

# The Relation of Prostate Tissue Protein Content, Nd : YAG Laser Transmissibility and Thermal Effect on Prostatic Hyperplasia

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As our society ages, safe and minimally invasive treatment for the frequent occurrence of prostatic hyperplasia have been sought. We have performed prostatic hightemperature treatment for prostatic hyperplasia with the Prostalase using neodymium : yatriumaluminum garnet (Nd : YAG) laser for patients suffering from a bladder outlet obstruction secondary to benign prostatic hyperplasia (BPH). We used agars which included various densities of protein and skim milk as test materials to determine whether the exothermic mechanism of the Nd : YAG laser irradiation has an effect on protein molecules. By measuring the temperature inside the test materials and the irradiation transmissibility, we verified that in tissues with the same degree of color, the higher the protein content, the stronger the exothermic action of the Nd : YAG laser. In addition, in three human prostates obtained through pathological autopsy, the measurement of the protein content and the temperature inside the prostatic tissue in which prostatic thermal treatment had been performed showed that the exothermic action of the Nd : YAG laser varied according to the protein content: the higher the protein content, the stronger was the exothermic action. The present findings suggest that the temperature inside prostatic tissue reaches at least 60~65°C with intissues with a protein content more than 23 g/100 g.

Key words : Nd : YAG laser, TUBL-T, Protein content

## Introduction

In the field of urology, the occurrence of benign prostaic hyperplasia (BPH) is already frequent and is expected to continue to increase with the aging of society. Methods of treatment for this condition that are safe and minimally invasive are thus desirable. Since Majin et al<sup>1)</sup>. first utilized local thermal stimulation of the prostate to treat prostatic diseases in 1980, various types of thermal devices have been developed. We currently use transurethral balloon laser thermotherapy (TUBAL-T) for BPH, in which a neodymium : yatriumaluminum garnet (Nd : YAG) laser is irradiated over 360° from a balloon probe

that is provided with a cooling water perfusion device so that the Nd : YAG irradiation is absorbed by the protein in the prostatic tissue to generate heat and therapy cause deep coagulonecrosis in the prostatic tissue. Generally, the effectiveness of this treatment varies depending upon the shape and size of the prostate and the quantity of energy delivered. However, even when TUBAL-T is performed at similar levels of energy to treat prostatic hyperplasia of similar size and shape, we find considerable variation in the effectiveness of the treatment. In the present study, to identify the causes of such differences, we focused on the point at which the Nd : YAG laser is converted from optical energy to thermal energy, and we investigated the relationship between the protein content in prostatic tissue and the effect of the Nd : YAG laser. We then considered the factors influencing changes in the protein content of the prostate resulting in differences in conservative treatment.

## Specimens and methods

### 1. Specimens

- A) We used coagulated agars with various densities of skim milk as test materials for the effect of the Nd : YAG laser on protein molecules.
- B) We used the prostatic tissue from six patients obtained through total prostatectomy and pathological autopsy. The ages of the patients ranged from 71~82 (average 77.7). Of these patients, two had been given hormonal therapy for more 3 months as a pre-operative treatment; both were given chlormadinone acetate. The remaining four patients had either been treated with non-hormonal therapeutic agents or were given no therapy (Table 1). We also used non-treated prostatic tissue from three other patients obtained through pathological autopsy to measure the temperature when TUBAL-T was performed at our department.

**Table 1.** Characteristics of patients, transmissibility, protein content and the pathological diagnosis

Patient	Age	Hormonal treatment over 3 months	Transmissibility (%)	Protein content (g/100 g)	Pathological diagnosis
1. N. T.	82	+	1.24	8.87	F
2. Y. T.	77	+	1.45	6.3	F
3. K. N.	75	-	1.04	14.08	G
4. M. M.	80	-	1.25	10.31	F
5. T. S.	81	-	0.98	18	G
6. F. Y.	71	-	1.04	13.48	G

