples were collected after each treatment (before meal) 1, 2 and 3 weeks after the first treatment; BP was also measured and blood samples collected before the first treatment (at body temperature and thoron level background) to used as the control. Body mass index (BMI) is calculated by the following equation:

$$BMI = \text{body weight (kg)}/(\text{height (m)}^2)$$

We entrusted the biochemical assays of the blood samples to the clinical analysis service. Briefly, each biochemical indicator was measured; SOD activity was measured by the nitroblue tetrazolium (NBT) method. High-density lipoprotein-cholesterol (HDL-cho) was measured by the direct method. The free fatty acid (FFA), creatinine (Cr), blood urea nitrogen (BUN), uric acid (UA), 1, 5-anhydro-D-glucitol (1, 5 AG), glycoalbumin (GA) and ketone bodies were measured enzymatically. Glucose was measured by the hexokinase UV method. Hemoglobin A_{1c} (HbA_{1c}) was analyzed by the latex agglutination-turbidimetric immunoassay (LA). Immunoreactive insulin (IRI) was analyzed by the radioimmunoassay (RIA). Total protein (TP) was measured by the biuret method. α-atrial natriuretic peptide (α-hANP) was analyzed by the chemiluminescent enzyme immunoassay (CLEIA). Concanavalin A (Con A) was measured by

the DNA quantitative method using a nucleic acid/fluorescent probe. CD4 and CD8 were measured by the monoclonal antibody assay.

Statistical analysis

Data are presented as the mean ± standard error of mean (SEM). Statistical significance of differences was determined using Student' t-test for comparison between two groups or two-way repeated measures analysis of variance (ANOVA).

RESULTS

Temporal changes in BMI of normal and each patient after thoron and thermal treatment

Before treatment (before the first treatment), the BMI in all groups was 22.4-24.4 (figure 1). In weeks 1, 2, and 3, the BMI in the RA group was significantly decreased compared to before the first treatment by thoron and thermal treatment.

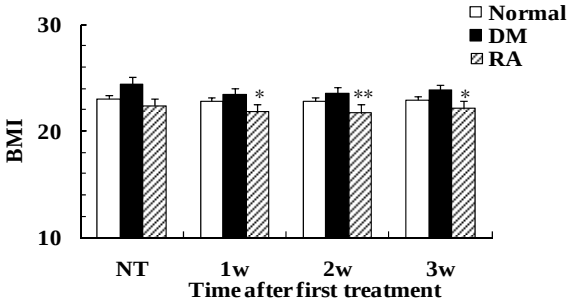

Figure 1. Temporal changes in BMI of normal and each patient after thoron and thermal treatment. Each value is the mean ± SEM. The number of subjects in each experiment was 9-22. Statistical significance: $^{*}p < 0.05$, $^{**}p < 0.01$ vs. each control (non-treatment) value.

Temporal changes in BP of normal and each patient after thoron and thermal treatment

Without treatment, the diastolic BP in DM and RA groups were significantly lower than in the normal group (figure 2). The systolic BP in each group was decreased by thoron and thermal treatment compared to non-treatment. In week 2 after the first treatment, in particular, the diastolic BP was significantly decreased in the RA group.

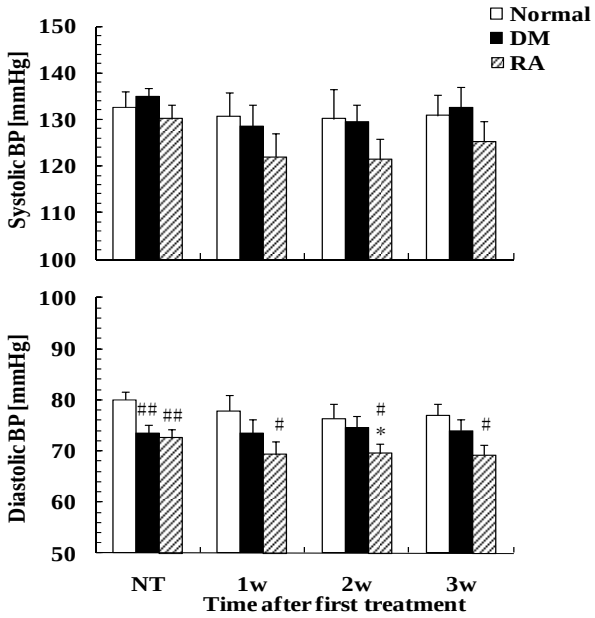

Figure 2. Temporal changes in systolic BP (A) and diastolic BP (B) of normal and each patient after thoron and thermal treatment. Each value is the mean ± SEM. The number of subjects in each experiment was 11-22. Statistical significance: $^{\#}p < 0.05$, $^{\#\#}p < 0.01$ vs. control (non-treatment) value of normal; $^{*}p < 0.05$ vs. each control (non-treatment) value.

