Journal of Innovative Optical Health Sciences
Vol. 4, No. 4 (2011) 421–428

DOI: 10.1142/S1793545811001538

POTENTIAL OF *IN VIVO* LATENT-TIME ESTIMATION BY LASER AND OPTICAL TECHNIQUES IN CLINICAL AND EXPERIMENTAL DERMATOLOGY

NATALJA SKREBOVA EIKJE
MC Professional OÜ, Võistluse 23/25-35, Tallinn 10132, Estonia
eikje.mcproffou@gmail.com
mcproffou@gmail.com

Accepted 10 April 2011

The lag (latency) time (LT) is known in dermatology clinic as an asymptomatic period till the development of skin eruptions. In the laboratory, the LT might determine the interval from "zero" point until the peak(s) of changes in measured laboratory parameter during the performed test. This paper discusses methodological and technical aspects of precise measurement of the LT in the living healthy and pathological skin by laser and optical technologies through clinical and experimental applications in dermatology. Based on a dynamics approach to measure, calculate and interpret the LT in blood and in interstitial fluid compartments of the skin tissue, this method has a potential to promote deeper understanding of the role of complex dynamic processes in the skin at a level of a molecule, and/or an organ in a whole organism. The method of the LT measurement *in vivo* also promotes new understanding of (patho)physiological, diagnostic and pharmacological aspects of certain dynamic skin lesions and dynamic complex processes that happen in the skin. Utilized laser and optical techniques showed high reliability and objectivity in collecting data from rapidly changed skin lesions and processes, demonstrating the LT measurement as a very easy-to-use calculation procedure with high informativity, which is extremely important for the clinical and laboratory environment.

Keywords: Lag/latency time; *in vivo* skin; laser and optical technologies.

1. Introduction

Many decades literature describes much quantitative work that has been done to ascertain how far any biological action runs in parallel with the amount of given physical stimulus, but this has been mostly done on plants, histological sections, cultures, samples, etc., and using methods for *in vitro* evaluation.[1] In clinical and experimental dermatology not only new methods to quantify changeable biological phenomena *in vivo* are much desired, but also the usage of appropriate metrology in cutaneous noninvasive investigations is very much wanted. The latter especially helps impressions to be replaced by objective facts and qualitative descriptions by quantitative assessments, to unveil new situations. Even the most simple phenomenon that starts from one fact could become complex when measured, consequently discovering possible variations to induce new hypotheses and to open pathways for new knowledge.[2]

Laser and optical technologies for measuring the skin tissue *in vivo* provide a possibility to evaluate dynamic processes in the living skin as on the level of a molecule, so as an organ in a whole organism.[3]

This has been already demonstrated by laser Doppler flowmetry (LDF) technique for measuring the local microcirculatory dynamics underlying urticarial phenomenon in the patients with several types of physical urticaria.[3−6] Also the utility of horizontally attenuated total reflection Fourier transform infrared (HATR-FTIR) spectroscopy for measuring the dynamical changes of glucose levels in interstitial fluid (IF) compartment in the uppermost skin of the patients with prediabetes and diabetes mellitus has been demonstrated.[7,14−16]

In dermatological clinic the lag (latency) time (LT) is known as an asymptomatic period until the development of symptoms in the skin, which can be reproduced experimentally with cutaneous stimulation in the clinical environment. So, the patients with some forms of physical urticaria have been involved in the studies demonstrating the utility of LDF for measuring the LT *in vivo* during provocation testing on their skin.[3,6]

In the laboratory, LT might mean the time interval determining the peak(s) of changes in measured laboratory parameter during the performed test. For LT determination, calculation and interpretation of dynamical changes of interstitial glucose values measured in epidermis during different metabolic conditions/tests, HATR-FTIR spectroscopy has been used in comparative studies on the skin of healthy, prediabetes and diabetes subjects, in comparison to the LT measured for glucose in capillary blood.

