METHOD FOR MONITORING INDIVIDUAL METABOLIC RESPONSE AND FOR GENERATING PREDICTIVE CLINICAL METRICS

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

The invention relates generally to monitoring metabolic response in a subject, that comprises the step of consecutive performance of a plurality of measurements and further calculations of glucose levels at 1030, 1041, 1080, 1118, 1153 cm^{-1}, obtained by HATR-FTIR (horizontally attenuated total reflection Fourier transform infrared) spectroscopy. Further, the invention comprises calculating the LT **(**lag/latency time) differences between measured in capillary blood the peak glucose level and by HATR-FTIR spectroscopy the peak levels of glucose values after achieved response in test subjects from the ingestion of quantified amount of pure glucose and post-prandially, allowing to assess stability of metabolic control in healthy, prediabetic and diabetic subjects. Furthermore, qualitative and quantitative interpretation of GV (glycemic variability) by calculation of the LT differences, based on simultaneous assessment of 5 glucose-specific values by HATR-FTIR spectroscopy, helps to generate parameters, their characteristics, patterns and, thus, to establish suitable metrics for GV in the clinical practice.

DESCRIPTION OF THE RELATED ART

There are numerous published metrics to quantify different aspects of GV, but still there is no method of GV that is accepted in the clinical practice of diabetes care.

Developing a new set of metrics to evaluate normal, as well as clinically relevant high and low interstitial glucose levels might open for clinicians a new way in the interpretation of the activity of glucose metabolism for diagnosis, treatment and management of the patients with diabetes mellitus and carbohydrate metabolism disorders.

The technique of using ATR-FTIR (attenuated total reflection Fourier transform infrared) spectroscopy has been long known for non-invasive glucose measurement, but through oral mucosa. The drawbacks of such measurements included glucose contamination of the measurement site by food and a highly variable rate of saliva.

Attempts have been made to demonstrate a proof of HATR-FTIR spectroscopy technique to detect, characterize and verify interstitial origin of glucose-specific signals at 1030, 1041, 1080, 1118 and 1153 cm^{-1} in the skin of healthy, prediabetic and diabetic subjects during OGTT (Oral Glucose Tolerance Test) and post-prandially, randomly and on mornings, i.e. fasting measurements.

Carbohydrate intolerance is one of the major criteria for a diagnosis of diabetes mellitus. OGTT

employs ingested carbohydrate in a predetermined form and an amount to quantify a test subject's response to a resulting glucose challenge. However, this test is only concerned with the peak blood level of glucose, but not with the rate of change in glucose levels or the amount of time it takes for glucose levels to fluctuate from a high point to a lower point.

The medical significance of blood glucose fluctuations, i.e. frequency and magnitude, has been a controversial topic and the subject of extensive research, proving that GV can be used to describe a general risk of hyperglycemia over long periods of time, or when focused on events of short duration, such as meals or overnight.

Since glucose on the surface of the skin and within the stratum corneum has been considered as a source for extraneous glucose contamination during testing of invasive glucose monitoring devices, there was not found any direct method for in vivo glucose molecule(s) characterization and monitoring directly on healthy, prediabetes and diabetes subjects.

SUMMARY OF THE INVENTION

An object of the present invention is to provide the user with in vivo method for monitoring individual metabolic response and a method for qualitative and quantitative characterization of GV, in order to further recognize patterns from patients data for establishing predictive clinical metrics.

The invented method is based on calculating the LT differences between the LT measured for the peak of CBG and the LT for the peaks of epidermally measured interstitial glucose levels by HATR-FTIR spectroscopy on healthy, prediabetic and diabetic subjects under OGTT with different doses (low, medium, high) and post-prandially, applicable for staging Type 2 diabetes and assessing diabetes control, including estimation of intra-day and intra-week risks, as well a general risk of hyperglycemia. More, the invention can be further applied for screening of disorders of glucose metabolism, such as impaired glucose tolerance and diabetes mellitus by means of evaluation of the time required for glucose to diffuse from the capillary to the living skin tissue. In addition, the invention can be also served for individual calibration of obtained glucose profiles by HATR-FTIR spectroscopy in a dynamic time-dependent manner in a qualified subject.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 schematically presents a method for calculation of the LT differences between the LT for the peak of CBG and for the peak of each epidermally measured interstitial glucose level at 1030, 1041, 1080, 1118 and 1153 cm^{-1} by HATR-FTIR spectroscopy in a subject.

Figure 2 A-D presents differences between GV obtained between CBG values (shown by dashed lines) and each glucose value (shown by solid lines) at 1030, 1041, 1118 and 1153 cm^{-1} by HATR-

FTIR spectroscopy during a 120-minute post-prandial monitoring of individual metabolic response in Subject 1 with Type 2 diabetes. The time of increment for each glucose value is indicated by a solid line along x-axis. In case of a biphasic increase, a first phase is indicated by a dashed line along x-axis.

Figure 3 A-D presents differences between GV obtained between CBG values (shown by dashed lines) and each glucose value (shown by solid lines) at 1030, 1041, 1118 and 1153 cm^{-1} by HATR-FTIR spectroscopy during a 120-minute post-prandial monitoring of individual metabolic response in Subject 2 with Type 2 diabetes. The time of increment for each glucose value is indicated by a solid line along x-axis. In case of a biphasic increase, a first phase is indicated by a dashed line along x-axis.

Figure 4 A-D presents differences between GV obtained between CBG values (shown by dashed lines) and each glucose value (shown by solid lines) at 1030, 1041, 1118 and 1153 cm^{-1} by HATR-FTIR spectroscopy during a 120-minute post-prandial monitoring of individual metabolic response in Subject 3 with Type 2 diabetes. The time of increment for each glucose value is indicated by a solid line along x-axis. In case of a biphasic increase, a first phase is indicated by a dashed line along x-axis.

Figure 5 A-C presents a comparative dose-dependent GV during monitoring of metabolic response by HATR-FTIR spectroscopy at 1030, 1041, 1118 and 1153 cm^{-1} during OGTT at different doses, at 5 g (low), 20 g (medium) and 75 g (high), in a healthy subject (Subject 4).

Figure 6 A-C presents a comparative dose-dependent GV during monitoring of metabolic response by HATR-FTIR spectroscopy simultaneously shown at 1030, 1041, 1118 and 1153 cm^{-1} during OGTT at different doses, at 5 g (low), 20 g (medium) and 75 g (high), in Subject 3 with Type 2 diabetes.

Figure 7 A-C illustrates examples of characteristic differences in the levels of glucose values and wavenumber shifts between a healthy subject (Subject 4) and a subject with Type 2 diabetes (Subject 3) under OGTT with different doses.

Figure 8 A-F illustrates a variety of examples of GV simultaneously shown at 1030, 1041, 1118 and 1153 cm^{-1} by HATR-FTIR spectroscopy in 2 Type 2 diabetes (Subject 3) under OGTT with 75 g and 20 g; in a prediabetic subject (Subject 5) under OGTT with 75 g and under OGTT with 75 g in 3 healthy subjects (Subject 1, Subject 3, Subject 4).

Figure 9 A-D presents GV simultaneously shown at 1030, 1041, 1118 and 1153 cm^{-1} by HATR-FTIR spectroscopy during a 120-minute post-prandial monitoring of individual metabolic response in 3 patients (Subjects 1-3) with Type 2 diabetes, in comparison to a healthy subject (Subject 5).

Figure 10 A-C presents day-to-day variations on GV during a 120-minute post-prandial monitoring of individual metabolic response in Subject 3 with Type 2 diabetes on 2 consecutive days, comparatively shown at 1030, 1041, 1080 and 1118 cm^{-1} by HATR-FTIR spectroscopy.

Figure 11 A-D comparatively presents GV during monitoring of individual metabolic response in 3

healthy subjects (Subjects 1, 2, 4), in 1 subject as a suspect of having impaired glucose tolerance, i.e. prediabetes (Subject 3), and in Subject 3 with Type 2 diabetes by HATR-FTIR spectroscopy.

BRIEF DESCRIPTION OF THE TABLES

Table 1. LT differences estimated within a 120-minute post-prandial monitoring of metabolic response in 3 subjects with Type 2 diabetes (S1, S2 and S3) by HATR-FTIR spectroscopy.

Table 2. LT differences between the LT for the peak of CBG and the LT peak for each measured glucose level at 1030, 1041, 1118 and 1153 cm^{-1}, obtained in a healthy subject during OGTT at different doses (5 g, 20 g, 75 g).

Table 3. LT differences between the LT for the peak of CBG and the LT peak for each measured glucose level at 1030, 1041, 1118 and 1153 cm^{-1}, obtained in a diabetic subject during OGTT at different doses (5 g, 20 g, 75 g).

Table 4. LT differences under OGTT with 75 g., i.e. clinical, a healthy subject vs. a subject with Type 2 diabetes.

