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Thermal coagulation-induced changes of the optical properties of normal and adenomatous human colon tissues *in vitro* in the spectral range 400–1100 nm

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Abstract

The absorption coefficients, the reduced scattering coefficients and the optical penetration depths for native and coagulated human normal and adenomatous colon tissues *in vitro* were determined over the range of 400–1100 nm using a spectrophotometer with an internal integrating sphere system, and the inverse adding–doubling method was applied to calculate the tissue optical properties from diffuse reflectance and total transmittance measurements. The experimental results showed that in the range of 400–1100 nm there were larger absorption coefficients ($P < 0.01$) and smaller reduced scattering coefficients ($P < 0.01$) for adenomatous colon tissues than for normal colon tissues, and there were smaller optical penetration depths for adenomatous colon tissues than for normal colon tissues, especially in the near-infrared wavelength. Thermal coagulation induced significant increase of the absorption coefficients and reduced scattering coefficients for the normal and adenomatous colon tissues, and significantly reduced decrease of the optical penetration depths for the normal and adenomatous colon tissues. The smaller optical penetration depth for coagulated adenomatous colon tissues is a disadvantage for laser-induced thermotherapy (LITT) and photodynamic therapy (PDT). It is necessary to adjust the application parameters of lasers to achieve optimal therapy.

1. Introduction

More than 85% of all cancers originate in the epithelia lining of the internal surfaces of the human body. In the human colon tissue, the lining of the mucosa, epithelium layer, is

commonly the cradle of malignant tumors. Thus cancer of the colon is one of the most common malignant tumors worldwide (Parkin *et al* 2005, Yoshimi and Sobue 2004). Surgery is currently the only potentially curative therapeutic option for treating colon carcinomas. However, almost half of all patients with colon carcinomas can no longer be considered for curative therapy at the time of diagnosis, considering various prognostic factors such as number and size of liver metastases, tumor-free resection margins, presence of extra hepatic metastases, extent of lymph node involvement and histology of the primary tumor. Local therapeutic application of laser light such as laser-induced thermotherapy (LITT) (Chapman 1998, Vogl *et al* 2003, Klingenberg *et al* 2000) and laser ablation (Panchenko *et al* 2004, Walfisch *et al* 1989) is considered a promising treatment, whereas laser recanalization (Kiefhaber *et al* 1986, Eckhauser *et al* 1989) of malignant intestinal stenose is a palliative treatment and purely experimental at present, especially with regard to the risk of intestinal perforations (Rao *et al* 2005). Precise knowledge about the spatial distribution of temperature and their induced thermal tissue damage in the specific target tissue is of decisive importance to control the extent of tumor destruction and ensure safe and effective treatments. Real-time monitoring techniques like MR are available for interstitial coagulation, but LITT-induced thermal tissue reactions are not immediately detectable morphologically and only become manifest after a delay of several days (Thomsen 1991, Johnson *et al* 1992).

Knowledge regarding light distribution is essential for safe and effective laser application. Light distribution is mainly determined by the optical properties of the target tissue (absorption coefficient μ_a, scattering coefficient μ_s, anisotropy factor g, optical penetration depth δ) (Jacques 1992, Wang *et al* 1995), which may considerably differ depending on the tissue structure and components (Bosman 1993). Especially in laser-induced thermotherapy of colon tumors, it is necessary to determine the parameters of healthy colon tissue and adenomatous tissue not only in the native but also in the coagulated state.

The optical properties of normal and adenomatous colon tissues in the native state have been reported previously by several groups (Hidović-Rowe and Claridge 2005, Marchesini *et al* 1994, Zonios *et al* 1996, Wei *et al* 2005). Hidović-Rowe and Claridge (2005) have calculated the spectral reflectance of the human colon tissue for ranges of histological parameters using Monte Carlo simulations. Marchesini *et al* (1994) have derived the absorption and reduced scattering coefficients of the *ex vivo* human colon tissue for the range 300–800 nm from reflectance and transmittance measurements by using the 1D diffusion approximation of the radiative transfer equation. Zonios *et al* (1996) have calculated the scattering and absorption coefficients of human normal and adenoma colon tissues in the range 300–700 nm by computing Kubelka–Munk coefficients. Wei *et al* (2005) have determined and compared differences in the absorption and scattering properties between the normal and adenomatous human colon mucosa/submucosa, and between the normal and adenomatous muscle layer/chorion *in vitro* in the range 630–890 nm. In all the above works, the experiments are only performed for the human colon tissue in the native state and the relatively narrow wavelength range. The aim of this experimental study was to compare the optical properties of healthy colon as well as adenomatous colon tissues with those of the coagulated ones, in order to test the effect of thermal coagulation on the optical parameters, since the optical properties of the tissue change by laser radiation due to coagulation (Ugryumova *et al* 2004).