Utilized laser and optical techniques showed high reliability in collecting data with objectivity from rapidly changed skin lesions and complex processes that happened in the skin tissue, based on a dynamics approach to measure, calculate and interpret the LT in blood and in IF compartments of the skin tissue.[6,7] Here, the article discusses methodological and technical aspects of LT estimation in the living healthy and pathological skin by these laser and optical techniques through clinical and experimental applications in dermatology.

2. Methods and Investigations

2.1. In vivo *measurement of the LT by LDF*

LDF is a well-known laser technology in clinical and experimental dermatology for measuring cutaneous blood flow (CBF) changes in the skin.[8,9] A contact-type (model ALF-2000), or a noncontact-type (model ALF 21 N), laser Doppler flowmeter (Advance Co., Ltd., Tokyo, Japan) that measures CBF from the skin surface of about 0.5 cm and the area of about 12 mm^3, has been utilized for measuring the LT in the patients with localized heat urticaria (LHU), solar urticaria (SU) and pressure-induced urticaria (PIU).

In all of its features, the urticarial reaction is analogous amongst all these forms of physical urticaria; however, LHU is sharply limited to heat-exposed areas, SU to light-exposed areas and PIU to pressure-exposed areas,[6,11,12] which appears very quickly on the skin after an exposure or after a LT by symptoms of itching, erythema, burning and whealing. To study the utility of LDF technique for measuring the LT *in vivo*, the patients with LHU, SU and PIU were accordingly exposed with heat, light source and pressure during variably designed provocative tests on their skin. Usually the patients with the above-mentioned forms of physical urticaria show various urticarial reactions by means of the severity of the appeared skin symptoms, dependent upon the length of exposure time and the intensity/degree of the physical stimulus, therefore the LT measurement by LDF has been thoroughly investigated in the relationship with those.

Technical preconditions for accurate measuring of the LT by LDF in the patients with physical urticaria during skin provocation tests have been the following: (1) CBF measurement only in the supine position; (2) CBF measurement after resting for at least 15 min in the supine position; (3) CBF measurement after resting in a temperature− humidity controlled room (19−21°C, 55−60%), according to the international guidelines for measurement of CBF by LDF.[8−10]

2.1.1. *Tests on the patients with physical urticaria*

In the patients with three above-mentioned forms of physical urticaria, the LT measurements by LDF have been performed during the following provocation tests: (1) exposure challenge tests by physical stimuli with differently ranged degrees/intensities and constant time of exposure in order to study the relationship between the degree of exposed physical stimulus and changes in the LT; (2) exposure challenge tests by physical stimuli with constant degrees and different stimulation/exposure time in order to study the relationship between the length

of exposure and changes in the LT; (3) re-exposure challenge tests by physical stimuli in order to study the effect of repeated exposure onto duration of the LT; (4) exposure challenge tests by physical stimuli after topical application of antihistamine cream(s) to study its effect on the duration of the LT; (5) exposure challenge tests by physical stimuli after application of topical anesthesia cream to assess changes in the LT; (6) exposure challenge tests by physical stimuli after administration of systemic antihistamines by prolongation in the LT. Details are provided in Refs. 4–6.

2.1.2. *Schematic demonstration of the LT by LDF*

Figure 1 schematically demonstrates the record of CBF changes by LDF during skin provocation test by a physical stimulus (temperature/pressure/light irradiation), dependent on the cause of certain type of physical urticaria (LHU/cold urticaria, PIU, SU). LDF precisely measures asymptomatic time interval registered immediately after the cessation of the physical stimulus on the skin until the start of the development of the urticarial reaction (various intensity erythema, itching, whealing) in the provoked skin area. This asymptomatic time interval measured in seconds is equivalent to unaffected CBF recorded as a plateau interval by LDF, and accordingly named as the LT. In other words, the LT measured by LDF is the interval from the cessation of the physical stimulus until the point of initiation of CBF changes.

