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 qualified subject, that comprises the step of consecutive performance of a plurality of measurements and further calculations of glucose molecule levels, obtained by horizontally attenuated total reflection Fourier transform infrared (HATR-FTIR) spectroscopy. More particularly, the invention further relates to calculating the lag/latency times (LT) differences between measured in capillary blood the peak glucose level and measured in the skin surface the peak levels of glucose molecule values by HATR-FTIR spectroscopy 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 glycemic variability (GV) based on a method of simultaneous assessment of 5 glucose-specific peak 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 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 about 1030, 1041, 1080, 1118 and 1153 cm^{-1} in the skin of healthy, prediabetic and diabetic subjects during Oral Glucose Tolerance Test (OGTT) 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 for qualitative and quantitative characterization of GV, in order to further recognize patterns from the patients data for establishing predictive clinical metrics.

Specifically, the invented method is based on calculating the LT differences between the LT measured for the peak of capillary blood glucose **(**CBG**)** and the LT's for the peaks of epidermally measured in the interstitial fluid glucose molecule 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 changes between the LT for the peak of CBG and for the peak of each epidermally measured interstitial glucose molecule level at about 1030 cm^{-1}, 1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1} by HATR-FTIR spectroscopy in a qualified subject.

Figure 2 A-D presents differences between GV obtained between CBG values (shown by dashed lines) and each glucose molecule value (shown by solid lines) at about 1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1} by HATR-FTIR spectroscopy during a 120-minute post-prandial

monitoring of individual metabolic response in a diabetic subject with Type 2 diabetes **(**Subject 1**)**. The time of increment for each glucose molecule 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 molecule value (shown by solid lines) at about 1030 cm^{-1}, 1080 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1} by HATR-FTIR spectroscopy during a 120-minute post-prandial monitoring of individual metabolic response in a diabetic subject with Type 2 diabetes **(**Subject 2**)**. The time of increment for each glucose molecule 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 molecule value (shown by solid lines) at about 1030 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1} by HATR-FTIR spectroscopy during a 120-minute post-prandial monitoring of individual metabolic response in a diabetic subject with Type 2 diabetes (Subject 3). The time of increment for each glucose molecule 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 about 1030-1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1} during OGTT at different glucose doses with 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 about 1030-1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1} during OGTT at different glucose doses with 5 g (low), 20 g (medium) and 75 g (high) in a diabetic subject with Type 2 diabetes (Subject 3).

Figure 7 A-C illustrates examples of characteristic differences in the levels of glucose molecule values and wavenumber shifts at about 1080 cm^{-1} and 1118 cm^{-1} between a healthy subject (Subject 4) and a diabetic subject with Type 2 diabetes (Subject 3) under OGTT with different glucose doses at 5 g (low), 20 g (medium) and 75 g (high).

Figure 8 A-F illustrates a variety of examples of GV simultaneously shown at about 1030-1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1} by HATR-FTIR spectroscopy in a diabetic subject with 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 in 3 healthy subjects (Subject 1, Subject 3, Subject 4) under OGTT with 75 g.

Figure 9 A-D presents GV simultaneously shown at about 1030-1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1} by HATR-FTIR spectroscopy during a 120-minute post-prandial monitoring of individual metabolic response in 3 diabetic 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 a diabetic subject with Type 2 diabetes (Subject 3) on 2 consecutive days, comparatively shown at about 1030-1041 cm^{-1}, 1080 cm^{-1} and 1118 cm^{-1} by HATR-FTIR spectroscopy.

Figure 11 A-D comparatively presents GV during monitoring of individual metabolic response at 1030-1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1} in 3 healthy subjects (Subjects 1, Subject 2, Subject 4), in 1 subject as a suspect of having impaired glucose tolerance, i.e. prediabetes (Subject 3), and in a diabetic subject with Type 2 diabetes (Subject 3) 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 diabetic subjects with Type 2 diabetes (Subject 1, Subject 2 and Subject 3) by HATR-FTIR spectroscopy.

Table 2. LT differences between the LT for the peak of CBG and the LT peak for each measured glucose molecule level at about 1030-1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1}, obtained in a healthy subject during OGTT with different glucose 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 molecule level at about 1030-1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1}, obtained in a diabetic subject during OGTT with different doses (5 g, 20 g, 75 g).