Temporal changes in antioxidative function -associated substances

SOD activities in the normal group (in week 2) and DM group (in weeks 1 and 2) were significantly decreased compared to each non-treatment by thoron and thermal treatment (figure 3); however, SOD activity in the RA group (in weeks 1 and 3) was significantly increased compared to non-treatment.

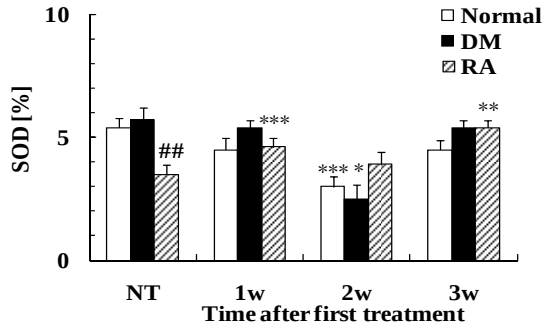

Figure 3. Comparison of SOD activities between normal and each patient in the control (A) and temporal changes in SOD activities of normal and each patient after thoron and thermal treatment (B). Each value is the mean ± SEM. The number of subjects in each experiment was 9-21. Statistical significance: $^{\#\#}p < 0.01$ vs. control (non-treatment) value of normal; $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ vs. each control (non-treatment) value.

Temporal changes in lipid-associated substances in normal and DM groups

The HDL-cho in the DM group was increased slightly by thoron and thermal treatment (figure 4). The FFA levels in the normal group (in weeks 2 and 3) and DM group were decreased by treatment compared to non-treatment. In week 2, in particular, it was significantly decreased compared to the normal group.

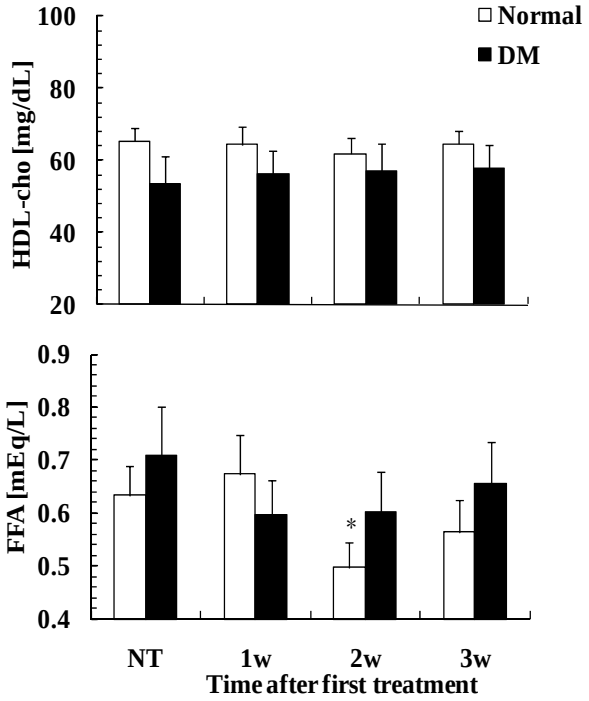

Figure 4. Temporal changes in lipid-associated substances of normal and patients with DM after thoron and thermal treatment. Each value is the mean ± SEM. The number of subjects in each experiment was 6-25. Statistical significance: $^{*}p < 0.05$ vs. each control (non-treatment) value.

Temporal changes in renal function-associated substances in normal and DM groups

Without treatment, BUN in the DM group was significantly higher than in the normal group (figure 5); however, BUN in the DM group (in week 3) was slightly decreased by thoron and thermal treatment compared to non-treatment and there was no significant difference compared to non-treatment in the normal group. There were no significant differences in other renal function-associated substances.