2.2. In vivo *measurement of the LT by HATR-FTIR spectroscopy*

ATR-FTIR spectroscopy is a well-known technique in clinical and experimental dermatology for molecular characterization and measurement of molecular profiles in the upper skin *in vivo*.[13] The utility of HATR-FTIR spectroscopy for measuring *in vivo* glucose-specific profiles at about 1030, 1041, 1080, 1118 and 1153 cm^{-1} has been already demonstrated on healthy, prediabetes and diabetes subjects.[7,14,15] With the help of the flat-plated prism of the PIKE Technologies Horizontal ATR (ATR-8200 HA, USA) accessory designed for a Shimadzu FTIR spectrometer (Shimadzu IRPrestige-21/8400S, Japan), it was possible to achieve a tight contact with the skin surface of the inner wrists of the measured subjects. This horizontal accessory with a mounted ATR crystal is of a trapezoid shape with carefully chosen dimensions ($80 \times 10 \times 4$ cm) by the manufacturer to maximize the signal-to-noise in the resulting spectra.

The skin of the inner wrist area of the subjects was not pretreated prior to *in vivo* spectral acquisition by HATR-FTIR spectrometer. *In vivo* infrared ATR spectra have been recorded in the wavenumber region between 700 and 4000 cm^{-1} at a resolution of 4 cm^{-1}. Each measured *in vivo* absorbance spectrum was treated by applied techniques in the following sequence: (1) normalization to amide I (approximately 1645 cm^{-1}); (2) multiple baseline correction; (3) assignment of glucose-specific peaks in the 1000–1160 cm^{-1} region. Since the

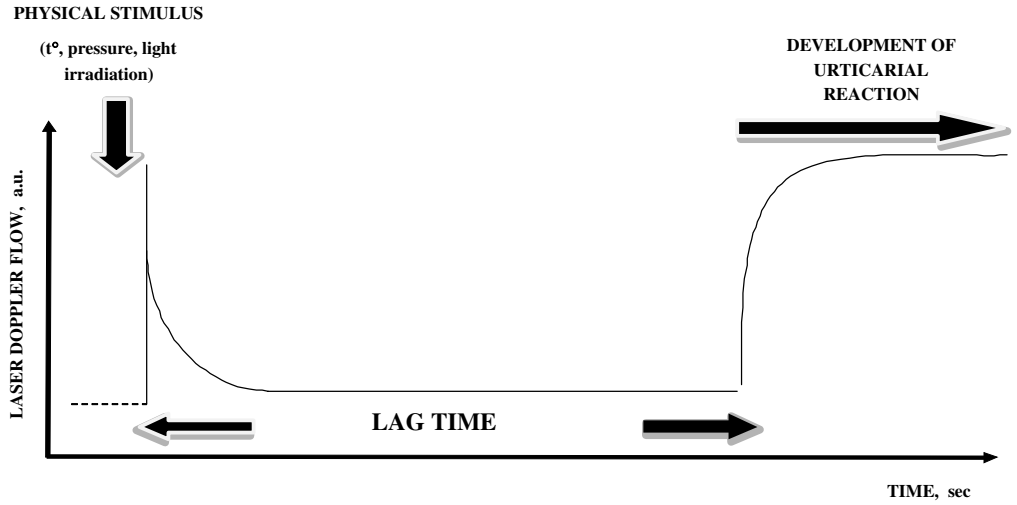

Fig. 1. The LT (s) by LDF schematically. Schematic record of the LT monitored by LDF in the patients with physical urticaria (localized heat urticaria, cold urticaria, solar urticaria, pressure-induced urticaria) during skin provocation test.

peaks at about 1030 and 1041 cm^{-1} have been always found bounded with the prominence of each of them, it needs further clarification (*unpublished data*), here in the presented data they were used as 1030−1041 cm^{-1}.

2.2.1. *Performed screening tests in healthy, prediabetes and diabetes subjects*

Measurement, calculation and interpretation of the LT of all obtained glucose levels in the upper skin by HATR-FTIR spectroscopy were performed during the following tests: (1) during post-prandial glucose monitoring, in comparison to pre-prandial levels; (2) during oral glucose tolerance tests (OGTT) with 75 g (clinical dose).