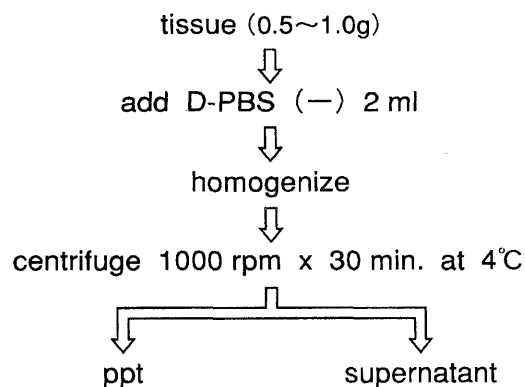
G = glandular hyperplasia > fibromuscular hyperplasia  
 F = fibromuscular hyperplasia > glandular hyperplasia

## 2. Methods

### A) Measurement of protein content in the prostatic tissue

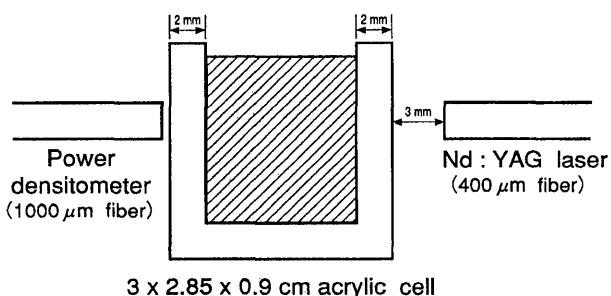
The prostatic tissue was cut into thin slices of 0.5~1.0 g. Two ml of phosphatebuffered saline (PBS) was added to the 0.5~1.0 g of tissue, and the mixture was homogenized and centrifuged for 30 minutes at 4°C at 1000 rpm. The protein content of the supernatant was measured using the Tonaine-TP method<sup>2)</sup> which was developed by improving the Bradford method<sup>3)</sup>, using Coomassie

#### A. Measurement of protein contents in prostatic tissue



After supernatant was collected, protein density was measured using Tonaine-TP.

#### B. Measurement of Nd : YAG transmissibility in prostatic tissue



**Fig. 1** The prostatic tissue was placed in an acrylic cell, and the Nd : YAG laser was output at 1W from a 400 μm fiber. The measurement was performed using a powerdensitometer.

Brilliant Blue G 250 (Fig. 1).

### B) Measurement of Nd : YAG laser transmissibility in the prostatic tissue

The prostatic tissue was placed in an acrylic cell, the Nd:YAG laser was output at 1 watt (W) from a 400 μm fiber, and the measurement of Nd : YAG laser power density was performed using a power densitometer (Fig. 1).

### C) Measurement of temperature

We measured the temperature of the specimens and that inside the human prostate using a 21G needle equipped with a K-thermal sensor. The temperature of the human prostate was measured at the point 5 mm outside the urethra and 2 mm towards the bladder neck from the center of the laser balloon.

### D) Histopathological probe

Six prostates were fixed in formalin, and embedded in paraffin. Hematoxylin- eosin (HE)-stained specimens were then prepared. The specimens were examined microscopically by only one pathologist to determine whether glandular hyperplasia or fibromuscular hyperplasia was dominant.

## Results

### 1. Measurement of the temperature inside agar and its transmissibility

The power densitometer result of the agar specimen with 5.6 g/100 g of protein content was 0.8 mW, the transmissibility of the Nd : YAG laser was 0.93%, and the cell temperature inside the specimen after 5 minutes was 40.4°C when 1W of the Nd : YAG laser was continuously irradiated. Under the same conditions, the agar specimen with 11.2 g/100 g protein content showed 0.5 mW on the power densitometer, the transmissibility was 0.52%, and the cell temperature inside the specimen was 52.5°C (Fig. 2). We examined the colors of the two specimens using a color comparing meter and confirmed that they were almost the same.

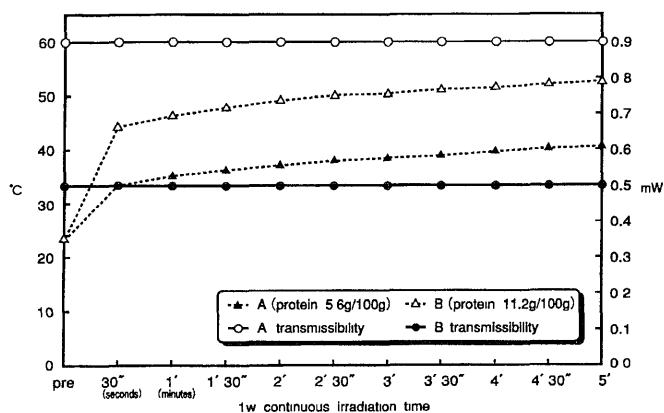


Fig. 2. Protein contents, temperature increase and transmissibility of the Nd : YAG laser irradiation in coagulated agar specimens with various densities of protein.