All tissue types were examined in the wavelength range of 400–1100 nm. In addition, the results were evaluated for inter-individual differences that might be important for individual calculations. To confirm the precision of our experimental setup, optical parameters were also assessed for intra-individual sample differences by measuring three independent samples from each patient and tissue type.

2. Materials and methods

2.1. Sample preparation

In vitro optical properties were investigated for four kinds of tissues: normal and adenomatous human colon, and coagulated normal and adenomatous human colon. Human colon tissue samples were obtained from six patients' colon resections which were performed to remove previously diagnosed adenocarcinomas. Each removed colon section was immediately rinsed briefly in saline to remove surface excess blood and peeled-off surface fats. Then, using a scalpel the polyps were smoothly resected with some surrounding tissue as the adenomatous colon tissue sample, the residual edge tissue studied as a normal colon tissue. The separate tissue sections were placed in a bottle with saline as soon as possible, stored in a refrigerator at -70 °C, and then sectioned by microtome before measurement. For each human colon, we only pick the first slice which is part of the mucosa layer or a combination slice of the mucosa layer and the submucosa layer. For the normal human colons, a total of six tissue samples, with a mean thickness of 0.40 mm, were used. For the adenomatous human colons, a total of six tissue samples, with a mean thickness of 0.40 mm, were used. All tissue samples were respectively clamped between two glass slides with 0.13 and 1.1 mm thickness, and were then placed between the two integrating spheres before tissue samples were measured. After measuring the optical properties in the native tissue state, each sample was put into a cuvette and together coagulated in a water bath at 80 °C for 10 min to evaluate the effect of thermal coagulation. The thickness of the coagulated tissue samples was measured after the water bath. Tissue samples were prepared and measurements were taken within 16 h after the removal.

2.2. Methods

2.2.1. Measurement of tissue optical properties. The integrating-sphere technique, which is widely used for the determination of the optical properties of biological tissues *in vitro* (Ugryumova *et al* 2004, Sardar *et al* 2005, Bashkatov *et al* 2005), is employed in this study. Diffuse reflectance and total transmittance measurements have been performed in the 400–1100 nm wavelength range with 5 nm intervals using the commercially available spectrophotometer (PerkinElmer, USA, LAMBDA 35) equipped with an internal integrating sphere system (Labsphere, RSA-PE-20). The inner diameter of the sphere is 50.8 mm, and the diameters of the entrance and exit ports are 12.5 mm. As a light source, a wolfram halogen lamp with filtering of the radiation in the studied spectral range has been used in the measurements. The diameter of the incident light beam on the tissue sample is 1 mm $\times$ 7.5 mm (width $\times$ height) with a 2 nm slit width. Scans were conducted at a speed of 240 nm min^{-1} without any smoothing. The measurements were carried out at a room temperature of about 20 °C.

Two measurements were done for each sample and wavelength. To measure the total transmission *Tt*, the sample holder was attached to the transmission port. The remission port was closed with a spectralon-coated standard, and the total light intensity penetrating the tissue was recorded. To measure the diffuse remission *Rd*, the sample holder was positioned at the remission port, and a significant portion of the backscattering was registered. It is important to note that both *Rd* exhibit an inherent systematic error because backscattered photons with scatter angle near π could eventually leave the transmission port without being detected. However, this systematic error was taken into consideration during the calculation of the optical parameters.