Performance of tests and their interpretation was similar to those used in the clinic worldwide.[14]

2.2.2. *Schematic demonstration of the LT and the LT changes between CBG and upper skin interstitial glucose levels measured by HATR-FTIR spectroscopy*

Figure 2 schematically demonstrates measurement of the LT and the LT changes between capillary blood glucose (CBG) and upper skin interstitial glucose levels obtained in epidermis at about 1030, 1041, 1080, 1118 and 1153 cm^{-1}.

During performed screening tests the LT has been measured, calculated and interpreted for each glucose-detected signal in epidermis, strictly in comparison to glucose levels in capillary blood obtained by a portable glucose meter (SKK Glu-TestS, Sanwa Chemical Institute, Nagoya, Japan). Then, the LT changes between the LT measured epidermally for each glucose-related signal and the LT for CBG was calculated by using the following equation [Eq. (1)]:

$$LT_{\text{changes}} = LT_{\text{CBG peak level}} - LT_{\text{HATR-FTIR peak level(s)}\ (1030/1041/1080/1118/1153\,\text{cm}^{-1}).} \quad (1)$$

3. Results

3.1. *Results by LDF*

The whealing reaction has been analogous amongst all forms of physical urticaria, that appeared very quickly on the skin after an exposure or after a LT by various intensity itching, erythema, burning and whealing. An example of the clinical records on the development of urticarial symptoms during skin provocation test can be seen in Table 1.[6]

By LDF it was possible to precisely determine the LT in seconds in each measured subject in all performed tests, that was influenced by the degree/intensity of exposed physical stimulus on the skin (Table 2), the duration/time of exposure (Table 3),

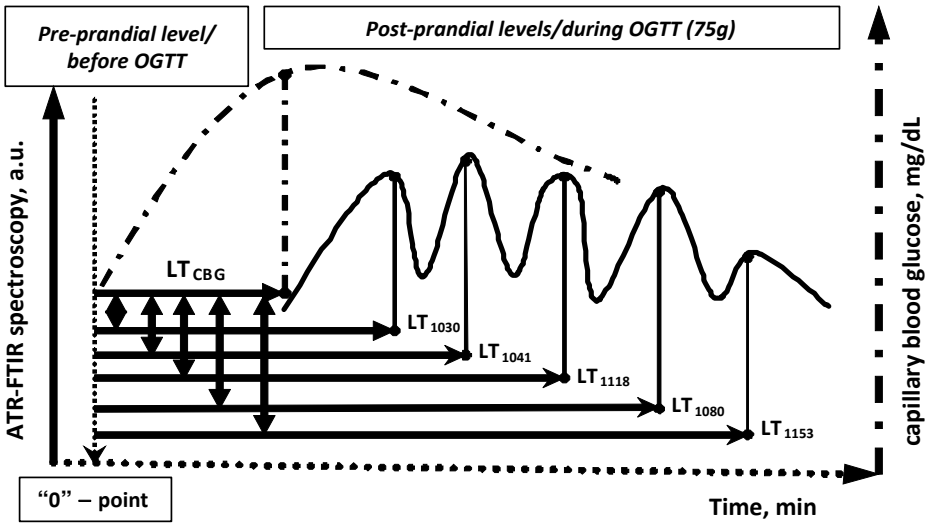

Fig. 2. Schematic measurement, determination and calculation of the LT and the LT changes between CBG and uppermost skin interstitial glucose levels obtained *in vivo* by HATR-FTIR spectroscopy post-prandially or during OGTT.

Table 1. An example of clinical record of the developed urticarial symptoms in relationship with exposed temperatures (42−46°C) and exposure times (3−6 min) during heat-provocation testing in a patient with localized heat urticaria.[6] Heat test results with different challenge times and temperatures in one patient with heat urticaria (Case 2).[a]

Challenge temperature, °C	Challenge time, min			
	3	4	5	6
42	−	+	++	++
43	±	++	++	+++
44	+/++	+++	+++	+++
45	++	+++	+++	+++
46	+++	+++	+++	+++

[a]−no reaction; ± faint erythema; + distinguished localized erythema; ++ intense erythema, urticaria; +++ intense erythema with a flare, urticaria.