Table 5. LT differences under OGTT with 20 g., i.e. clinical, a healthy subject vs. a subject with Type 2 diabetes.

Table 6. LT differences estimated for the same subject with Type 2 diabetes on 2 consecutive days.

Table 7. OGTT (75 g)., i.e. clinical OGTT, demonstrate estimated LT differences for healthy, prediabetic and diabetic subjects.

DETAILED DESCRIPTION OF THE EMBODIMENT

As described further herein, in vivo glucose spectral measurements from the skin surface of the inner wrists of measured subjects have been performed on a commercially available FT-IR spectrometer (Shimadzu IRPrestige - 21/8400S, Japan), that measures the absorbance spectra in the 700-4000 cm^{-1} region at a resolution of 4 cm^{-1}, using 20 frames of accumulation to collect interferogram. Non-invasive glucose monitoring is achieved by tight contact of the measured site with a specially designed flat-plated prism with a mounted ATR crystal for the PIKE Technologies Horizontal accessory (ATR-8200 HA). This horizontal accessory is of a trapezoid shape with carefully chosen dimentions by a manufacturer (80 x 10 x 4 cm), in order to maximize S/N (signal-to-noise) ratio in the measured spectra.

A portable glucosemeter (SKK GluTestS, Sanwa Chemical Institute, Nagoya, Japan) has been used for CBG determinations in mg/dL.

Noninvasive spectroscopic interstitial glucose monitor to an individual necessitates a calibration. Generating such a calibration requires reference CBG values that are uncorrelated to sampling

factors. The invention provides a method to calibrate dynamic measurements of interstitial glucose values in vivo by HATR-FTIR spectroscopy, based on referenced CBG values, that are described in Figure 1.

A test subject's CBG values are controlled or manipulated through the oral ingestion of meals, and/or through oral consumption of dissolved in water pure glucose at different determined doses (f.e. 5 g, 20 g, 75 g) in such a way that the changes of the targeted glucose profiles of Figures 1-4 are reproduced by the subject's own glucose profiles. Thus, since the subject's CBG is under active control, the influence of other sampling factors are eliminated.

Steps of the invented formula and method:

* performing reference CBG measurements at pre-determined intervals prior to spectral acquisition by HATR-FTIR spectroscopy;
* gathering *in vivo* HATR-FTIR spectra from the forearm of a tested subject at predetermined intervals in the 700-4000 cm^{-1} region with further spectra normalization to amide I, at 1650 cm^{-1}, always after a background scan collection by HATR-FTIR spectroscopy;
* multiple baseline correction of the 1000-1180 cm^{-1} region with assignment of glucose-specific peaks at 1030 cm^{-1}, 1041 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1}, where the peaks at 1030 cm^{-1} and 1041 cm^{-1} are always mentioned together;
* subject's forearm repositioning after each measured spectrum for avoidance of hydration effect;
* manipulating a subject's capillary blood glucose levels in order to obtain meaningful time-dependent LT's and their changes by subject himself/herself under OGTT with different doses (5 g, 20 g, 75 g), post-prandially, or under any other screening metabolic test;
* manipulating a subject's glucose values by HATR-FTIR such those produce meaningful time-dependent changes in the levels of CBG and in the levels of glucose values at 1030, 1041, 1118 and 1153 cm^{-1} by subject himself/herself under OGTT with different doses (5 g, 20 g, 75 g), post-prandially, or under any other screening metabolic test;
* calculation of the LT differences between the LT for the peak of CBG and the LT for the peaks of each glucose value at 1030, 1041, 1118 and 1153 cm^{-1} measured by HATR-FTIR spectroscopy;
* determining the spectral pattern of individual metabolic response, based on spectral qualitative and quantitative parametric evaluation of GV with its dynamics and the LT calculation with its difference with the LT in CBG.

The invention utilizes the targeted glucose profiles by HATR-FTIR spectroscopy schematically presented in Figure 1. "0"- point is pre-prandial, i.e. fasting, and/or before OGTT.

The CBG values and the spectral measurements furnish a data set upon which a calculation of the LT changes is made by using Equation 1, and which a calibration is also based in a qualified subject.

Equation 1 utilizes only parameters described in Figure 1:

LT changes=LT(CBG peak level) - LT(HATR-FTIR peak level(s) (1030/1041/1080/1118/1153 cm^{-1})

The various aspects of the invention are described in greater detail below.

Examples of inducing levels fluctuations/shifts in the subject's CBG values and epidermal glucose values by HATR-FTIR, in order to obtain meaningful time-dependent and dose-dependent glucose values, their LT's for maximum peaks and their LT changes towards monitored characterization of GV in a qualified subject, with or without hyperglycemia, stable or unstable, that can be used to predict the patient's risk of hyperglycemia, to stage Type II diabetes and, in general, to be considered as a new metrics of assessing the quality of metabolic control, are presented in Tables 1-5 and in Figures 2-6.

SUBJECTS

Type 2 diabetes (totally 3 subjects):

Subject 1, Male, age 67, insulin therapy because of recurrent/persistent hyperglycemia, due to no response to orally prescribed tabletes of Metformin for the last 7 years;

Subject 2, Female, age 70, orally prescribed tabletes of Metformin has been changed to a diet control;

Subject 3, Male, age 69, insulin therapy because of recurrent/persistent hyperglycemia, due to no response to orally prescribed tabletes of Metformin for the last 2 years.

Impaired glucose tolerance, i.e. prediabetic subjects, and subjects as suspects of having impaired glucose tolerance due to occasional post-prandial hyperglycemia, based on accepted in the clinical practice interpretation of blood glucose units obtained under different conditions (mg/dL) and according to WHO Diabetes Criteria (totally 3 subjects):

Subject 1, Male, age 49, occasional post-prandial hyperglycemia;

Subject 2, Male, age 58, occasional post-prandial hyperglycemia;

Subject 3, Male, age 49, prediabetes.

Healthy (totally 5 subjects):

Subject 1, Male, age 23;

Subject 2, Male, age 24;

Subject 3, Male, age 60;

Subject 4, Female, age 35;

Subject 5, Male, age 59.

RESULTS

1. METHOD FOR MONITORING INDIVIDUAL METABOLIC RESPONSE IN A QUALIFIED SUBJECT

(i) individually at each glucose value;

(ii) simultaneously at all glucose values.

2. METHOD FOR MONITORING INDIVIDUAL METABOLIC RESPONSE IN A QUALIFIED SUBJECT

(i) in one subject;

(ii) between the subjects.

3. METHOD FOR MONITORING INDIVIDUAL METABOLIC RESPONSE IN A QUALIFIED SUBJECT

(i) within one group of disease/condition;

(ii) between different groups/conditions.

4. METHOD FOR MONITORING INDIVIDUAL METABOLIC RESPONSE IN A QUALIFIED SUBJECT

(i) under one screening test;

(ii) comparatively, under different screening tests.

5. METHOD FOR MONITORING INDIVIDUAL METABOLIC RESPONSE IN A QUALIFIED SUBJECT

(i) for qualitative interpretation;

(ii) for quantitative interpretation.

6. METHOD FOR MONITORING INDIVIDUAL METABOLIC RESPONSE AND FOR GENERATING PREDICTIVE CLINICAL METRICS IN A PATIENT

(i) for generating a pattern and parameters characterizing GV in the patients with Type 2 diabetes;

(ii) for generating a pattern and parameters characterizing GV in the patients with impaired glucose tolerance, i.e. the patients with prediabetes;

(iii) for generating a pattern and parameters characterizing GV in healthy subjects.

Tables 1-5 describe that:
the LT differences show dose-dependency in healthy, prediabetic and diabetic subjects, that differ at duration;
the LT differences are the shortest in a diabetes subject and the longest in a healthy subject, independent of intaken dose of glucose under OGTT;
the LT differences differ at single, bi-phasic and a cascade appearance between healthy subjects, subjects as suspects of having impaired glucose tolerance, i.e. prediabetes, and subjects with Type 2 diabetes;
the LT differences show pattern recognition for healthy subjects, prediabetic subjects and subjects with Type 2 diabetes, based on the assessed LT differences (in minutes);
the LT differences show day-to-day variations, connected to a pattern recognition.

Figures 2-11, in addition to the results, shown in Tables 1-7, show differences in GV between healthy, prediabetic and diabetic subjects towards their pattern recognition, based on specific characteristics:
recognized to healthy and prediabetic/diabetic subjects wavenumber changes, i.e. shifts of glucose-specific peaks to the left or to the right;
recognized glucose levels as low, medium and high, for healthy, prediabetic and diabetic subjects, assessed at determined time intervals under OGTT with different doses;
recognized meaningful time-dependent fluctuations of GV assessed at each glucose-specific value, having common and specific features for healthy, prediabetic and diabetic subjects.