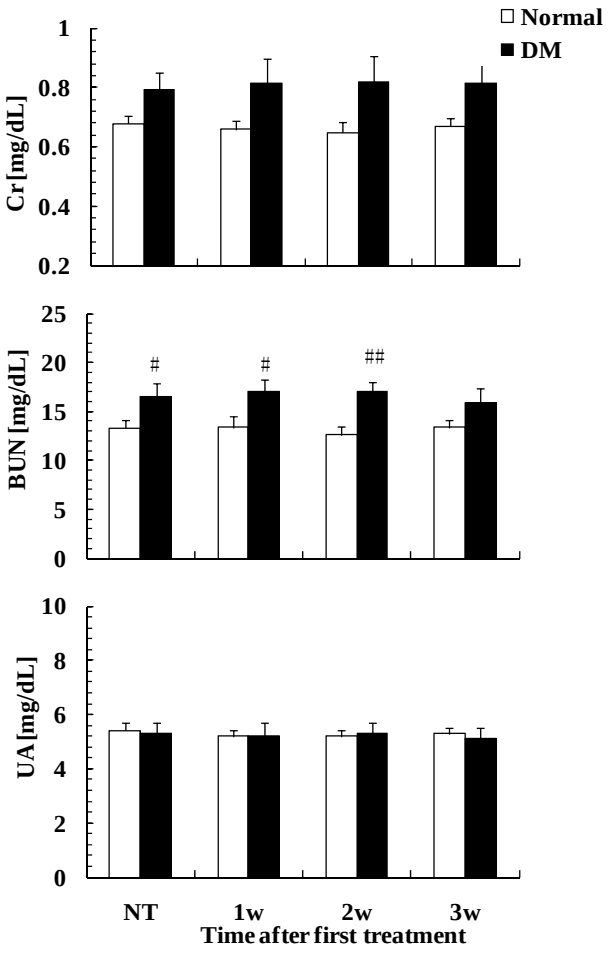

Figure 5. Temporal changes in renal function-associated substances of normal and patients with DM after thoron and thermal treatment. Each value is the mean ± SEM. The number of subjects in each experiment was 7-25. Statistical significance: $^{\#}p < 0.05$, $^{\#\#}p < 0.01$, vs. control (non-treatment) value of normal.

Temporal changes in DM-associated substances of normal and DM groups

Without treatment, glucose, HbA_{1c}, IRI and GA in the DM group were significantly higher and 1, 5AG in the DM group was significantly lower than in the normal group (figure 6). In week 1, IRI in the normal group was significantly decreased by thoron and thermal treatment compared to non-treatment. The IRI in the DM group was decreased compared to non-treatment, and there was no significant difference compared to non-treatment in the normal group. In week 3, the GA in the normal group was significantly increased compared to non-treatment, but this was a reference value.