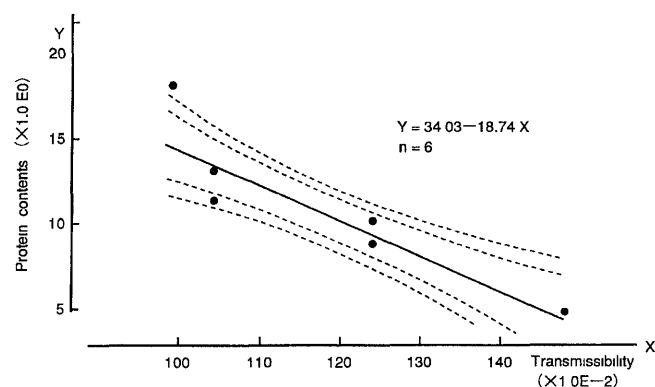


Fig. 3. Regression curves of the protein contents in the prostatic tissue and Nd : YAG laser transmissibility.

A striking inverse correlation with  $\gamma$  being -0.903 is shown, suggesting that protein contents influence the conversion of the Nd : YAG laser irradiation from optical energy to thermal energy.

2. Protein content in the prostatic tissue

The protein content of the six patients ranged from 8.3~18 (average 12.2) g/100 g. The protein content of two patients previously treated with hormonal agents ranged from 6.3~8.87 (average 7.59) g/100 g, and that of the group not previously treated with hormonal agents ranged from 10.31~18 (average 13.97) g/100 g. The group not previously treated with hormonal agents demonstrated higher levels of protein content (Table 1).

3. Nd : YAG laser transmissibility in the prostatic tissue

The Nd : YAG laser transmissibility in the prostatic tissue of the six patients ranged from 0.98~1.45 (average 1.17)%. The transmissibility in the patients previously treated with hormonal agents was from 1.24~1.45 (average 1.34)%, and that of the group not previously treated

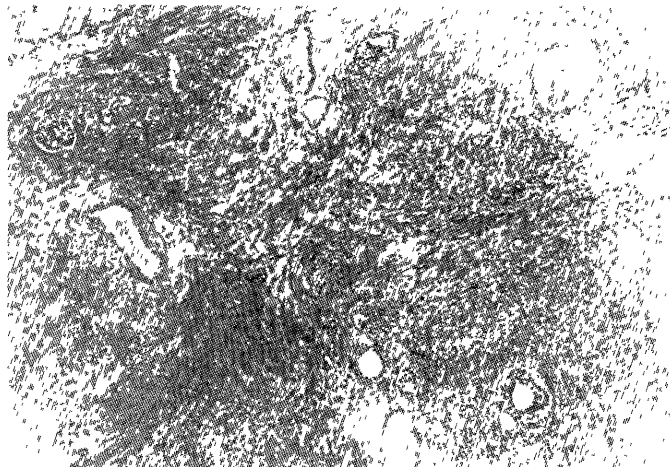


Fig. 4. A prostate tissue specimen from a patient showing a dominance of fibromuscular hyperplasia. The number and the size of the glandular tubes were decreased, the height of the secretory epithelia was lower, and the shape of the secretory epithelia was cubic or flat. A striking increase in fibromuscular tissue is seen (HE stain ; x100).