EXAMPLES

EXAMPLE 1

Figure 2 A-D presents differences between GV obtained between CBG values (shown by dashed lines) and each glucose value (shown by solid lines) at 1030, 1041, 1118 and 1153 cm^{-1} by HATR-FTIR spectroscopy during a 120-minute post-prandial monitoring of individual metabolic response in Subject 1 with Type 2 diabetes. The time of increment for each glucose value is indicated by a solid line along x-axis. In case of a biphasic increase, a first phase is indicated by a dashed line along x-axis.
Figure 3 A-D presents differences between GV obtained between CBG values (shown by dashed lines) and each glucose value (shown by solid lines) at 1030, 1041, 1118 and 1153 cm^{-1} by HATR-FTIR spectroscopy during a 120-minute post-prandial monitoring of individual metabolic response

in Subject 2 with Type 2 diabetes. The time of increment for each glucose value is indicated by a solid line along x-axis. In case of a biphasic increase, a first phase is indicated by a dashed line along x-axis.

Figure 4 A-D presents differences between GV obtained between CBG values (shown by dashed lines) and each glucose value (shown by solid lines) at 1030, 1041, 1118 and 1153 cm^{-1} by HATR-FTIR spectroscopy during a 120-minute post-prandial monitoring of individual metabolic response in Subject 3 with Type 2 diabetes. The time of increment for each glucose value is indicated by a solid line along x-axis. In case of a biphasic increase, a first phase is indicated by a dashed line along x-axis.

Table 1 displays LT changes estimated within a 120-minute post-prandial monitoring of metabolic response in 3 subjects with Type 2 diabetes (S1, S2 and S3) by HATR-FTIR spectroscopy.

Subjects	1030-1041 cm^{-1}	1080 cm^{-1}	1118 cm^{-1}	1153 cm^{-1}
S1	0'	0'	0'	30'
S2	0'	0' & 60'	0' & 60'	30'
S3	0'	60'	0'	60'

EXAMPLE 2

Figure 5 A-C presents a comparative dose-dependent GV during monitoring of metabolic response by HATR-FTIR spectroscopy at 1030, 1041, 1118 and 1153 cm^{-1} during OGTT at different doses, at 5 g (low), 20 g (medium) and 75 g (high), in a healthy subject (Subject 4).

Table 2 displays LT changes between the LT for the peak of CBG and the LT peak for each measured glucose level at 1030, 1041, 1118 and 1153 cm^{-1}, obtained in a healthy subject during OGTT at different doses (5 g, 20 g, 75 g).

Healthy	LT	OGTT (5 g)	OGTT (20 g)	OGTT (75 g)
1030-1041 cm^{-1}	LT	15' & 30'	10'	5' & 30'

	differences			
1080 cm^{-1}	LT differences	15' & 30'	0' & 10' & 20'	5'
1118 cm^{-1}	LT differences	10' & 25'	10'	5 '& 25'
1153 cm^{-1}	LT differences	35' & 50'	10' & 15'	10'

Figure 6 A-C presents a comparative dose-dependent GV during monitoring of metabolic response by HATR-FTIR spectroscopy simultaneously shown at 1030, 1041, 1118 and 1153 cm^{-1} during OGTT at different doses, at 5 g (low), 20 g (medium) and 75 g (high), in Subject 3 with Type 2 diabetes.

Table 3 displays LT changes between the LT for the peak of CBG and the LT peak for each measured glucose level at 1030, 1041, 1118 and 1153 cm^{-1}, obtained in a diabetic subject during OGTT at different doses (5 g, 20 g, 75 g).

Type 2 diabetes	LT	OGTT (5 g)	OGTT (20 g)	OGTT (75 g)
1030-1041 cm^{-1}	$LT_{differences}$	0' & 10'	0'	0'
1080 cm^{-1}	$LT_{differences}$	10'	15'	0'
1118 cm^{-1}	$LT_{differences}$	0' & 10 & 25'	5'	0'
1153 cm^{-1}	$LT_{differences}$	15' & 25'	25' & 40'	30'

EXAMPLE 3

Figure 7 A-C illustrates examples of characteristic differences in the levels of glucose values and

wavenumber shifts between a healthy subject (Subject 4) and a subject with Type 2 diabetes (Subject 3) under OGTT with different doses.

Table 4 displays LT differences under OGTT with 75 g., i.e. clinical, a healthy subject vs. a subject with Type 2 diabetes.

Subjects	healthy	Type 2 diabetes
1030-1041 cm^{-1}	15' & 30'	10'
1080 cm^{-1}	15' & 30'	10'
1118 cm^{-1}	10' & 25'	0' & 10' & 25'
1153 cm^{-1}	35' & 50'	15' & 25'

Table 5 displays LT differences under OGTT with 20 g., a healthy subject vs. a subject with Type 2 diabetes.

Subjects	healthy	Type 2 diabetes
1030-1041 cm^{-1}	10'	0'
1080 cm^{-1}	0' & 10' & 20'	15'
1118 cm^{-1}	10'	5'
1153 cm^{-1}	10' & 15'	25' & 40'

EXAMPLE 4

Figure 8 A-F illustrates a variety of examples of GV simultaneously shown at 1030, 1041, 1118

and 1153 cm^{-1} by HATR-FTIR spectroscopy in Type 2 diabetes (Subject 3) under OGTT with 75 g and 20 g; in a prediabetic subject (Subject 5) under OGTT with 75 g and under OGTT with 75 g in 3 healthy subjects (Subject 1, Subject 3, Subject 4).

EXAMPLE 5

Figure 9 A-D presents GV simultaneously shown at 1030, 1041, 1118 and 1153 cm^{-1} by HATR-FTIR spectroscopy during a 120-minute post-prandial monitoring of individual metabolic response in 3 patients (Subjects 1-3) with Type 2 diabetes, in comparison to a healthy subject (Subject 5). A 120-minute post-prandial monitoring of metabolic response in 3 subjects (S1, S2, and S3) with Type 2 DM and 1 healthy control subject ("0"-point is pre-prandial). CBG levels in mg/dL are shown in numbers along curves for each measured subject.

EXAMPLE 6

Fig. 10 A-C presents day-to-day variations on GV during a 120-minute post-prandial monitoring of individual metabolic response in Subject 3 with Type 2 diabetes on 2 consecutive days, comparatively shown at 1030, 1041, 1080 and 1118 cm^{-1} by HATR-FTIR spectroscopy.

Table 6 displays LT changes estimated for the same subject with Type 2 diabetes on 2 consecutive days.

Subjects	1030-1041 cm^{-1}	1080 cm^{-1}	1118 cm^{-1}	1153 cm^{-1}
S3 (Day 1)	0'	60'	0'	60'
S3 (Day 2)	0'	0'	60'	-

EXAMPLE 7

Figure 11 A-D comparatively presents GV during monitoring of individual metabolic response in 3 healthy subjects (Subjects 1, 2, 4), in 1 subject as a suspect of having impaired glucose tolerance, i.e. prediabetes (Subject 3), and in Subject 3 with Type 2 diabetes by HATR-FTIR spectroscopy. Table 7 displays OGTT (75 g)., i.e. clinical OGTT, demonstrate LT differences for healthy, prediabetic and diabetic subjects.

Subjects	healthy	prediabetes	Type 2 diabetes
1030-1041 cm^{-1}	5' & 30'	5' & 20' & 30' & 45'	0'
1080 cm^{-1}	5'	5' & 20' & 45'	0'
1118 cm^{-1}	5' & 25'	5' & 20' & 30' & 40'	0'
1153 cm^{-1}	10'	0' & 15' & 25' & 55'	30'

CLAIMS

1. A method of patterned data analysis for evaluating individual metabolic response and for generating predictive clinical metrics for disorders of glucose metabolism, such as prediabetes and diabetes on HATR-FTIR spectrometer, comprising of:

(i) assigning glucose-specific peaks with characteristic absorption wave numbers at 1030 cm^{-1},1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1} in the mid-IR spectra of a subject under post-prandial glucose test or OGTT (Oral Glucose Tolerance Test) at the different doses of 5 g, 20 g and/or 75 g, wherein assigned peaks within 1030 cm^{-1} and 1041 cm^{-1} are always bounded bands in the 700-4000 cm^{-1} region by HATR-FTIR (Horizontal attenuated total reflection Fourier transform infrared) spectroscopy;

(ii) determining characteristic spectral parameters for each assigned glucose-specific peak in correlation with its position and shift in the mid-IR spectra, wherein characteristic predominant peak position with its shift within 1030 cm^{-1} or 1041 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1}, to be specific for healthy, prediabetic and diabetic subjects;

(iii) further determining characteristic spectral parameters for each assigned glucose-specific peak in correlation with its level in the mid-IR spectra under a continuous 120-minute monitoring at pre-determined time-intervals from the starting till the ending time-points of the test, wherein characteristic determination of the peak with the highest level at 1030 or 1041 cm^{-1} within 1030-1041 cm^{-1}, determination of the peak with the highest level among all assigned glucose-specific peaks, to be specific for healthy, prediabetic and diabetic subjects;