2.2.2. Calculation of tissue optical parameters. The inverse adding–doubling (IAD) (Prahl *et al* 1993) numerical procedure is applied to determine the optical properties from the total diffuse reflectance (R_d), total transmittance (Tt) and the physical thickness of the sample. A set of optical properties is estimated by the IAD program and the values of Rd and Td are calculated iteratively until these values match the experimental values of Rd and Td. When the calculated values of Rd and Td match the experimental values, the estimated optical properties are regarded to represent the real optical properties of the tissue sample; these values are then given as the output of the program in terms of the two dimensionless quantities: albedo α and optical thickness τ, which are defined as follows (Prahl *et al* 1993):

$$\alpha = u_s(u_s + u_a)^{-1}, \tag{1}$$

$$\tau = d(u_s + u_a), \tag{2}$$

where d is the physical thickness of the sample and is measured in mm. The values of α and τ provided by the IAD method are then used to calculate the absorption coefficient (μ_a) and scattering coefficient (μ_s):

$$u_s = \alpha\tau d^{-1}, \tag{3}$$

$$u_a = \tau(1 - \alpha)d^{-1}. \tag{4}$$

The algorithm accounts for the refractive index of the glass slides ($n \approx 1.55$) and for the tissue ($n \approx 1.4$) (Bolin *et al* 1989). For all the IAD calculations, the scattering anisotropy factors of all colon tissue samples are assumed to be constant. Ritz *et al* (2001) demonstrated that the values of the anisotropy factor g over the wavelength range from 400 to 2400 nm do not vary considerably for the liver. Holmer *et al* (2006) measured that the average value of the anisotropy factor g for the colon is 0.9 between 800 and 1100 nm. We used $g = 0.925$, which is an unpublished datum measured by Wei *et al* (2005) in the late study. The specular reflectance and refraction at the tissue/glass/saline boundary have been corrected. See Jacques *et al* (1987) for a complete description.

3. Result

This investigation involves four kinds of tissue samples, normal colon in the native and coagulated states and adenomatous colon in the native state and each kind of tissue involves a total of six tissue samples. Each tissue sample was measured twice for each incision area of the tissue slice, respectively, and each measured value at each wavelength under the same condition of experimentation was the average of 24 ($2 \times 2 \times 6$) repeated measurements for each kind of tissue sample. There are no significant differences in the measured values Rd or Td between the two incision areas for a particular sample irradiated by a particular wavelength. Consequently, the mean values of Rd and Td of the two incision areas of all samples per tissue kind were obtained from these measurement data. After coagulation by water bath, the thickness of the sample reduced by an average of 19%, which was taken into consideration in the calculation of the optical properties.

Typical spectra of reflectance and transmittance are presented in figure 1. In the reflectance and transmittance spectra of the adenomatous colon tissue in the native state, figures 1(b) and (d), three spectral bands corresponding to blood absorption in the visible were clearly seen. There is the Soret band with the maximum at 415 nm, the α-band with the maximum at 540 nm and the β-band with the maximum at 575 nm of oxyhemoglobin absorption. Besides that, a peak around 965 nm presented itself in all these spectra. It was observed that the reflectance of