Table 2. An example of the LT measured and determined by LDF in relationship with UVA exposure (305−365 nm, mW/cm^2) at different distances (cm) from the skin at constant exposure time (5 min) during light provocation testing in a patient with solar urticaria.

Irradiation distance	10 cm	20 cm	30 cm	40 cm
LT	48 s	84 s	144 s	174 s

re-exposure (Fig. 3), by the effect of topically applied antihistamine cream (Table 4), by the effect of systemic administration of antihistamines (H_1-, and/or H_2-antihistamines and/or H_1- and H_2-antihistamines).

After administration of systemic antihistamines in all patients, there were observable LT changes, dependent on the type of antihistamines, dosage and therapy duration (*unpublished data*). Based on achieved results, it was possible to evaluate therapeutic effect individually, comparing the patient's LT before, during and after cessation of treatment. For example, administration of mequitadine and cimetidine prolonged the LT from 210 to 320 s (43°C, 2 min) after a two-day therapy in one patient with LHU, and from 320 to 426 s (43°C, 4 min) after a four-day therapy in two patients with LHU.[6] In the patient with SU a 5-min exposure with UVA light, irradiated at a distance of 30 cm, LT was prolonged from 144 to 276 s after one week of therapy, and was already 312 s after 2.5 weeks with medication. In a patient with severe symptoms of pressure-induced urticaria, who underwent a 5-s pressure challenge test at 1.0, 1.5, 2.0 and 2.5 kg/cm^2, the LT was not detectable before daily administration of oral antihistamine. However, it became measurable by the third day of therapy, being thrice lengthier after 2.5 months of treatment.

Table 3. An example of the LT measured and determined by LDF in relationship with different time (4−6 min) of UVA exposure (305−365 nm, mW/cm^2) at constant distance (30 cm) from the skin during light provocation testing in a patient with solar urticaria.

Exposure time	4 min	5 min	6 min
LT	276 s	162 s	132 s

3.2. *Results by HATR-FTIR spectroscopy*

Tables 5 and 6 show the LT changes between the LTs for interstitially measured glucose values in epidermis at about 1030−1041, 1080, 1118 and 1153 cm^{-1} and the LTs measured in CBG among healthy, prediabetes and diabetes subjects.

In subjects with type 2 diabetes, the resulting LT changes ranged within 0−60 min, being in agreement between post-prandial and OGTT (75 g) monitoring. The time required for glucose to diffuse from the capillary to epidermal tissue was longer in healthy and prediabetes subjects, in comparison to diabetes patients. Two-phase LT changes were observed in a healthy subject and one subject with type 2 diabetes, being on a diet control. The LT changes showed characteristic multi-level appearances at 1030, 1041, 1080, 1118 and 1153 cm^{-1}.

4. Discussion

LDF has demonstrated its technical advantage to noninvasively measure and precisely determine the LT of the urticarial response in the provoked skin by different physical stimuli in the patients with several forms of physical urticaria. LDF could precisely and quantitatively register the LT changes in relationship with the degree/intensity of the exposed physical stimulus on the skin and the time/duration of exposure in the chosen ranges, even at a difference of one unit. The lower the degree/intensity of the exposed stimulus, the longer the LT, and vice versa. Such an objective assessment of the LT of the urticarial response showed an outstanding advantage over subjective clinical assessment of the severity of the urticarial symptoms during skin

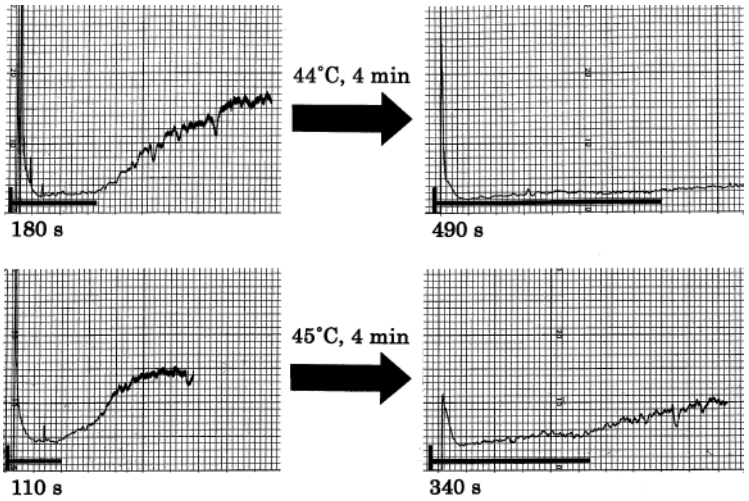

Fig. 3. An example of the LT by LDF measured in re-exposed skin 18 h later in a patient with LHU during a 4-min heat stimulation test at 44 and 45°C.[4]