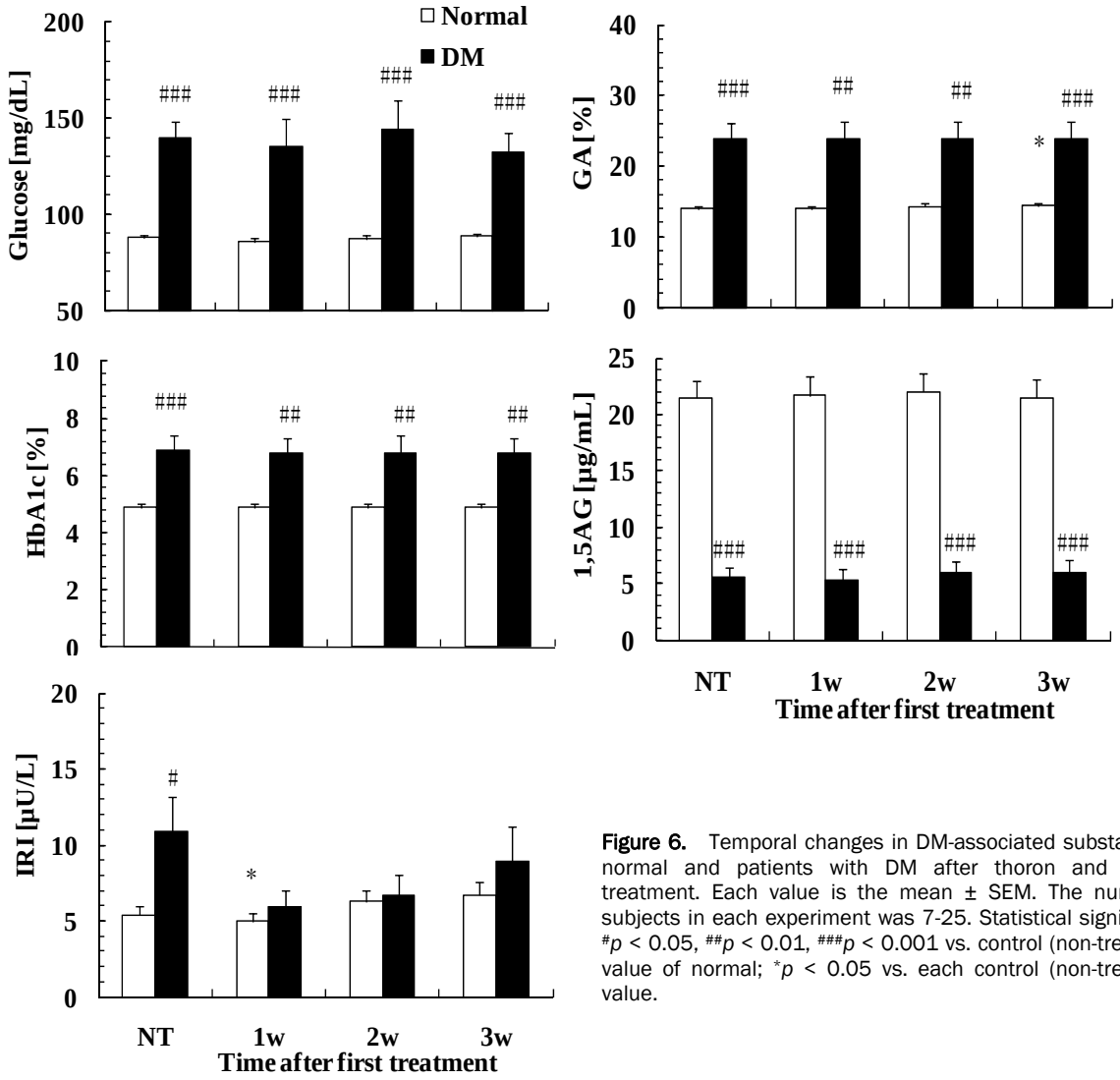

Figure 6. Temporal changes in DM-associated substances of normal and patients with DM after thoron and thermal treatment. Each value is the mean ± SEM. The number of subjects in each experiment was 7-25. Statistical significance: $^{\#}p < 0.05$, $^{\#\#}p < 0.01$, $^{\#\#\#}p < 0.001$ vs. control (non-treatment) value of normal; $^{*}p < 0.05$ vs. each control (non-treatment) value.

Without treatment, the ketone bodies in the DM group were higher than in the normal group, but there was no significant difference (figure 7). Further, the ketone bodies in the normal group (in week 2) and DM group were decreased by treatment. In week 2, TP in the normal group was significantly decreased by treatment compared to non-treatment (figure 8).

Temporal changes in RA-associated substances in normal and RA groups

Without treatment, α-hANP in the RA group was significantly higher than in the normal group (figure 9). The α-hANP in the normal group (in weeks 1, 2 and 3) was significantly increased by thoron and thermal treatment. The α-hANP level in the RA group was also increased by treatment.

Temporal changes in immune-associated substances in normal and RA groups

Con A in the normal group (in week 1) and RA group (in week 2) was significantly increased by thoron and thermal treatment compared to each non-treatment (figure 10-A). In weeks 1 and 2, CD4-positive cells in the RA group were significantly increased, and CD8-positive cells were significantly decreased by treatment compared to non-treatment (figure 10-B).

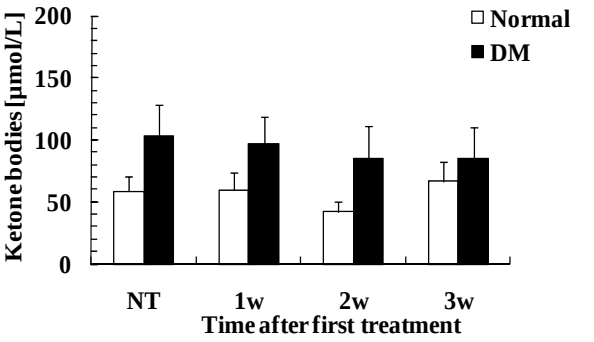

Figure 7. Temporal changes in ketone bodies (glucose metabolism abnormality-associated substances) of normal and patients with DM after thoron and thermal treatment. Each value is the mean ± SEM. The number of subjects in each experiment was 13-21.