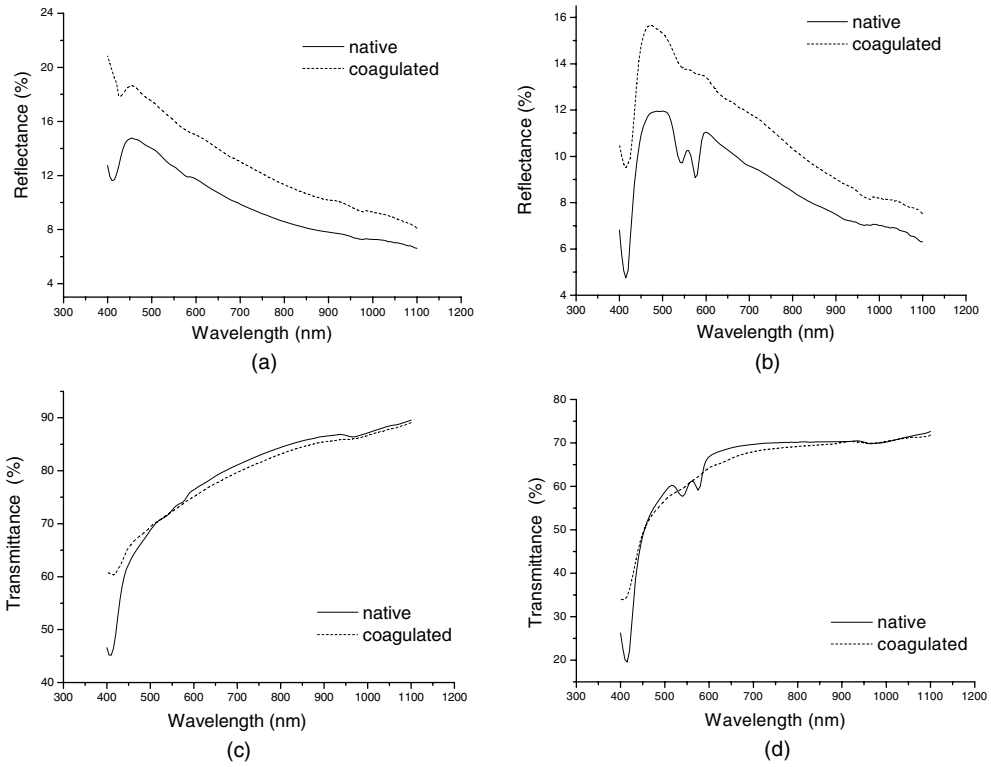

Figure 1. The raw experimental spectra of the human colon tissue in native (—) and coagulated (. . .) states: (a) reflectance spectra of normal tissue, (b) reflectance spectra of adenomatous tissue, (c) transmittance spectra of normal tissue and (d) transmittance spectra of adenomatous tissue.

normal and adenomatous human colon mucosa/submucosa increased about 30% after thermal coagulation, as seen in figures 1(a) and (b). However, there was no significant change in the transmittance spectra except for the decrease of the peak related to hemoglobin, figures 1(c) and (d).

By the IAD method we derived the wavelength dependence of the absorption coefficients and the scattering coefficients for these tissues from these measurements, and the reduced scattering coefficient ($\mu_s' = \mu_s(1 - g)$), and the optical penetration depth ($\delta = 1/\sqrt{3\mu_a(\mu_a + \mu_s')}$), were calculated from the measured optical properties.

The absorption coefficient μ_a of human normal and adenomatous colon mucosa/submucosa and those then coagulated ones are shown in figures 2(a) and (b), respectively. Both the native normal and adenomatous colon mucosa/submucosa showed absorption peaks at about 415 nm, reaching a value of 0.560 mm^{-1} and 1.121 mm^{-1}, respectively. The coagulated normal colon tissue had absorption behavior similar to that of the native one, but the maximum absorption is shifted to 425 and 410 nm (0.358 mm^{-1}, 0.784 mm^{-1}) for the normal and adenomatous colon tissues, respectively. The two absorption maxima at 540 and 575 nm of the native adenomatous colon disappeared after coagulation. Coagulation increased the absorption coefficient on average in the range 450–1100 nm by about 0.04 mm^{-1} for the normal colon, and by 0.06 mm^{-1} for the adenomatous colon. The greatest changes of coagulation on absorption coefficients for normal and adenomatous colon mucosa/submucosa were at 410 nm (0.23 mm^{-1}) and 415 nm (0.35 mm^{-1}), respectively.

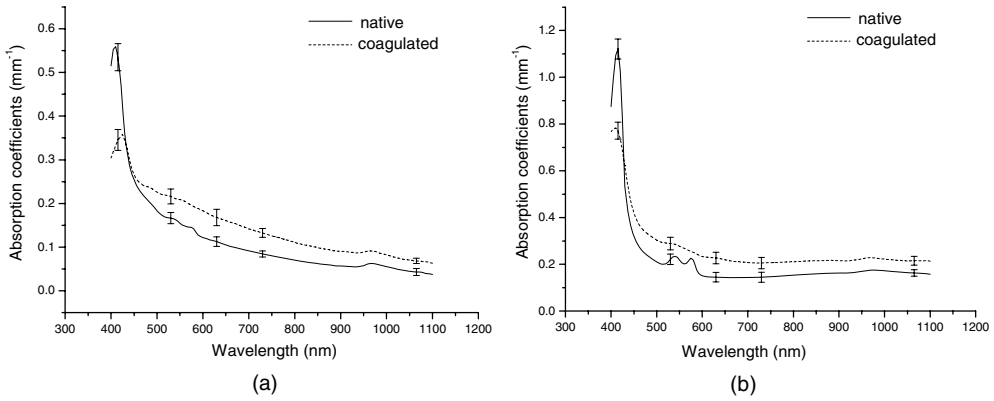

Figure 2. The absorption coefficients of normal (a) and adenomatous (b) human colon mucosa/submucosa at native (—) and coagulated (. . .) states, calculated with the IAD method.