Table 4. The dynamics of changes of the LT by LDF after topical application of antihistamines during heat stimulation tests at different anatomical sites in two patients with localized heat urticaria.[6] Topical effect of antihistamines on the LT period of urticarial response by LDF in relationship with the degree of heat stimuli and anatomical sites.

		The LTs		
Anatomical site	Heat challenge	Vehicle	Topical antihistamine	Differences
Patient 1				
Forearm	43°C, 2 min	240	552	312
Patient 2				
Forearm	44°C, 5 min	144	222	78
Back	45°C, 4 min	114	150	36
Chest	45°C, 4 min	96	132	36
Forearm	46°C, 5 min	60	114	54

provocation testing, especially in the cases when there was no possibility to detect any differences of those on the skin by eye. As a result of that, it was technically possible to detect maximum and minimum threshold of the urticarial reaction and that might explain the rate of released chemical mediator(s) in relationship with that. Literature states that the pathophysiology of LHU, SU and PIU has not been delineated.[4] Hopefully, the method of measuring the LT by LDF could further answer to many unsolved questions in connection to physiology and pathophysiology of these dynamic skin lesions.

Though LHU, SU and PIU are very easy to recognize and confirm by provocative testing in the clinic, treatment management of these patients is very difficult because of the long duration and resistance to treatment conditions. Therefore, optimal treatment options have not been established yet.[4,11] Presented results on measuring the LT by LDF after application of a variety of topical and systemic antihistamines have proved the utility of this method to evaluate the efficacy of tried treatment regimes directly on the patients with physical urticaria. In all cases it was possible to objectively assess the LT changes by means of the observation of the dynamics of the LT when compared before and after treatment, with the change of treatment scheme during administration of one type of drug and/or a combination of drugs.

HATR-FTIR spectroscopy technique has demonstrated its outstanding advantage to study dynamic complex processes of glucose metabolism in the living epidermis of healthy, prediabetes and diabetes subjects. Again this technique has proved itself as a method for fast glucose spectral

Table 5. Estimated LT changes (min) between epidermal glucose values (1030, 1041, 1080, 1118, 1153 cm^{-1}) and CBG within a 120-min post-prandial monitoring in three subjects (S1, S2, S3) with type 2 diabetes.[7]

Subjects	1030−1041 cm^{-1}	1080 cm^{-1}	1118 cm^{-1}	1153 cm^{-1}
S1	0′	0′	0′	30′
S2	0′	[0′ and 60′]	[0′ and 60′]	30′
S3 (D1)	0′	60′	0′	60′
S3 (D2)	0′	0′	60′	—

Table 6. Estimated LT changes (min) between epidermal glucose values (1030, 1041, 1080, 1118, 1153 cm^{-1}) and CBG during OGTT at 75 g monitored within 120 min in healthy, prediabetes (suspect) and diabetes subjects.

	$LT_{Changes}$		
Wavenumber, cm^{-1}	Diabetes	Healthy	Prediabetes
1030−1041	0′	5′ and 30′	5′ and 20′ and 30′ and 45′
1080	0′	5′	55′ and 20′ and 45′
1118	0′	5′ and 25′	5′ and 20′ and 30′ and 40′
1153	30′	10′	0′ and 15′ and 25′ and 55′