(iv) further determining characteristic spectral parameters for each assigned glucose-specific peak level dynamic changes in dose-response correlation to oral glucose *per os* between low, medium and high doses under a continuous 120-minute monitoring at pre-determined time-intervals from the starting till the ending time-points of OGTT test with 5 g (low), 20 g (medium) and/or 75 g (high) glucose, wherein characteristic dose-indifferentiated dynamical changes of the level of the peaks within 1030-1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1} to be specific for healthy subjects, characteristic dose-differentiated dynamical changes of the level of the peaks

within 1030-1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1} to be specific for prediabetic and diabetic subjects;

(v) calculation of the LT (latency time) for each assigned glucose-specific peak identified in step (i), in comparison with calculated LT for CBG (capillary blood glucose) measurements in the same subject, for calculation of their LTs differences, wherein single, bi-phase or cascadic LT's appearance, to be specific for healthy, prediabetic and diabetic subjects;

(vi) determining the spectral characteristics of the LT differences for each assigned glucose-specific peak in dose-response correlation to oral glucose *per os* between low, medium and high doses under a continuous 120-minute monitoring at pre-determined time-intervals from the starting till the ending time-points of OGTT test with 5 g (low), 20 g (medium) and/or 75 g (high) glucose, wherein the time duration of the LT differences to be specific for healthy, prediabetic and diabetic subjects; and

(vii) determining the spectral pattern of individual metabolic response, based on spectral qualitative and quantitative parametric evaluation of GV (glycemic variability) with its dynamics identified in steps (ii)-(iv), the LT calculation with its difference with the LT in CBG identified in steps (v-vi), to be specific for healthy, prediabetic or diabetic subjects,

wherein

the spectral pattern with characteristic

predominant mean peak position near 1030 cm^{-1} within 1030 - 1041 cm^{-1} according to Figure 8 c-e and Figure 11 a,

predominant left-shifted mean peak position within 1116-1118 cm^{-1} according to Figure 5 c and Figure 7 a, predominant left-shifted mean peak position within 1149-1153 cm^{-1} according to Figure 8 e and Figure 11 d,

the highest glucose peak levels within 1030-1041 cm^{-1} among all detected glucose peak levels according to Figure 8 c-e,

the lowest glucose peak levels within 1153 cm^{-1} among all detected glucose peaks levels according to Figure 8 e, indifferentiated to dose-response peak levels at 1030 cm^{-1}, 1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1} according to Figure 5 a-c,

bi-phase LTs and the LTs differences with CBG at 1030-1041 cm^{-1} with the time intervals of 15` and 30` under OGTT (5 g) with reference to Table 2 (column 3, row 2),

single-phase LTs and the LTs differences with CBG at 1030-1041 cm^{-1} with the time intervals of 10` under OGTT (20 g) with reference to Table 2 (column 4, row 2),

bi-phase LTs and the LTs differences with CBG at 1030-1041 cm^{-1} with the time intervals of 5`and 30`under OGTT (75 g) with reference to Table 2 (column 5, row 2),

bi-phase LTs and the LTs differences with CBG at 1080 cm^{-1} with the time intervals of 15` and 30` under OGTT (5 g) with reference to Table 2 (column 3, row 3),

three-phase LTs and the LTs differences with CBG at 1080 cm^{-1} with the time intervals of 0`, 10`and 20` under OGTT (20 g) with reference to Table 2 (column 4, row 3),

single-phase LTs and the LTs differences with CBG at 1080 cm^{-1} with the time intervals of 5`under OGTT (75 g) with reference to Table 2 (column 5, row 3),

bi-phase LTs and the LTs differences with CBG at 1118 cm^{-1} with the time intervals of 10` and 25` under OGTT (5 g) with reference to Table 2 (column 3, row 4),

single-phase LTs and the LTs differences with CBG at 1118 cm^{-1} with the time intervals of 10` under OGTT (20 g) with reference to Table 2 (column 4, row 4),

bi-phase LTs and the LTs differences with CBG at 1118 cm^{-1} with the time intervals of 5`and 25`under OGTT (75 g) with reference to Table 2 (column 5, row 4),

bi-phase LTs and the LTs differences with CBG at 1153 cm^{-1} with the time intervals of 35` and 50`under OGTT (5 g) with reference to Table 2 (column 3, row 5),

single-phase LTs and the LTs differences with CBG at 1153 cm^{-1} with the time intervals of 10`and 15` under OGTT (20 g) with reference to Table 2 (column 4, row 5),

single-phase LTs and the LTs differences with CBG at 1153 cm^{-1} with the time intervals of 10` under OGTT (75 g) with reference to Table 3 (column 5, row 5),

the longest LT's differences with CBG at 1030-1041 cm^{-1} of 5`-30`, at 1080 cm^{-1} of 0`-30`, at

1118 cm^{-1} of 5`-25`, at 1153 cm^{-1} of 10`-50` under post-prandial glucose test and/or OGTT at the different doses of 5 g, 20 g and/or 75 g,

the longest intervals within 5-50 minutes of the LT's differences with CBG with characteristic single-, bi- and three-phase appearance at 1030-1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1} under OGTT with 75 g, as compared with characteristic LT shortest durations within 0-30 minutes of the LT's differences with CBG with characteristic single-phase appearance at 1030-1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1} on HATR-FTIR spectrometer under OGTT with 75 g for a diabetic subject as shown in Table 3 (column 5), Table 4 (column 3) and/or Table 7 (column 4) and characteristic durations of the LTs differences with CBG within 0-55 minutes with characteristic multi-phase cascade appearance at 1030-1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1} on HATR-FTIR spectrometer under OGTT with 75 g,

dose-independent durations of the LT's and the LT's differences with CBG for each assigned glucose-specific peak under any OGTT with different doses of 5 g, 20 g and 75 g,

bi-phase LT's appearance with calculated LT's differences of 15` and 30` at 1030-1041 cm^{-1}, 15` and 30` minutes at about 1080 cm^{-1}, 10` and 25` minutes at 1118 cm^{-1}, 35` and 50` minutes at 1153 cm^{-1} under OGTT (5 g) with reference to Table 2 (column 3),

single-, bi- and three-phase LT's appearance with calculated LT's differences of 10`at 1030-1041 $cm^{-1}$, 0` & 10` and 20` at 1080 cm^{-1}, 10` at 1118 $cm^{-1}$, 10` and 15`at 1153 cm^{-1} under OGTT (20 g) with reference to Table 2 (column 4),

single- and bi-phase LT's appearance with calculated LT's differences of 5` & 30`at 1030-1041 cm^{-1}, 5` at 1080 $cm^{-1}$, 5` & 25`at 1118 $cm^{-1}$, 10` at 1153 cm^{-1} under OGTT (75 g) with reference to Table 2 (column 5),

to be specific for a healthy subject, or

the spectral pattern with

predominant mean peak position within 1037-1041 cm^{-1} according to Figure 8f and Figure 11a,

predominant right-shifted mean peak position within 1120-1122 cm^{-1} according to Figure 11 c,

the highest peak levels at 1030-1041 cm^{-1} and at 1118 cm^{-1} at similar levels against other 2 glucose peak levels according to Figure 8 f,

the lowest glucose peak levels within 1153 cm^{-1} among other 4 glucose peaks levels according to Figure 11d,

differentiated high dose-response peak levels with 75 g at 1030 cm^{-1},1041 cm^{-1}, 1080 cm^{-1} and 1118 cm^{-1},

multi-phase LTs and the LTs differences with CBG at 1030-1041 cm^{-1} with the time intervals of 5`, 20`, 30`and 45`under OGTT (75 g) with reference to Table 7 (column 3, row 2),

three-phase LTs and the LTs differences with CBG at 1080 cm^{-1}, with the time intervals of 5`, 20`and 45`under OGTT (75 g) with reference to Table 7 (column 3, row 3),

cascading multi-phase LTs and the LTs differences with CBG at 1118 cm^{-1} with the time intervals of 5`, 20`, 30` and 40`under OGTT (75 g) with reference to Table 7 (column 3, row 4),

cascading multi-phase LTs and the LTs differences with CBG at 1153 cm^{-1} with the time intervals of 0`, 15`, 25`and 55` under OGTT (75 g) with reference to Table 7 (column 3, row 5),

multi-phase LTs and the LTs differences with CBG within 5`- 45` at 1030-1041 cm^{-1}, 5`- 45` at 1080 cm^{-1}, 5`- 40` at 1118 cm^{-1}, 0`- 55` at 1153 cm^{-1} under OGTT with 75 g as shown in Table 7 (column 3, rows 2-5),