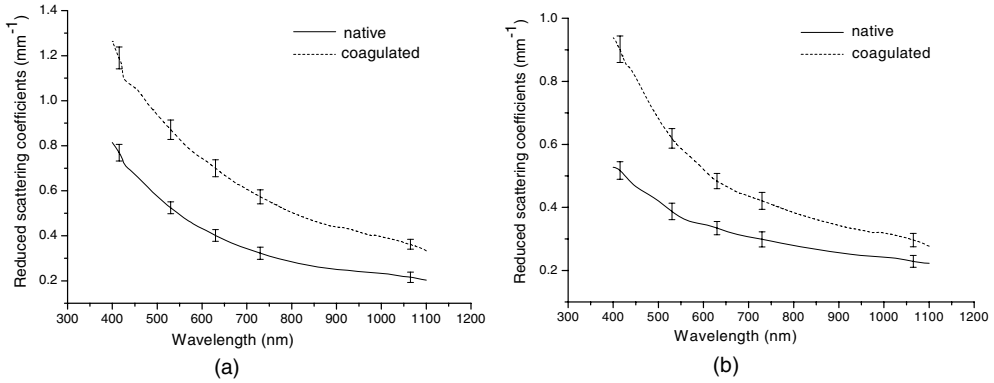

Figure 3. The reduced scattering coefficients of normal (a) and adenomatous (b) human colon mucosa/submucosa at native (—) and coagulated (. . .) states, calculated with the IAD method.

Figures 3(a) and (b) show the comparison of reduced scattering coefficients μ_s' of human native colon mucosa/submucosa to those coagulated ones for healthy and adenomatous tissues, respectively. The reduced scattering coefficients of all the four kinds of tissue samples decreased with wavelength. Coagulation changed the reduced scattering coefficients of the normal and adenomatous human colon mucosa/submucosa by increasing them by 0.13–0.45 mm^{-1} and 0.05–0.41 mm^{-1}, respectively, in the 400–1100 nm range. The reduced scattering coefficients for normal colon mucosa/submucosa in the native and coagulated states at 400 nm are 0.815 mm^{-1} and 1.264 mm^{-1}, respectively, and for adenomatous colon mucosa/submucosa in the native and coagulated states at 400 nm are 0.528 mm^{-1} and 0.939 mm^{-1}, respectively. The reduced scattering coefficients for normal colon mucosa/submucosa in the native and coagulated states at 1100 nm are 0.203 mm^{-1} and 0.333 mm^{-1}, respectively, and for adenomatous colon mucosa/submucosa in the native and coagulated states at 1100 nm are 0.223 mm^{-1} and 0.277 mm^{-1}, respectively.

The optical penetration depths of health and adenomatous colon mucosa/submucosa compared with those coagulated ones are illustrated in figure 4. As a result of the absorption and reduced scattering coefficient changes, the optical penetration depth of normal native

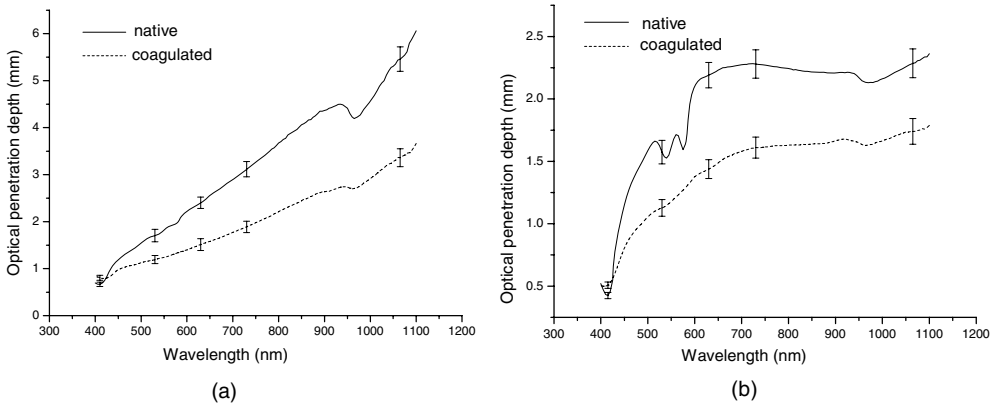

Figure 4. The optical penetration depths of normal (a) and adenomatous (b) human colon mucosa/submucosa at native (—) and coagulated (. . .) states, calculated with the IAD method.