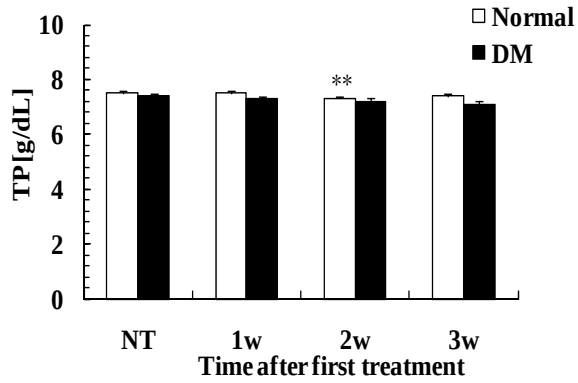

Figure 8. Temporal changes in TP (blood-aggregation index) of normal and patients with DM after thoron and thermal treatment. Each value is the mean ± SEM. The number of subjects in each experiment was 13-25. Statistical significance: $^{**}p < 0.01$ vs. each control (non-treatment) value.

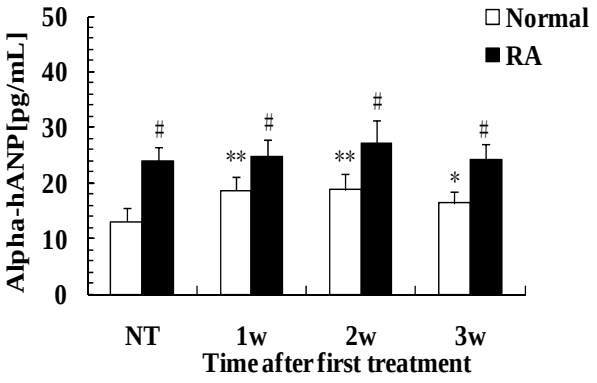

Figure 9. Temporal changes in RA-associated substances of normal and patients with RA after thoron and thermal treatment. Each value is the mean ± SEM. The number of subjects in each experiment was 14-26. Statistical significance: $^{\#}p < 0.05$ vs. control (non-treatment) value of normal; $^{*}p < 0.05$, $^{**}p < 0.01$ vs. each control (non-treatment) value.

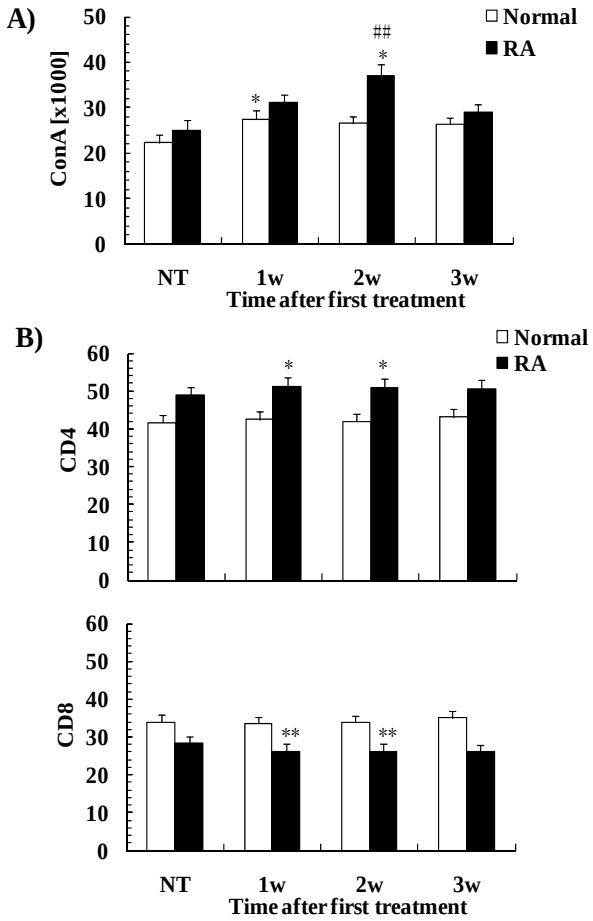

Figure 10. Temporal changes in immune-associated substances of normal and patients with RA after thoron and thermal treatment. Each value is the mean ± SEM. The number of subjects in each experiment was 14-25. Statistical significance: $^{\#\#}p < 0.01$ vs. control (non-treatment) value of normal; $^{*}p < 0.05$, $^{**}p < 0.01$ vs. each control (non-treatment) value.

DISCUSSION

Low-dose irradiation induces various stimulating effects on living organs, especially the activation of a biological defense system such as antioxidative [13-17] and immune functions [18, 19]. For example, low-dose X- or γ-irradiation activated antioxidative functions in some organs and inhibited oxidative injury [20-25]. In addition, recent reports suggested that the exposure dose to activate antioxidative functions with X- or γ-irradiation is much lower than with radon inhalation [26]. As discussed previously, it is highly possible that low-dose X-irradiation activates defense systems in the

living body and therefore contributes to preventing or reducing reactive oxygen species (ROS)-related injuries, which are thought to involve peroxidation.