Table 4. LT differences between the LT for the peak of CBG and the LT peak for each measured glucose molecule level at about 1030-1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1}, obtained under OGTT with 75 g., i.e. clinically tested dose, in a healthy subject and in a diabetic subject with Type 2 diabetes.

Table 5. LT differences between the LT for the peak of CBG and the LT peak for each measured glucose molecule level at about 1030-1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1}, obtained under OGTT with 20 g., i.e. clinically tested dose, in a healthy subject and in a diabetic subject with Type 2 diabetes.

Table 6. LT differences between the LT for the peak of CBG and the LT peak for each measured glucose molecule level at about 1030-1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1}, obtained estimated for the same subject with Type 2 diabetes on 2 consecutive days.

Table 7. LT differences between the LT for the peak of CBG and the LT peak for each measured glucose molecule level at about 1030-1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1}, obtained under OGTT (75 g)., i.e. clinical OGTT, demonstrate estimated LT changes 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 FTIR 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 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 monitoring 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 carbohydrate, i.e. 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 molecule profiles of Figures 1-4 are reproduced by the subject's own glucose molecule profiles. Thus, since the subject's CBG is under active control, the influence of other sampling factors are eliminated.

Steps of the invented 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 about 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 with characteristic absorption wavenumbers at about 1030 cm^{-1}, 1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1}, where the peaks at about 1030 cm^{-1} and 1041 cm^{-1} are always mentioned together because of bounded appearance with predominance of one of them in the mid-IR spectra
* 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 about 1030-1041, 1080 cm^{-1}, 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 changes between the estimated LT for the peak of CBG and the estimated LT for the peaks of each glucose value at about 1030-1041, 1080 cm^{-1}, 1118 and 1153 cm^{-1} measured by HATR-FTIR spectroscopy
* determining the characteristics of the LT changes for each assigned glucose-specific peak under the test
* determining the pattern on the dynamics of glycemic variability at each assigned glucose-specific peak at 1030 cm^{-1} or 1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1}, and/or 1153 cm^{-1} by HATR-FTIR spectroscopy to be specific for healthy, prediabetic or diabetic subjects
* determining the pattern on the LT changes to be specific for healthy, prediabetic or diabetic subjects

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 differences 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*differences=*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 differences 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 provides monitoring and evaluation:

(i) individually at each glucose molecule value

(ii) simultaneously at all glucose molecules values

2. METHOD FOR MONITORING INDIVIDUAL METABOLIC RESPONSE IN A QUALIFIED SUBJECT provides monitoring and evaluation:

(i) in one subject

(ii) between the subjects

3. METHOD FOR MONITORING INDIVIDUAL METABOLIC RESPONSE IN A QUALIFIED SUBJECT provides monitoring and evaluation:

(i) within one group of disease/condition
(ii) between different groups of diseases/conditions

4. METHOD FOR MONITORING INDIVIDUAL METABOLIC RESPONSE IN A QUALIFIED SUBJECT provides monitoring and evaluation:
(i) under one screening test
(ii) comparatively under different screening tests

5. METHOD FOR MONITORING INDIVIDUAL METABOLIC RESPONSE IN A QUALIFIED SUBJECT provides monitoring and evaluation:
(i) for qualitative interpretation of GV
(ii) for quantitative interpretation of GV

6. METHOD FOR MONITORING INDIVIDUAL METABOLIC RESPONSE IN A QUALIFIED SUBJECT provides monitoring and evaluation:
(i) for generating specific pattern and parameters characterizing GV in the patients with Type 2 diabetes
(ii) for generating specific pattern and parameters characterizing GV in the patients with impaired glucose tolerance, i.e. the patients with prediabetes
(iii) for generating specific 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 taken 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 diabetic 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, accordingly;

- 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 peak value, having common and specific features for healthy, prediabetic and diabetic subjects.

EXAMPLES

EXAMPLE 1

PATTERN for DIABETIC SUBJECTS

(post-prandial monitoring at individual glucose molecules)

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 about 1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1} by HATR-FTIR spectroscopy during a 120-minute post-prandial monitoring of individual metabolic response in a diabetic subject with Type 2 diabetes (Subject 1). The time of increment for each glucose molecule 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 about 1030 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1} by HATR-FTIR spectroscopy during a 120-minute post-prandial monitoring of individual metabolic response in a diabetic subject with Type 2 diabetes (Subject 2). The time of increment for each glucose molecule 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 about 1030 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1} by HATR-FTIR spectroscopy during a 120-minute post-prandial monitoring of individual metabolic response in a diabetic subject with Type 2 diabetes (Subject 3). 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 differences estimated within a 120-minute post-prandial monitoring of metabolic response in 3 diabetic subjects with Type 2 diabetes (Subjects 1-3) by HATR-FTIR spectroscopy.