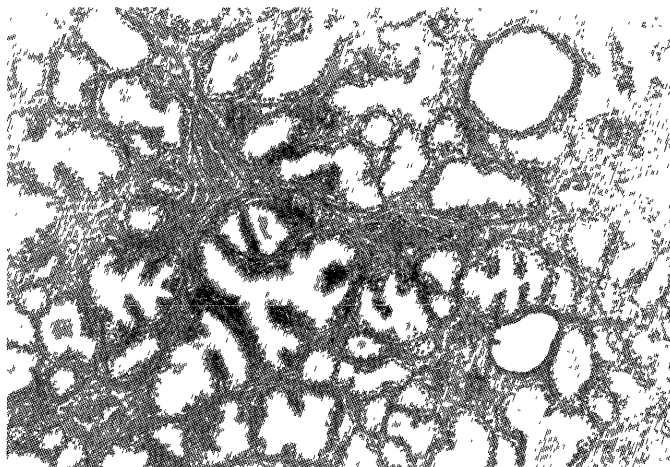


Fig. 5. A prostate tissue specimen with a dominance of glandular hyperplasia. The size of the glandular tubes has become bigger, with two-strata disposition of tall cylindrical secretory epithelia and a basal cell stratum (HE stain ; x100).

with hormonal agents ranged from 0.98~1.25 (average 1.08)%. The Nd : YAG laser transmissibility was lower in the group not previously treated with hormonal agents (Table 1). These results showed a striking inverse correlation between the protein content in the prostatic tissue and the effect of the Nd : YAG laser on the prostatic tissue, with  $\gamma$  being -0.903 : this inverse correlation is represented in regression curves (Fig. 3).

4. Histopathological probe

Three of the six patients showed a dominance of fibromuscular hyperplasia, and the other three showed a dominance of glandular hyperplasia (Table 1). In the

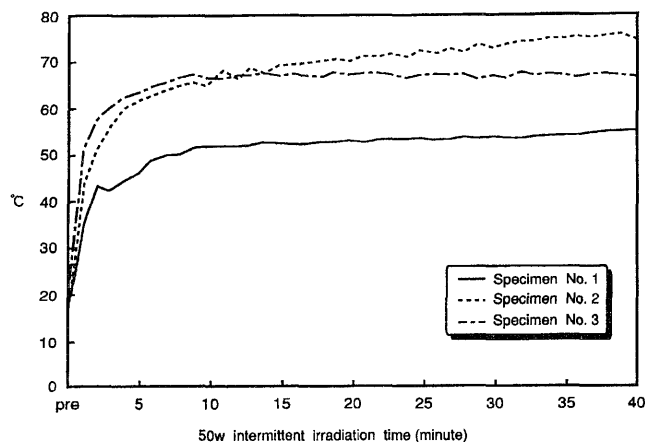


Fig. 6. Highest temperature of human prostate specimens obtained with Nd : YAG laser irradiation.

group that showed a dominance of fibromuscular hyperplasia, the number and size of the glandular tubes were reduced, the height of the secretory epithelia was lower, and the shape of the secretory epithelia had become cubic or flat (Fig. 4). A striking increase in fibromuscular tissue was observed. In contrast, in the patient group showing a dominance of glandular hyperplasia, the size of the glandular tubes had become bigger, and the tubes consisted of two-strata disposition of tall cylindrical secretory epithelia and a basal cell stratum (Fig. 5). The relation between the histopathological findings and previous hormonal treatment was as follows: the two patients previously treated with hormonal agents showed a dominance of fibromuscular hyperplasia, while three of the four patients in the group with no previous hormonal treatment showed a dominance of glandular hyperplasia.

##### 5. Measurement of the protein content in human prostatic tissue

We inserted a laser balloon catheter into the prostatic tissue specimens as we do clinically and irradiated intermittently for 40 minutes at 50W. The measurement of the protein content was performed at the points where the power density became the highest and at sites 5 mm from the right and left sides of that point before irradiating the Nd : YAG laser. The protein content of specimen No.1 was 19.95~22.83 (average 20.9) g/100 g, of No.2 was 22.3~26.6 (average 24.5) g/100g, and of No.3 was 21.4~23.9 (average 22.5) g/100 g. In regard to the highest temperature of these human prostatic tissue 40 minutes after this TUBAL-T was performed, that of specimen No.1 was 55.3 °C, that of No.2 was 78.1° and that of No.3 was 67.7°C (Fig. 6).