investigations, technically achieved by using 20 frames of accumulation to collect interferogram from the surface of the skin in the desired region. Epidermally assessed glucose levels at about 1030, 1041, 1080, 1118 and 1153 cm^{-1} before and during a variety of metabolic conditions/tests showed dynamical changes of glucose levels, that have differentiated not only between each measured glucose biomolecule but also between measured subjects. By means of calculating the peak level(s) for each glucose molecule, in comparison to calculated peak level for glucose in capillary blood before and during performed screening tests, it was possible not only to precisely determine the LT for interstitial glucose and CBG but also to calculate the LT changes between them. Such a method of the LT measurement and calculation gives a possibility to follow the dynamical changes in glucose levels, providing insight into behavior of glucose between the blood and IF compartment in the upper layers of skin tissue during different metabolic tests and conditions (pre-prandial versus post-prandial, OGTT).

Among three patients with type 2 diabetes monitored post-prandially and during OGTT at 75 g estimated LT changes ranged from 0 to 60 min (see Tables 5 and 6), being stable for glucose levels at about 1030−1041 cm^{-1} with the LT change of 0 min. Also, in the same patients there were noticeable similarities in the LT changes among all glucose biomolecules that showed sharply the times at 0, 30, and 60 min, with exception to some LTs with a bi-phasic determination of the LT changes of 0 and 60 min for glucose biomolecules at about 1080 and 1118 cm^{-1} post-prandially.

Based on the above data and data from other researchers, it is possible to conclude that sugars, composing of the IF in the intercellular spaces in epidermis, can be surely assessed by mid-IR spectroscopy technique *in vivo*.[18] As such, it might serve dermatologists, physiologists, researchers in medical science and engineers to assess the same phenomenon in order to help answering their particular questions.

5. Conclusion

Utilized laser and optical techniques demonstrated their technical advantage to noninvasively measure and precisely determine the LT in the living healthy and pathological skin tissue of the measured subjects, with further interpretation as on the level of a molecule, so as an organ in a whole organism. Based on the obtained results by LDF from dynamic urticarial lesions during provocation skin testing in the patients with several types of physical urticaria, the measurement of the LT has showed to be highly informative to study issues of clinical importance: noninvasive diagnosis with objective assessment of the severity of skin symptoms, new aspects of pathophysiology and objective comparative evaluation of the efficacy of therapy. Further, the measurement of the LT has a potential to be used for analytical interpretation of the dynamics of skin glucose metabolism and diffusion from the capillary to the epidermal tissue *in vivo*, which has not been described before. The LT measurement method is simple for analytical treatment and easy for performance in the clinical and laboratory environment.

Acknowledgment

The author is grateful to Prof. Seiji Arase (retired) and Assoc. Prof. Hirotsugu Takiwaki (retired), Dr. Y. Nameda (retired), Dr. M. Sagawa (retired), Dr. Y. Miyaoka (retired) at the Dept. of Dermatology,

School of Medicine, The University of Tokushima; Prof. M. Kanazawa from the Third Department of Internal Medicine at Tokyo Medical University; Prof. Takayuki Sota, Dr. A. Nakamura and Prof. Katsuo Aizawa (retired) from the Dept. of Electrical Engineering and Bioscience at Waseda University, Tokyo, Japan. N.S.E. is also grateful to JSPS (Japan Society for Promotion and Science) for their acceptance and financial support as a postdoctoral fellow between 2006 and 2008. She also acknowledges financial support from the Japanese Ministry of Education (Monbusho) as a Ph.D. student between 1999 and 2002.