Subjects	1030-1041 cm^{-1}	1080 cm^{-1}	1118 cm^{-1}	1153 cm^{-1}
Subject 1	0'	0'	0'	30'
Subject 2	0'	0' & 60'	0' & 60'	30'
Subject 3	0'	60'	0'	60'

EXAMPLE 2

PATTERNS for HEALTHY SUBJECTS and DIABETIC SUBJECTS

(monitoring under OGTT with different doses at individual glucose molecules)

HEALTHY SUBJECT

Figure 5 A-C presents a comparative dose-dependent GV during monitoring of metabolic response by HATR-FTIR spectroscopy at about 1030-1041 cm^{-1}, 1080 cm^{-1} and 1118 cm^{-1} during OGTT with different glucose doses at 5 g (low), 20 g (medium) and 75 g (high) in a healthy subject (Subject 4).

Table 2 dislays LT differences between the LT for the peak of CBG and the LT peak for each measured glucose level at about 1030-1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1}, obtained in a healthy subject during OGTT at different glucose doses (5 g, 20 g, 75 g).

Healthy	LT	OGTT (5 g)	OGTT (20 g)	OGTT (75 g)
1030-1041 cm^{-1}	$LT_{diffferences}$	15' & 30'	10'	5' & 30'
1080 cm^{-1}	$LT_{diffferences}$	15' & 30'	0' & 10' & 20'	5'
1118 cm^{-1}	$LT_{diffferences}$	10' & 25'	10'	5 '& 25'
1153 cm^{-1}	$LT_{diffferences}$	35' & 50'	10' & 15'	10'

DIABETIC SUBJECT

Figure 6 A-C presents a comparative dose-dependent GV during monitoring of metabolic response by HATR-FTIR spectroscopy simultaneously shown at about 1030-1041 cm^{-1}, 1080 cm^{-1} and 1118 cm^{-1} during OGTT with different glucose doses at 5 g (low), 20 g (medium) and 75 g (high) in a diabetic subject with Type 2 diabetes (Subject 3).

Table 3 displays LT differences between the LT for the peak of CBG and the LT peak for each measured glucose level at about 1030-1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1}, obtained in a diabetic subject during OGTT at different glucose 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

PATTERN for HEALTHY SUBJECTS vs. DIABETIC SUBJECTS

(monitoring under OGTT with different doses at individual glucose molecules)

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

values and wavenumber shifts at about 1080 cm^{-1} and 1118 cm^{-1} between a healthy subject (Subject 4) and a diabetic subject with Type 2 diabetes (Subject 3) under OGTT with different glucose doses under OGTT with different glucose doses at 5 g (low), 20 g (medium) and 75 g (high).

Table 4 displays LT differences between the LT for the peak of CBG and the LT peak for each measured glucose molecule level at about 1030-1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1}, obtained under OGTT with 75 g., i.e. clinically tested dose, in a healthy subject and in a diabetic 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 between the LT for the peak of CBG and the LT peak for each measured glucose molecule level at about 1030-1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1}, obtained under OGTT with 20 g., a healthy subject vs. a diabetic 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

PATTERNS for HEALHY, PREDIABETIC and DIABETIC SUBJECTS

(monitoring under OGTT with different doses simultaneously at all glucose molecules)

Figure 8 A-F illustrates a variety of examples of GV simultaneously shown at about 1030-1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1} by HATR-FTIR spectroscopy in a diabetic subject with 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 in 3 healthy subjects (Subject 1, Subject 3, Subject 4) under OGTT with 75 g.