## Discussion

In today's aging society, the incidence of cases of dysuria caused by prostatic hyperplasia are bound to increase, and the number of such patients with various complications (such as cardiac disorders) will also increase. Methods which are less invasive such as urethral dilatation and placement of an intraurethral stent, have been developed to treat patients in whom transurethral resection of the prostate (TUR-P) cannot be performed due to serious complications, and to improve the quality of life of the patients. The ProstateLase irradiates Nd : YAG laser to internal region of the prostate from a flexible laser balloon catheter, causes necrosis and coagulation and, by perfusion of the inside of the balloon with cooling water, keeps the temperature of the prostatic urethra below body temperature down to a depth of several millimeters to protect the urethral mucosa. The purpose of this method is to cause a second-phase reaction in the human body by Nd : YAG laser irradiation, i.e., to make the tissue temperature 60~65°C, to induce a non-reversible change in the protein, and to cause necrosis to the tissue structure. On that point, the treatment by the ProstateLase is different from the vaporization of visual laser ablation of the prostate (VLAP) and interstitial laser coagulation (ILCP). The effective mechanism of TUBAL-T on prostatic hyperplasia in the canine was reported by Suzuki et al<sup>4)</sup>, and that of human prostatic hyperplasia was reported by Furuya et al<sup>5)</sup>. Furuya stated that TUBAL-T improved dysuria due to prostatic hyperplasia by inducing the degeneration and necrosis of smooth muscle tissue surrounding the urethra. This degeneration is caused by the high temperature.

The results we obtained in the present study show that in prostate tissue of the same color, the higher the protein content, the higher the temperature by the Nd : YAG laser and the lower the Nd : YAG laser transmissibility. These findings suggest that (1) protein molecules influence the conversion of the Nd : YAG laser irradiation from optical energy to thermal energy, and (2) the higher the protein content, the greater the exothermic action of the Nd : YAG laser.

The relation between the protein content of human prostatic tissue and transmissibility of the Nd : YAG laser indicates a striking inverse correction, with an  $\gamma$  value of  $-0.903$ . Along with the results mentioned above, the higher the protein content, the more easily is the optical energy of the Nd : YAG laser converted from optical energy to thermal energy and the lower the Nd : YAG laser transmissibility is. The human prostatic protein content findings and the temperature measurements showed that the higher the protein content, the higher was the tissue temperature. Because the prostates were obtained through pathological autopsy, the heat radiation by blood flow was not taken into consideration: however, in approxi-

mately 25 g/100 g of the protein content, we obtained an ideal tissue temperature higher than the second temperature phase (60~65°C), at which the laser influences human tissue. Generally speaking, tissue change caused by the administration of an anti-androgen agent can be seen in the tubular epithelia of prostatic tissue, especially secretory epithelia, and the major changes are the degeneration of tubular epithelia, and progressive changes such as detachment and dropping from the basal tissue stratum. These changes have been observed 3~6 months after the start of the anti-androgen administration<sup>7-9)</sup>. In the histopathological probe experiment of the present study, similar changes tended to be occur in the patients previously given hormonal therapeutic agents. The difference of the clinical effectiveness of the Nd : YAG laser irradiation caused by whether or not hormonal agents were previously administered lies in the following mechanism : in patients in whom an anti-androgen agent has been administered over a long period of time, the amount of prostatic fluid decrease with the reduction of the glandular components. As a result, since a reduction of the protein content is observed, this inhibits the conversion of the optical energy of the Nd : YAG laser to the thermal energy. The clinical effectiveness varies according to whether or not hormonal agents were previously administered, because an effective increase in the temperature cannot be achieved when such pretreatment was administered.

## Conclusion

1. The exothermic action of the Nd : YAG laser is influenced by the protein content of prostate tissue besides color. The higher the protein content, the greater the exothermic effect.
2. The two patients in whom hormonal therapy had been administered as a pre-operative treatment showed

protein contents lower than those of the group who had not received hormonal treatment.

3. A clear inverse correlation was observed between the protein content of the prostatic tissue and the transmissibility of the Nd : YAG laser in the prostatic tissue.
4. The higher the protein content in the prostatic tissue, the more efficiently the optical energy of the Nd : YAG laser is converted to the thermal energy ; the temperature of the prostatic tissue was high when TUBAL-T had been administered.

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