It has been reported that the activity of SOD, which is a scavenger of superoxide radicals, is increased in cultured cells [28] in various organs of rats [29], rabbits [30] and mice [31] by exposure to radon; however, there have been only a few studies on thoron effects in humans. Thoron is slightly different from radon. The half-life of thoron (55.6 seconds), which is an isotope of radon, is shorter than that of radon (3.824 days), and the α-particle energy of thoron (6.288 MeV) is larger than that of radon (5.490 MeV).

To clarify the health effects of thoron and thermal treatment, we examined the BMI after thoron and thermal treatment. Obesity is a condition resulting from excess body fat, and is associated with several disease risk factors. High BMI is a risk for lifestyle diseases [32], and BMI is used as an indicator of health and obesity. The definition of obesity by the Japan Society for the Study of Obesity is BMI ≥25, and the normal value is 22 [27]. Warm-water bathing enhances the blood circulation and increases energy consumption [33]. In addition, radon inhalation enhances tissue perfusion [8]. In this study, the BMI in the RA group was significantly decreased by thoron and thermal treatment. This might be because of the enhancement of metabolism by thoron and thermal effect.

Nest, to clarify the clinical effects of thoron and thermal treatment on DM or RA, the SOD activity was examined; that is, we examined whether thoron and thermal treatment could improve the reduced enzymatic antioxidant activities in the study. Our results showed that SOD activity in normal and DM groups was significantly decreased in week 2 after the first treatment, but not after 3 weeks in the normal and DM groups. On the other hand, it was significantly increased by treatment in the RA group. These findings suggest that clinical effects were observed even after SOD activities decreased to the initial level. The same effect was observed in our previous study and the reports suggest that the decrease of SOD activities was a symptom similar to slight "yuatari", that is the effect of taking a hot bath for too long [34].

Ketone bodies are the generic name for acetoacetic acid, 3-hydroxybutyric acid, and acetone, and are the imperfect resolution product of fatty acid and amino acid. Increased release of unesterified fatty acids from adipose tissue into the blood is especially common in Type 2 diabetes [35]. Ketone bodies are produced as byproducts when these fats are broken down for energy, and the risk of ketoacidosis is very high in Type 2 diabetic patients. We previously reported that thoron inhalation decreased FFA and total ketone bodies in diabetes, suggesting that thoron inhalation prevents diabetic ketoacidosis [11]. In this study, thoron and thermal treatment significantly decreased FFA in normal group. In addition, total ketone bodies decreased by about 20% in both group, but this difference was not significant. These findings may indicate that thoron inhalation has role in reducing FFA and total ketone bodies.

Controlled clinical trials on the effects of radon therapy for the treatment of RA are rare. Falkenbach et al. found that five trials meeting the inclusion criteria, three with a double-blind study design, showed beneficial effects of radon therapy as compared to interventions without radon inhalation; that is, interventions including radon showed significantly better pain reduction than those without radon [36]. In this study, the α-hANP in normal and RA groups increased and BP decreased, suggesting relaxation of the vascular smooth muscle. This finding indicates what may be part of the mechanism of increased tissue perfusion, namely, the decreased BP brought about by radon inhalation. These findings were consistent with the inhibitory action of

α-hANP. Furthermore, thoron and thermal treatment enhanced a ConA-induce mitogen response and increased the level of CD4-positive cells (CD4; antigen, which is a marker of helper T cells) and decreased the level of CD8-positive cells (CD8; antigen, which is a common marker of killer T cells and suppresser T cells). These findings suggest that thoron and thermal treatment contributes to the prevention of aging-related disease, which is related to immune suppression, by enhancement of the immunity function.

These findings suggest that thoron and thermal treatment contributes to alleviation of the symptoms of aging-related diseases, such as activation of the biological defense mechanism, or promoting physiologic changes such as tissue perfusion.

In this study, we did not elucidate the detailed mechanism of the effects of thoron and thermal treatment. In the future, detailed clarification of the mechanisms of these phenomena is required to understand the effects of thoron and thermal treatment on the functions of the living body, including adaptive responses.

ACKNOWLEDGMENTS

The authors are indebted to Dr. Akira Yoshida and his staff (Iwate Health Service Association, Japan) for assays and bathing guidance for the subjects.

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