References

1. M. D. Waller, "The measurement of actinic erythema produced by ultra-violet radiation with special reference to the latent time," *Proc. R. Soc. London, Ser. B* **108**(757), 258 (1931).
2. P. Agache, P. Humbert, *Measuring the Skin*, Springer-Verlag, Berlin, Heidelberg (2004).
3. N. S. Eikje, "Potential of *in vivo* measured latency time by lasers and optical technologies," in *Biophysics in Medicine*, V. V. Tuchin, Ed., Proc. Saratov Fall Meeting 2010, Saratov State University, Russia (2010).
4. N. S. Eikje, S. Arase, "Fiber optic LDF to monitor vascular dynamics of urticarial dermographism in pressure-tested patients before and after treatment with antihistamines," in *Biomedical Applications of Light Scattering II*, A. Wax and A. Backman, Eds., Proc. SPIE, the International Society for Optical Engineering, Washington, USA, **68640E** (2008).
5. N. Skrebova, Y. Nameda, H. Takiwaki, S. Arase, "Severe dermographism after topical therapy with diphenylcyclopropenone for alopecia universalis," *Contact Dermatitis* **42**, 212−215 (2000).
6. N. Skrebova, H. Takiwaki, Y. Nameda, S. Arase, "Localized heat urticaria: A clinical study using laser Doppler flowmetry," *J. Dermatol. Sci.* **26**, 112−118 (2001).
7. N. S. Eikje, "Diabetic interstitial glucose in the skin tissue by ATR-FTIR spectroscopy versus capillary blood glucose," *JIOHS* **3**(2), 81−90 (2010).
8. A. Bircher *et al.*, "Guidelines for measurement of cutaneous blood flow by laser Doppler flowmetry," *Contact Dermatitis* **30**, 65−72 (1994).
9. E. Berardesca, P. Elsner, H. I. Maibach, *Bioengineering of the Skin: Cutaneous Blood Flow and Erythema*, CRC Press (1994).
10. L. Bernardi, E. Berardesca, "Measurement of skin blood flow by laser Doppler flowmetry," in *Bioengineering of the Skin: Methods and Instrumentation*, E. Berardesca, P. Elsner, K.-P. Wilhelm, H. I. Maibach, Eds., CRC Press, Boca Raton (1995).
11. A. Kobza Black, R. H. Champion, "Urticaria," in *Textbook of Dermatology*, R. H. Champion, J. L. Burton, D. A. Burns and S. M. Breathnach, Eds., Vol. 3, 6th Edition, pp. 2128−2134, Blackwell Science Ltd., Oxford (1998).
12. R. Roelandts, S. Ryckaert, "Solar urticaria: The annoying photodermatosis," *Int. J. Dermatol.* **38**, 411−418 (1999).
13. L. Brancaleon, M. P. Bamberg, T. Sakamaki, N. Kollias, "Attenuated total reflection — Fourier transform infrared spectroscopy as a possible method to investigate biophysical parameters of stratum corneum *in vivo*," *J. Invest. Dermatol.* **116**, 380−386 (2001).
14. N. S. Eikje, T. Sota, K. Aizawa, "Cutaneous approach towards clinical and pathophysiological aspects of hyperglycemia by ATR-FTIR spectroscopy," in *Diagnostic Optical Spectroscopy in Biomedicine IV*, D. Schweitzer and M. Fitzmaurice, Eds., Proc. SPIE, the International Society for Optical Engineering, Washington, USA, **66281M** (2007).
15. N. S. Eikje, K. Aizawa, Y. Ozaki, S. Arase, "Identification and characterization of skin biomolecules for drug targeting and monitoring by vibrational spectroscopy," *TOMCJ* **2**, 38−48 (2008).
16. N. S. Eikje, "*In vivo* interstitial glucose characterization and monitoring by ATR-FTIR spectroscopy," in *Optical Diagnostics and Sensing XI: Toward Point-of-Care Diagnostics*, G. Cote, Ed., Proc. SPIE, the International Society for Optical Engineering, Washington, USA, 79060F (2011).
17. N. S. Eikje, "Lag time changes between capillary blood glucose and *in vivo* skin interstitial glucose levels by HATR-FTIR spectroscopy," in *Dynamics and Fluctuations in Biomedical Photonics VI*, V. V. Tuchin, D. D. Duncan, K. V. Larin, M. J. Leahy and R. K. Wang, Eds., Proc. SPIE, the International Society for Optical Engineering, Washington, USA, 78980S (2011).
18. H. V. von Lilienfeld-Toal, M. Weidenmuller, A. Xhelaj, W. Mantele, "A novel approach to non-invasive glucose measurement by MID-IR spectroscopy: The combination of quantum cascade lasers (QCL) and photoacoustic detection," *Vibra. Spectrosc.* **38**(1−2), 209−215 (2005).