LTs differences with CBG within 0-55 minutes with characteristic multi-phase cascade appearance at 1030-1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1} on HATR-FTIR spectrometer under OGTT with 75 g, as compared with characteristic shortest intervals within 0-30 minutes of the LT's differences with CBG with characteristic single-phase appearance at 1030-1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1} on HATR-FTIR spectrometer under OGTT with 75 g for a diabetic subject as shown in Table 3 (column 5), Table 4 (column 3) and Table 7 (column 4) and with characteristic longest intervals within 5-50 minutes of the LT's differences with CBG with characteristic single-, bi- and three-phase appearance at 1030-1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1} under OGTT with 75 g for a healthy subject as shown in Table 2 (column 5),

dose-dependent durations of the LT’s and the LT’s differences with CBG with multi-phase cascade appearance at 5, 20, 30 and 45 minutes at 1030-1041 cm^{-1}, at 5, 20 and 45 minutes at 1080 cm^{-1}, at 5, 20, 30 and 40 minutes at 1118 cm^{-1}, at 0, 15, 25 and 55 minutes at 1153 cm^{-1} under OGTT with 75 g,

to be specific for a prediabetic subject, or

the spectral pattern with characteristic

predominant mean peak position at 1041 cm^{-1} within 1030 - 1041 cm^{-1} according to Figure 6a, 8 a-b and 11a,

dominant right-shifted mean peak position at 1120-1122 cm^{-1} according to Figure 6c,

predominant right-shifted mean peak position within 1153-1157 cm^{-1} according to Figure 8b, the highest glucose peak levels at 1118 cm^{-1} among other 3 glucose peak levels according to Figure 8 a-b,

the lowest glucose peak levels within 1153 cm^{-1} below the other 3 glucose peaks levels according to Figure 8f and Figure 11d,

well-differentiated low, medium and high dose-response peak levels at 1030-1041 cm^{-1}, 1080 cm^{-1} and 1118 cm^{-1} according to Figure 6 a-c,

bi-phase LTs and the LTs differences with CBG at 1030-1041 cm^{-1} with the time intervals of 0` and 10` under OGTT (5 g) with reference to Table 3 (column 3, row 2),

single-phase LTs and the LTs differences with CBG at 1030-1041 cm^{-1} with the time intervals of 0` under OGTT (20 g) with reference to Table 3 (column 4, row 2),

single-phase LTs and the LTs differences with CBG at 1030-1041 cm^{-1} with the time intervals of 0` under OGTT (75 g) with reference to Table 3 (column 5, row 2),

single-phase LTs and the LTs differences with CBG at 1080 cm^{-1} with the time interval of 10`under OGTT (5 g) with reference to Table 3 (column 3, row 3),

single-phase LTs and the LTs differences with CBG at 1080 cm^{-1} with the time interval of 15`under OGTT (20 g) with reference to Table 3 (column 4, row 3),

single-phase LTs and the LTs differences with CBG at 1080 cm^{-1} with the time interval of 0`under OGTT (75 g) with reference to Table 3 (column 5, row 3) and to Table 7 (column 4, row

3),

three-phase LTs and the LTs differences with CBG at 1118 cm^{-1} with the time intervals of 0`, 10` and 25`under OGTT (5 g) with reference to Table 3 (column 3, row 4),

single-phase LTs and the LTs differences with CBG at 1118 cm^{-1} with the time intervals of 5` under OGTT (20 g) with reference to Table 3 (column 4, row 4),

single-phase LTs and the LTs differences with CBG at 1118 cm^{-1} with the time intervals of 0` under OGTT (75 g) with reference to Table 3 (column 5, row 4),

bi-phase LTs and the LTs differences with CBG with the time intervals of 15`and 25` under OGTT (5 g) with reference to Table 3 (column 3, row 5),

bi-phase LTs and the LTs differences with CBG with the time intervals of 25`and 40` under OGTT (20 g) with reference to Table 3 (column 4, row 5),

bi-phase LTs and the LTs differences with CBG with the time intervals of 30` under OGTT (75 g) with reference to Table 3 (column 5, row 5),

the shortest LTs differences at 1030-1041 cm^{-1} of 0`and 10`, at 1080 cm^{-1} of 0`, 10`, 15` and 60`, at 1118 cm^{-1} of 0`, 5`, 10`, 25`and 60`, at 1153 $cm^{-1}$ of 15`, 25`, 30` and 40` under post-prandial glucose test and/or OGTT at the different doses of 5 g, 20 g and/or 75 g,

the shortest LTs within the shortest intervals of the LTs differences at 1030-1041 cm^{-1} of 0` as shown in Table 1 (column 2), at 1080 $cm^{-1}$ of 0`, 0`& 60`and 60`as shown in Table 1 (column 3), at 1118 $cm^{-1}$ of 0`and 0`& 60` as shown in Table 1 (column 4), at 1153 cm^{-1} of 30`and 60`as shown in Table 1 (column 4) under post-prandial glucose test,

dose-dependent durations of the LT's differences with CBG for glucose-specific peaks at 1030-1041 cm^{-1}, 1080 cm^{-1} and 1118 cm^{-1} under any OGTT with different doses of 5 g, 20 g and 75 g glucose,

single-, bi- and three-phase LT's differences for 1030-1041 cm^{-1} at 0 and 10 minutes, for 1080 cm^{-1} at 10 minutes, for 1118 cm^{-1} at 0, 10 and 25 minutes, for 1153 cm^{-1} at 15 and 25 minutes under OGTT (5 g),

single- and bi-phase LT's and their calculated differences with CBG for 1030-1041 cm^{-1} at 0 minutes, for 1080 cm^{-1} at 15 minutes, for 1118 cm^{-1} at 5 minutes, for 1153 cm^{-1} at 15 and 40 minutes under OGTT (20 g),

single-phase LT's and their calculated differences with CBG for 1030-1041 cm^{-1} at 0 minutes,

for 1080 cm^{-1} at 0 minutes, for 1118 cm^{-1} at 0 minutes, for 1153 cm^{-1} at 30 minutes under OGTT (75 g),

the time duration of the LT's differences of within 0-30 minutes with characteristic predominant single-phase detection at 1030-1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1}, as compared under OGTT with 75 g for a prediabetic subject with the LT's differences of within 0-55 minutes with characteristic multi-phase cascade detection at 1030-1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1} on HATR-FTIR spectrometer as shown in Table 7 (column 3), or as compared with the LT differences with the time duration of within 5-50 minutes with characteristic single- and/or bi-phase detection at 1030-1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1},

to be specific for a diabetic subject.

2. A method of monitoring the spectral pattern of individual metabolic response in the interstitial fluid of the epidermal skin tissue by HATR-FTIR spectroscopy based on spectral qualitative and quantitative parametric evaluation of GV with its dynamics and the LT calculation with its difference with the LT in CBG under a continuous 120-minute monitoring at pre-determined time-intervals from the starting till the ending time-points of post-prandial glucose test and/or OGTT at the different doses of 5 g, 20 g and/or 75 g for diagnosing prediabetes and diabetes type 2 in a subject, or for screening prediabetes and diabetes type 2 in a subject, or for predicting the risk of hyperglycemia in a subject, or for staging diabetes type 2 in a subject, or for monitoring diabetes control in a subject, said method is comprising of the steps (i-vii) in Claim 1.

3. HATR-FTIR spectrometer by recognizing the spectral pattern of individual metabolic response in the interstitial fluid of the epidermal skin tissue by spectral qualitative and quantitative parametric evaluation of GV with its dynamics and the LT calculation with its difference with the LT in CBG under a continuous 120-minute monitoring at pre-determined time-intervals from the starting till the ending time-points of post-prandial glucose test and/or OGTT at the different doses of 5 g, 20 g and/or 75 g suitable for diagnosing disorders of glucose metabolism such as prediabetes and diabetes type 2 in a subject, or for screening and follow-up disorders of glucose metabolism such as prediabetes and diabetes type 2 in a subject, or for predicting the risk of hyperglycemia in a subject, or for staging diabetes type 2 in a subject, or for managing hyperglycemia in a subject, or for monitoring diabetes control in a subject, or for assessing the quality of metabolic control in a subject, comprising the steps (i-vii) according to Claim 1.

4. The method of Claims 1-2, or the device of Claim 3, wherein the LT in the interstitial fluid of epidermal skin tissue is the time interval from the time-point of induction of glucose excursions till the time-point of maximum detected levels of said glucose-specific peaks by HATR-FTIR spectroscopy under a continuous 120-minute monitoring at pre-determined time-intervals from the starting till the ending time-points of post-prandial glucose test and/or OGTT at the different doses of 5 g, 20 g and/or 75 g in a subject.

5. The method of Claims 1-2, or the device of Claim 3, wherein the LT in CBG is the time interval from the time-point of induction of glucose excursions in capillary blood till the time-point of maximum detected levels of CBG by a portable glucosemeter under a continuous 120-minute monitoring at pre-determined time-intervals from the starting till the ending time-points of post-prandial glucose test and/or OGTT at the different doses of 5 g, 20 g and/or 75 g in a subject.