Table 1. Optical properties of human colon mucosa/submucosa at selected wavelengths.

	Wavelength	Native			Coagulated		
Condition	(nm)	μ_a	μ_s'	δ	μ_a	μ_s'	δ
Health	415	0.535 ± 0.031	0.769 ± 0.037	0.069 ± 0.046	0.346 ± 0.024	1.190 ± 0.049	0.793 ± 0.053
	530	0.166 ± 0.013	0.524 ± 0.026	0.170 ± 0.134	0.216 ± 0.017	0.871 ± 0.043	1.191 ± 0.086
	630	0.113 ± 0.011	0.396 ± 0.026	2.402 ± 0.120	0.168 ± 0.019	0.670 ± 0.048	1.513 ± 0.127
	730	0.084 ± 0.007	0.322 ± 0.027	3.117 ± 0.163	0.132 ± 0.010	0.573 ± 0.031	1.889 ± 0.121
	1065	0.043 ± 0.008	0.216 ± 0.023	5.460 ± 0.261	0.068 ± 0.006	0.363 ± 0.022	3.361 ± 0.193
Adenomatous	415	1.121 ± 0.043	0.517 ± 0.028	0.426 ± 0.025	0.772 ± 0.036	0.902 ± 0.042	0.508 ± 0.026
	530	0.221 ± 0.022	0.387 ± 0.026	1.574 ± 0.094	0.289 ± 0.027	0.619 ± 0.031	1.127 ± 0.067
	630	0.145 ± 0.020	0.334 ± 0.021	2.191 ± 0.102	0.227 ± 0.025	0.484 ± 0.024	1.437 ± 0.076
	730	0.145 ± 0.021	0.299 ± 0.024	2.280 ± 0.113	0.205 ± 0.024	0.421 ± 0.027	1.610 ± 0.084
	1065	0.163 ± 0.014	0.229 ± 0.019	2.285 ± 0.116	0.216 ± 0.019	0.296 ± 0.021	1.739 ± 0.103

colon mucosa/submucosa increased with wavelength except for around the absorption peak at 415 nm and 965 nm. The optical behavior of normal colon mucosa/submucosa tissue in a coagulated state resembles that of tissue in the native state. Corresponding to the two maxima absorption in the native adenomatous colon, the optical penetration depth of the native adenomatous tissue had two minima penetration depths at 540 and 575 nm, which disappeared after coagulation. Coagulation decreases the optical penetration depth significantly in the range 450–1100 nm both for health and adenomatous colon mucosa/submucosa. The optical penetration depth for normal colon mucosa/submucosa at 1100 nm is 6.06 mm, which decreases to 3.66 mm after being coagulated. The optical penetration depth for adenomatous colon mucosa/submucosa at 1100 nm is 2.36 mm which decreases to 1.79 mm. Obvious negative peaks are found in the optical penetration depth spectra; they are 4.193 mm at 965 nm and 2.701 mm at 960 nm for normal colon mucosa/submucosa, and 2.130 mm at 970 nm and 1.628 mm at 960 nm for adenomatous colon mucosa/submucosa.

The optical properties of the native and thermal coagulated human colon mucosa/submucosa at selected wavelengths are summarized in table 1.