6. The method of Claims 1-2, or the device of Claim 3, wherein induction of glucose excursions in the blood glucose is influenced by consumption of meal, or pure glucose *per os* at the different doses of 5 g, 20 g and/or 75 g in a subject.

7. The method of Claims 1-2, or the device of Claim 3, wherein a calibration prior a collection of mid-IR spectra by HATR-FTIR spectroscopy is performed on a subject by using CBG values pre-prandially and/or before the OGTT, used as referenced CBG values before any post-prandial glucose test or the OGTT at the different doses of 5 g, 20 g and/or 75 g in the same subject.

8. The method of Claims 1-2, or the device of Claim 3, wherein collection of mid-IR spectra by HATR-FTIR spectroscopy is performed from the skin surface of the inner wrist in a subject.

9. A glucose molecule with characteristic spectral parameters at consistent and significant absorption wave number at 1030 cm^{-1} or 1041 cm^{-1}, characterized by spectral bounded bands of glucose in the mid-IR spectra corresponding to identity and secondary structures to glucose molecules in correlation with characteristic measurements of the peak position and/or its shift, the peak levels and its dynamic changes, the peak LT calculation on HATR-FTIR spectrometer in the interstitial fluid of the epidermal skin tissue in comparison with the LT in CBG for calculation of the peak LT's difference on a healthy, prediabetic or diabetic subject under a continuous 120-minute

monitoring at pre-determined time-intervals from the starting till the ending time-points of post-prandial glucose test and/or OGTT at the different doses of 5 g, 20 g and/or 75 g, when used for evaluating individual metabolic response and for generating predictive clinical metrics needed for diagnosing disorders of glucose metabolism such as prediabetes and diabetes, or for screening and follow-up of disorders of glucose metabolism such as prediabetes and diabetes, which is one selected from:

(i) a glucose molecule with

characteristic predominant mean peak position at 1030 cm^{-1} within 1030-1041 cm^{-1} according to Figure 8 c-e and Figure 11 a,

characteristic the highest glucose peak levels within 1030-1041 cm^{-1} against the other glucose peaks levels at 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1} according to Figure 8 c-e,

characteristic indifferentiated peak levels to low, medium and high glucose dose under OGTT with 5 g, 20 g and/or 75 g according to Figure 5 a,

characteristic bi-phase LTs and the LTs differences with CBG with the time intervals of 15` and 30` under OGTT (5 g) with reference to Table 2 (column 3, row 2),

characteristic single-phase LTs and the LTs differences with CBG with the time intervals of 10` under OGTT (20 g) with reference to Table 2 (column 4, row 2) in Example 2,

characteristic bi-phase LTs and the LTs differences with CBG with the time intervals of 5`and 30`under OGTT (75 g) with reference to Table 2 (column 5, row 2),

to be specific for a healthy subject; or

(ii) a glucose molecule with

characteristic predominant mean peak position at 1037-1041 cm^{-1} within 1030 - 1041 cm^{-1} according to Figure 8 f and Figure 11 a,

characteristic the highest glucose peak levels within 1030 - 1041 cm^{-1} similar to the peak levels at about 1118 cm^{-1} according to Figure 8 f,

characteristic dose-differentiated peak levels to high dose of glucose at 75 g under OGTT (75 g) according to Figure 8 f and Figure 11 a,

characteristic multi-phase LTs and the LTs differences with CBG with the time intervals of 5`, 20`, 30`and 45`under OGTT (75 g) with reference to Table 7 (column 3, row 2),

to be specific for a prediabetic subject; or

(iii) a glucose molecule with

characteristic predominant mean peak position at 1039-1041 cm^{-1} within 1030 - 1041 cm^{-1} according to Figure 11 a,

characteristic differentiated to low, medium and high glucose dose peak levels under OGTT with 5 g, 20 g and/or 75 g according to Figure 6 a,

characteristic single-phase LTs and the LTs differences with CBG with the time intervals of 0` under post-prandial glucose test according to Table 1 (column 2, rows 1-4), Figures 2 a, 3 a and 4 a,

characteristic bi-phase LTs and the LTs differences with CBG with the time intervals of 0` and 10` under OGTT (5 g) with reference to Table 3 (column 3, row 2),

characteristic single-phase LTs and the LTs differences with CBG with the time intervals of 0` under OGTT (20 g) with reference to Table 3 (column 4, row 2),

characteristic single-phase LTs and the LTs differences with CBG with the time intervals of 0` under OGTT (75 g) with reference to Table 3 (column 5, row 2),

to be specific for a diabetic subject.

10. A glucose molecule with characteristic spectral parameters at consistent and significant absorption wave number at 1080 cm^{-1}, characterized by spectral band of glucose in the mid-IR spectra corresponding to identity and secondary structures to glucose molecules in

correlation with characteristic measurements of the peak position and/or its shift, the peak levels and its dynamic changes, the peak LT calculation on HATR-FTIR spectrometer in the interstitial fluid of the epidermal skin tissue in comparison with the LT in CBG for calculation of the peak LT's difference on a healthy, prediabetic or diabetic subject under a continuous 120-minute monitoring at pre-determined time-intervals from the starting till the ending time-points of post-prandial glucose test and/or OGTT at the different doses of 5 g, 20 g and/or 75 g, when used for evaluating individual metabolic response and for generating predictive clinical metrics needed for diagnosing disorders of glucose metabolism, such as prediabetes and diabetes, or for screening and follow-up of disorders of glucose metabolism, such as prediabetes and diabetes, which is one selected from:

(i) a glucose molecule with

characteristic indifferentiated peak levels to low, medium and high glucose doses under OGTT with 5 g, 20 g and/or 75 g according to Figure 5 b,

characteristic bi-phase LTs and the LTs differences with CBG with the time intervals of 15` and 30` under OGTT (5 g) with reference to Table 2 (column 3, row 3),

characteristic three-phase LTs and the LTs differences with CBG with the time intervals of 0`, 10`and 20` under OGTT (20 g) with reference to Table 2 (column 4, row 3),

characteristic single-phase LTs and the LTs differences with CBG with the time intervals of 5`under OGTT (75 g) with reference to Table 2 (column 5, row 3),

to be specific for a healthy subject; or

(ii) a glucose molecule with

characteristic differentiated peak levels to high glucose dose under OGTT with 75 g according to Figure 11 b,

characteristic three-phase LTs and the LTs differences with CBG with the time intervals of 5`, 20`and 45`under OGTT (75 g) with reference to Table 7 (column 3, row 3),

to be specific for a prediabetic subject; or

(iii) a glucose molecule with

characteristic dose-differentiated peak levels to low, medium and high glucose dose under OGTT with 5 g, 20 g and/or 75 g according to Figure 6 b,

characteristic single-phase LTs and the LTs differences with CBG with the time interval of 10`under OGTT (5 g) with reference to Table 3 (column 3, row 3),

characteristic single-phase LTs and the LTs differences with CBG with the time interval of 15`under OGTT (20 g) with reference to Table 3 (column 4, row 3),

characteristic single-phase LTs and the LTs differences with CBG with the time interval of 0`under OGTT (75 g) with reference to Table 3 (column 5, row 3) and to Table 7 (column 4, row 3),

to be specific for a diabetic subject.

11. A glucose molecule with characteristic spectral parameters at consistent and significant absorption wave number at about 1118 cm^{-1}, characterized by spectral band of glucose in the mid-IR spectra corresponding to identity and secondary structures to glucose molecules in correlation with characteristic measurements of the peak position and/or its shift, the peak levels and its dynamic changes, the peak LT calculation on HATR-FTIR spectrometer in the interstitial fluid of the epidermal skin tissue in comparison with the LT in CBG for calculation of the peak LT's difference on a healthy, prediabetic or diabetic subject under a continuous 120-minute monitoring at pre-determined time-intervals from the starting till the ending time-points of post-prandial glucose test and/or OGTT at the different doses of 5 g, 20 g and/or 75 g, when used for evaluating individual metabolic response and for generating predictive clinical metrics needed for diagnosing disorders of glucose metabolism, such as prediabetes and diabetes on a subject except for a human being, or for screening and follow-up of disorders of glucose metabolism, such as prediabetes and diabetes on a subject except for a human being, which is one selected from:

(i) a glucose molecule with

characteristic predominant left-shifted mean peak position within 1114-1118 cm^{-1} according to Figure 5 c, wherein mean peak position at 1118 cm^{-1} is characteristic under OGTT at 5 g, mean peak position at 1114-1118 cm^{-1} is characteristic under OGTT at 20 g, mean peak position at 1116-1118 cm^{-1} is under OGTT at 75 g,

characteristic indifferentiated peak levels to low, medium and high glucose dose under OGTT with 5 g, 20 g and/or 75 g according to Figure 5 c,

characteristic bi-phase LTs and the LTs differences with CBG with the time intervals of 10` and 25` under OGTT (5 g) with reference to Table 2 (column 3, row 4),

characteristic single-phase LTs and the LTs differences with CBG with the time intervals of 10` under OGTT (20 g) with reference to Table 2 (column 4, row 4),

characteristic bi-phase LTs and the LTs differences with CBG with the time intervals of 5`and 25`under OGTT (75 g) with reference to Table 2 (column 5, row 4),

to be specific for a healthy subject; or

(ii) a glucose molecule with

characteristic predominant right-shifted mean peak position within 1120-1122 cm^{-1} according to Figure 8 f,

characteristic the highest glucose peak levels similar to glucose peak levels at 1030 - 1041 cm^{-1} over the other 2 glucose peak levels at 1080 cm^{-1} and 1153 cm^{-1} according to Figure 8 f,

characteristic dose-differentiated peak levels to high dose of glucose at 75 g under OGTT (75 g) according to Figure 8 f and Figure 11 c,

characteristic cascading multi-phase LTs and the LTs differences with CBG with the time intervals of 5`, 20`, 30` and 40`under OGTT (75 g) with reference to Table 7 (column 3, row 4),

to be specific for a prediabetic subject; or

(iii) a glucose molecule with

characteristic dominant right-shifted mean peak position at 1120-1122 cm^{-1} according to Figures 6 c, 8 a, 8 c and 11 c,

characteristic the highest glucose peak levels within 1120-1122 cm^{-1} against the other glucose peaks levels within 1030-1041 cm^{-1}, 1080 cm^{-1} and 1153 cm^{-1} according to Figure 8 b and Figure 11 c,

characteristic dose-differentiated peak levels to low, medium and high doses of glucose at 5 g, 20 g and 75 g under OGTT (5 g, 20 g, 75 g) according to Figure 6 c and Figure 7 b,

characteristic three-phase LTs and the LTs differences with CBG with the time intervals of 0`, 10` and 25`under OGTT (5 g) with reference to Table 3 (column 3, row 4),

characteristic single-phase LTs and the LTs differences with CBG with the time intervals of 5` under OGTT (20 g) with reference to Table 3 (column 4, row 4),

characteristic single-phase LTs and the LTs differences with CBG with the time intervals of 0` under OGTT (75 g) with reference to Table 3 (column 5, row 4),

to be specific for a diabetic subject.

12. A glucose molecule with characteristic spectral parameters at consistent and significant absorption wave number at about 1153 cm^{-1}, characterized by spectral band of glucose in the mid-IR spectra corresponding to identity and secondary structures to glucose molecules in correlation with characteristic measurements of the peak position and/or its shift, the peak levels and its dynamic changes, the peak LT calculation on HATR-FTIR spectrometer in the interstitial fluid of the epidermal skin tissue in comparison with the LT in CBG for calculation of the peak LT's difference on a healthy, prediabetic or diabetic subject under a continuous 120-minute monitoring at pre-determined time-intervals from the starting till the ending time-points of post-prandial glucose test and/or OGTT at the different doses of 5 g, 20 g and/or 75 g, when used for evaluating individual metabolic response and for generating predictive clinical metrics needed for diagnosing disorders of glucose metabolism, such as prediabetes and diabetes, on a subject except for a

human being, or for screening and follow-up of disorders of glucose metabolism, such as prediabetes and diabetes, on a subject except for a human being, which is one selected from:

(i) a glucose molecule with

characteristic predominant left-shifted mean peak position within 1149-1153 cm^{-1} according to Figure 8 e,

characteristic the lowest glucose peak levels within 1153 cm^{-1} below the other glucose peaks levels at 1030-1041 cm^{-1}, 1080 cm^{-1} and 1118 cm^{-1} according to Figure 8 e,

characteristic bi-phase LTs and the LTs differences with CBG with the time intervals of 35` and 50`under OGTT (5 g) with reference to Table 2 (column 3, row 5),

characteristic single-phase LTs and the LTs differences with CBG with the time intervals of 10`and 15` under OGTT (20 g) with reference to Table 2 (column 4, row 5),

characteristic single-phase LTs and the LTs differences with CBG with the time intervals of 10` under OGTT (75 g) with reference to Table 3 (column 5, row 5),

to be specific for a healthy subject; or

(ii) a glucose molecule with

characteristic the lowest glucose peak levels within 1153 cm^{-1} below the other glucose peaks levels within 1030-1041 cm^{-1}, 1080 cm^{-1} and 1118 cm^{-1} according to Figure 8 f and Figure 11 d,

characteristic cascading multi-phase LTs and the LTs differences with CBG with the time intervals of 0`, 15`, 25`and 55` under OGTT (75 g) with reference to Table 7 (column 3, row 5),

to be specific for a prediabetic subject; or

(iii) a glucose molecule with

characteristic predominant right-shifted mean peak position within 1153-1157 cm^{-1} according to Figure 8 b,

characteristic the lowest glucose peak levels within 1153 cm^{-1} below the other glucose peaks levels within 1030-1041 cm^{-1}, 1080 cm^{-1} and 1118 cm^{-1} according to Figure 8 f and Figure 11 d,

characteristic bi-phase LTs and the LTs differences with CBG with the time intervals of 15`and 25` under OGTT (5 g) with reference to Table 3 (column 3, row 5),

characteristic bi-phase LTs and the LTs differences with CBG with the time intervals of 25`and 40` under OGTT (20 g) with reference to Table 3 (column 4, row 5),

characteristic bi-phase LTs and the LTs differences with CBG with the time intervals of 30` under OGTT (75 g) with reference to Table 3 (column 5, row 5),

to be specific for a diabetic subject.

13. A combination group of glucose molecules with characteristic spectral parameters at consistent and significant absorption wave number at 1030 cm^{-1}, 1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1}, characterized by spectral band of glucose in the mid-IR spectra corresponding to identity and secondary structures to glucose molecules in correlation with characteristic measurements of the peak position and/or its shift, the peak levels and its dynamic changes, the peak LT calculation on HATR-FTIR spectrometer in the interstitial fluid of the epidermal skin tissue in comparison with the LT in CBG for calculation of the peak LT's difference on a healthy, prediabetic or diabetic subject under a continuous 120-minute monitoring at pre-determined time-intervals from the starting till the ending time-points of post-prandial glucose test and/or OGTT at the different doses of 5 g, 20 g and/or 75 g, when used for evaluating individual metabolic response and for generating predictive clinical metrics needed for diagnosing disorders of glucose metabolism, such as prediabetes and diabetes on a subject except for a human being, or for screening and follow-up of disorders of glucose metabolism, such as prediabetes and diabetes, on a subject except for a human being, which is one selected from:

(i) a combination group of glucose molecules with

characteristic the highest peak levels at 1030-1041 cm^{-1} over the other 3 glucose-specific peak levels according to Figure 8 c and 8 d,

characteristic the lowest glucose peak levels within 1153 cm^{-1} below the other glucose peaks levels at 1030-1041 cm^{-1}, 1080 cm^{-1} and 1118 cm^{-1} according to Figure 8 e,

characteristic indifferentiated to dose-response peak levels at 1030-1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1},

characteristic bi-phase LT's differences for 1030-1041 cm^{-1} at 15 and 30 minutes, for 1080 cm^{-1} at 15 and 30 minutes, for 1118 cm^{-1} at 10 and 25 minutes, and for 1153 cm^{-1} at 35 and 50 minutes under OGTT (5 g) with reference to Table 2 (column 3),

characteristic single-, bi- and three-phase LT's differences for 1030-1041 cm^{-1} at 10 minutes, for 1080 cm^{-1} at 0, 10 and 20 minutes, for 1118 cm^{-1} at 10 minutes, for 1153 cm^{-1} at 10 and 15 minutes under OGTT (20 g) with reference to Table 2 (column 4),

characteristic single- and bi-phase LT's differences for 1030-1041 cm^{-1} at 5 and 30 minutes, for 1080 cm^{-1} at 5 minutes, for 1118 cm^{-1} at 5 and 25 minutes, and for 1153 cm^{-1} at 10 minutes under OGTT (75 g) with reference to Table 2 (column 5),

to be specific for a healthy subject; or

(ii) a combination group of glucose molecules with

characteristic multi-phasic LT's differences for 1030-1041 cm^{-1} at 5, 20, 30 and 45 minutes, for 1080 cm^{-1} at 5, 20 and 45 minutes, for 1118 cm^{-1} at 5, 20, 30 and 40 minutes, and for 1153 cm^{-1} at 0, 15, 25 and 55 minutes under OGTT (75 g) with reference to Table 7 (column 3),

to be specific for a prediabetic subject; or

(iii) a combination group of glucose molecules with

characteristic comparative dose-dependent GV dynamics of glucose peak levels at 1030 - 1041 cm^{-1}, 1080 cm^{-1} and 1118 cm^{-1} according to Figure 6 a-c during OGTT with different doses of glucose, wherein said glucose peaks levels are dosedependent and well-differentiated between intaken doses of glucose from starting to the ending point of the test;

characteristic predominant high glucose peak levels at 1118 cm^{-1} over the other glucose peaks levels according to Figure 8 a-b,

characteristic predominant glucose peak position at 1041 cm-1 within 1030 - 1041 cm^{-1} according to Figure 6 a, Figure 8 a-b and Figure 11 a,

characteristic dominant right-shifted mean positions of the peak at 1118 cm^{-1} according to Figure 6 c, Figure 7 a-b, Figure 8 a-b and Figure 11 c,

characteristic differences in the levels of glucose values and/or wavenumber shifts at 1030 - 1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1}, and/or 1153 cm^{-1} obtained at the different glucose doses as compared with characteristic differences for healthy and diabetic subjects as shown in Figure 7 a-c, Figure 9 a-d and Figure 11 a-d,

characteristic single-, bi- and three-phase LTs differences for 1030-1041 cm^{-1} at 0 and 10 minutes, for 1080 cm^{-1} at 10 minutes, for 1118 cm^{-1} at 0, 10 and 25 minutes, for 1153 cm^{-1} at 15 and 25 minutes under OGTT (5 g) with reference to Table 3 (column 3),

characteristic single- and bi-phase LTs differences for 1030-1041 cm^{-1} at 0 minutes, for 1080 cm^{-1} at 15 minutes, for 1118 cm^{-1} at 5 minutes, and for 1153 cm^{-1} at 15 and 40 minutes under OGTT (20 g) with reference to Table 5 (column 3),

characteristic single-phase LT's differences for 1030-1041 cm^{-1} at 0 minutes, for 1080 cm^{-1} at 0 minutes, for 1118 cm^{-1} at 0 minutes, for 1153 cm^{-1} at 30 minutes under OGTT (75 g) with reference to Table 7 (column 4),

to be specific for a diabetic subject.

14. Use of a glucose molecule with characteristic spectral parameters at consistent and significant absorption wave number at 1030 cm^{-1} or 1041 cm^{-1}, specific for healthy, prediabetic

and diabetic subjects, characterized by spectral bounded bands of glucose in the mid-IR spectra corresponding to identity and secondary structures to glucose molecules in correlation with characteristic measurements of the peak position and/or its shift, the peak levels and its dynamic changes, the peak LT calculation on HATR-FTIR spectrometer in the interstitial fluid of the epidermal skin tissue in comparison with the LT in CBG for calculation of the peak LT's difference on a healthy, prediabetic or diabetic subject under a continuous 120-minute monitoring at pre-determined time-intervals from the starting till the ending time-points of post-prandial glucose test and/or OGTT at the different doses of 5 g, 20 g and/or 75 g, for diagnosis of disorders of glucose metabolism such as prediabetes and diabetes type 2 in a subject, or for screening and follow-up disorders of glucose metabolism such as prediabetes and diabetes type 2 in a subject, or for predicting the risk of hyperglycemia in a subject, or for staging diabetes type 2 in a subject, or for managing hyperglycemia in a subject, or for monitoring diabetes control in a subject, or for assessing the quality of metabolic control in a subject, comprising its spectral characteristics according to Claim 9.

15. Use of a glucose molecule with characteristic spectral parameters at consistent and significant absorption wave number at 1080 cm^{-1}, specific for healthy, prediabetic and diabetic subjects, characterized by spectral bounded bands of glucose in the mid-IR spectra corresponding to identity and secondary structures to glucose molecules in correlation with characteristic measurements of the peak position and/or its shift, the peak levels and its dynamic changes, the peak LT calculation on HATR-FTIR spectrometer in the interstitial fluid of the epidermal skin tissue in comparison with the LT in CBG for calculation of the peak LT's difference on a healthy, prediabetic or diabetic subject under a continuous 120-minute monitoring at pre-determined time-intervals from the starting till the ending time-points of post-prandial glucose test and/or OGTT at the different doses of 5 g, 20 g and/or 75 g, for diagnosis of disorders of glucose metabolism such as prediabetes and diabetes type 2 in a subject, or for screening and follow-up disorders of glucose metabolism such as prediabetes and diabetes type 2 in a subject, or for predicting the risk of hyperglycemia in a subject, or for staging diabetes type 2 in a subject, or for managing hyperglycemia in a subject, or for monitoring diabetes control in a subject, or for assessing the quality of metabolic control in a subject, comprising its spectral characteristics according to Claim 10.

16. Use of a glucose molecule with characteristic spectral parameters at consistent and significant absorption wave number at 1118 cm^{-1}, specific for healthy, prediabetic and diabetic subjects, characterized by spectral bounded bands of glucose in the mid-IR spectra

corresponding to identity and secondary structures to glucose molecules in correlation with characteristic measurements of the peak position and/or its shift, the peak levels and its dynamic changes, the peak LT calculation on HATR-FTIR spectrometer in the interstitial fluid of the epidermal skin tissue in comparison with the LT in CBG for calculation of the peak LT's difference on a healthy, prediabetic or diabetic subject under a continuous 120-minute monitoring at pre-determined time-intervals from the starting till the ending time-points of post-prandial glucose test and/or OGTT at the different doses of 5 g, 20 g and/or 75 g, for diagnosis of disorders of glucose metabolism such as prediabetes and diabetes type 2 in a subject, or for screening and follow-up disorders of glucose metabolism such as prediabetes and diabetes type 2 in a subject, or for predicting the risk of hyperglycemia in a subject, or for staging diabetes type 2 in a subject, or for managing hyperglycemia in a subject, or for monitoring diabetes control in a subject, or for assessing the quality of metabolic control in a subject, comprising its spectral characteristics according to Claim 11.

17. Use of a glucose molecule with characteristic spectral parameters at consistent and significant absorption wave number at 1118 cm^{-1}, specific for healthy, prediabetic and diabetic subjects, characterized by spectral bounded bands of glucose in the mid-IR spectra corresponding to identity and secondary structures to glucose molecules in correlation with characteristic measurements of the peak position and/or its shift, the peak levels and its dynamic changes, the peak LT calculation on HATR-FTIR spectrometer in the interstitial fluid of the epidermal skin tissue in comparison with the LT in CBG for calculation of the peak LT's difference on a healthy, prediabetic or diabetic subject under a continuous 120-minute monitoring at pre-determined time-intervals from the starting till the ending time-points of post-prandial glucose test and/or OGTT at the different doses of 5 g, 20 g and/or 75 g, for diagnosis of disorders of glucose metabolism such as prediabetes and diabetes type 2 in a subject, or for screening and follow-up disorders of glucose metabolism such as prediabetes and diabetes type 2 in a subject, or for predicting the risk of hyperglycemia in a subject, or for staging diabetes type 2 in a subject, or for managing hyperglycemia in a subject, or for monitoring diabetes control in a subject, or for assessing the quality of metabolic control in a subject, comprising its spectral characteristics according to Claim 12.

18. Use of a combination group of glucose molecules with characteristic spectral parameters at consistent and significant absorption wave numbers at 1030-1041 cm^{-1}, 1080 cm^{-}

^{1}, 1118 cm^{-1}, 1153 cm^{-1} specific for healthy, prediabetic and diabetic subjects, characterized by spectral bounded bands of glucose in the mid-IR spectra corresponding to identity and secondary structures to glucose molecules in correlation with characteristic measurements of the peak position and/or its shift, the peak levels and its dynamic changes, the peak LT calculation on HATR-FTIR spectrometer in the interstitial fluid of the epidermal skin tissue in comparison with the LT in CBG for calculation of the peak LT's difference on a healthy, prediabetic or diabetic subject under a continuous 120-minute monitoring at pre-determined time-intervals from the starting till the ending time-points of post-prandial glucose test and/or OGTT at the different doses of 5 g, 20 g and/or 75 g, for diagnosis of disorders of glucose metabolism such as prediabetes and diabetes type 2 in a subject, or for screening and follow-up disorders of glucose metabolism such as prediabetes and diabetes type 2 in a subject, or for predicting the risk of hyperglycemia in a subject, or for staging diabetes type 2 in a subject, or for managing hyperglycemia in a subject, or for monitoring diabetes control in a subject, or for assessing the quality of metabolic control in a subject, comprising its spectral characteristics according to Claim 13.

METHOD FOR MONITORING INDIVIDUAL METABOLIC RESPONSE AND FOR GENERATING PREDICTIVE CLINICAL METRICS

ABSTRACT

Provided is a formula and method for monitoring individual metabolic response that involve calculation of the lag/latency time (LT) for the peak levels of measured a variety of glucose values by HATR-FTIR (horizontally attenuated total reflection Fourier transform infrared) spectroscopy and the LT for the peak level of capillary blood glucose (CBG), with subsequent calculation of the LT changes between them. Obtained meaningful time-dependent and dose-dependent glucose values and their LT changes characterize glycemic variability (GV) in a qualified subject, that can be used to predict the patient's risk of hyperglycemia, to stage Type II diabetes and, in general, to be considered as a new metrics of assessing the quality of metabolic control.