4. Discussion

In this study, we analyzed the effects of coagulation on the optical properties of the human normal and adenomatous colon mucosa/submucosa *in vitro*. Optical properties were measured according to the single integrating sphere principle in the native state and after thermal coagulation in the wavelength range of 400–1100 nm and analyzed by the IAD method. It is found that after thermal coagulation, the absorption coefficient increased slightly above 450 nm up to 1100 nm as seen in figures 2(a) and (b). The increase in the absorption coefficient is basically a result of denser packing of cells owing to shrinkage of the tissue samples, while the number of chromophores remained constant (Germer *et al* 1998, Pickering *et al* 1993, Bosman 1993, Zhu *et al* 2003). However, around the peak at 415 nm the absorption coefficient is decreased by coagulation for both health and adenomatous colon tissues, which is probably due to denaturizing of tissue chromophores hemoglobin. Hemoglobin acts as a strong light absorber in the visible range and has a feature absorption at 414 nm and two maxima at 540 and 575 nm (for oxy-hemoglobin) (Takatani and Graham 1987, Meinke *et al* 2007). Nevertheless, the hemoglobin peaks (540 and 575 nm) seem disappeared after thermal coagulation. The interpretation for this observation should be the formation of methemoglobin during human colon tissue heated in an 80 °C water bath. Oxidation of hemoglobin (ferrous state) to methemoglobin (ferric state) due to heat or photo-induced heat has been reported previously by several authors (Barton *et al* 2001, Randeberg *et al* 2002). Methemoglobin has characteristic absorption peaks at 404, 508 and 635 nm (Fishkin *et al* 1995, Randeberg *et al* 2004, Barton *et al* 2001). Following the formation of methemoglobin, oxyhemoglobin absorption peaks at 415, 542 and 576 nm decrease, and this phenomenon is obvious especially in the adenomatous colon mucosa/submucosa tissue, see figure 2(b), because of the increased blood volume in the carcinoma tissue, most likely due to neovascularization. Furthermore, the water absorb peak around 965 nm is still observable after tissue coagulation both in normal and adenomatous colon mucosa/submucosa, which indicates the incomplete dehydration by coagulation.

However, the reduced scattering coefficient increased by thermal coagulation at all wavelengths investigated as seen in figures 3(a) and (b). This can be caused by the disarrangement and fragmentation of the collagen fibers, the disintegration of cells and subcellular organelles, and by the vaporization of the extracellular and intracellular fluid. Human colon mucosa/submucosa tissue can be described by different sizes of scattering particles of various refractive indices distributing in the ground medium. Small capillaries, collagen fibers, cells, cell nuclei and subcellular organelles, such as mitochondria, are assumed to be the most important scatterers, and extracellular and intracellular fluid are the major ground medium. Tissue's scattering properties depend on the refractive index of the scattering particles and the ground medium, on the size of the scattering particle and on their arrangement (or distribution) (Wang *et al* 2005, Meinke *et al* 2007). For non-interacting Mie scatters, the reduced scattering coefficient of spheres is determined by the ratio of the refractive indices of scattering center and ground matter (Brezinski *et al* 2001, Graaff *et al* 1992). If the mismatch between scattering centers and the ground substance decreases, it would result in less scattering at the interface between the ground substance and cellular components. Bosman's (1993) transmission electron microscopy (TEM) observations on myocardium demonstrated that the average size of the subcellular organelles and their fragments such as myofilaments, mitochondria and granules arising inside the mitochondria decreased as a function of temperature from 45 °C to 75 °C. Also they observed disarrangement of the regular packing of myofilaments at 50 °C, and the most pronounced change in optical properties starts at 45 °C.

Consequently, the optical penetration depth of the colon mucosa/submucosa decreased by the coagulation processing above 450 nm as seen in figures 4(a) and (b). The highest optical penetration depth for all tissue types was obtained at the end of the spectral range investigated. The highest penetration depths of 6.061 mm (healthy colon), 2.363 mm (colon carcinoma tissue) were at 1100 nm, the values decreased significantly to 3.662 mm and 1.788 mm after thermal coagulation.

5. Conclusion

In conclusion, the optical properties of healthy and adenomatous human colon mucosa/submucosa are affected by thermal coagulation. Coagulation increases the absorption coefficient above 450 nm and increases the reduced scattering coefficient at all wavelengths investigated. The change in the absorption coefficient by coagulation around 415 nm is obviously larger than the other wavelength range. The change behavior of coagulation on the optical properties for adenomatous colon mucosa/submucosa is not the same as that of healthy tissue for their difference on component and their structure. The optical penetration depth of coagulated adenomatous human colon mucosa/submucosa significantly differs from that of the native one. We believe these differences are available for LITT.

Further more works on light distribution dependence on selected application parameters, temperature distribution dependency on light distribution, tissue damage dependence on temperature should be devoted.

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