EXAMPLE 5

PATTERN FOR DIABETIC SUBJECTS vs HEALTHY SUBJECTS

(post-prandial monitoring individually at each glucose molecule)

Figure 9 A-D presents GV simultaneously shown at about 1030-1041 cm^{-1} , 1080 cm^{-1}, 1118 and 1153 cm^{-1} by HATR-FTIR spectroscopy during a 120-minute post-prandial monitoring of individual metabolic response in 3 diabetic 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 diabetic subjects (Subjects 1-3) with Type 2 diabetes 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

PATTERN FOR DIABETIC SUBJECTS

(day-to-day post-prandial monitoring simultaneously at all glucose molecules)

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

Table 6 displays LT differences between the LT for the peak of CBG and the LT peak for each measured glucose molecule level at about 1030-1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1}, 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}
Day 1	0'	60'	0'	60'
Day 2	0'	0'	60'	-

EXAMPLE 7

PATTERNS for HEALTHY, PREDIABETIC and DIABETIC SUBJECTS

(monitoring under OGTT (75 g) simultaneously at all glucose molecules)

Figure 11 A-D comparatively presents GV during monitoring of individual metabolic response at 1030-1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1} 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 a diabetic subject (Subject 3) with Type 2 diabetes by HATR-FTIR spectroscopy.

Table 7 displays LT differences between the LT for the peak of CBG and the LT peak for each measured glucose molecule level at about 1030-1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1}, obtained under OGTT (75 g)., i.e. clinical OGTT, demonstrate estimated 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:

induction of glucose excursions in the blood glucose, influenced by consumption of meal, or pure glucose *per os* at the different doses of 5 g, 20 g and/or 75 g in the subject;

gathering non-invasive skin subsurface spectral glucose measurements at assigned glucose-specific peaks with characteristic absorption wave numbers at 1030 cm^{-1},1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and/or 1153 cm^{-1} by HATR-FTIR spectroscopy at pre-determined regular time intervals in the subject's forearm under the test, wherein glucose-specific peaks at 1030 cm^{-1} and 1041 cm^{-1} are always bounded with predominant detection of one of these in the mid-IR spectra;

determining the characteristics of each assigned glucose peak value dynamical changes at pre-determined regular time intervals in the subject from the starting till the ending point of the test;

determining the characteristics of each assigned glucose peak position dynamical changes at pre-determined regular time intervals in the subject from the starting till the ending point of the test;

simultaneous performance of reference CBG measurements at pre-determined regular time intervals in the subject from the starting till the ending point of the test;

calculation of the LT for CBG measurements, wherein said latency time is the time interval from the time-point of induction of glucose excursions in the blood glucose till the time-point of maximum detected levels of said CBG measurements;

calculation of the LT for each assigned glucose-specific peak at 1030-1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1} by HATR-FTIR spectroscopy, wherein said latency time is the time interval from the time-point of induction of glucose excursions in the interstitial fluid of skin tissue till the time-point of maximum detected levels of said glucose-specific peaks by HATR-FTIR spectroscopy at 1030-1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1};

calculation of the LT differences between the estimated LT for each glucose-specific peak measurement by HATR-FTIR spectroscopy at 1030-1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1} and the estimated LT for CBG;

determining the characteristics of the LT differences for each assigned glucose peak under the test;

determining the pattern for qualitative and quantitative parametric evaluation of GV dynamics at each assigned glucose-specific peak at 1030-1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1} by HATR-FTIR spectroscopy to be specific for healthy, prediabetic or diabetic subjects; and

determining the pattern on the LT differences to be specific for healthy, prediabetic or diabetic subjects.

2. The method of Claim 1, wherein the pattern of individual metabolic response for healthy subject is further comprising:

detecting 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 5 a-c during OGTT with different doses of glucose, wherein said glucose peaks levels are dose-independent and indifferentiated between intaken doses of glucose from starting to the ending point of the test;

detecting characteristic predominant high glucose peak levels within 1030-1041 cm^{-1} over the other glucose peaks levels under OGTT with different doses of glucose according to Figure 8 c-e;

detecting predominant glucose peak position at 1030 cm^{-1} within 1030-1041 cm^{-1} according to Figure 8 c-e and/or Figure 11 a;

detecting predominant left-shifted peak positions of the peak at 1118 cm^{-1} under OGTT with different doses of glucose according to Figure 5 c and/or Figure 7 a;

detecting predominant left-shifted mean positions of the peak at 1153 cm^{-1} under OGTT according to Figure 11 d;

detecting characteristic differences in the levels of glucose values and 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 prediabetes and diabetes as shown in Figure 7 a-c, Figure 9 a-d and/or Figure 11 a-d;

detecting characteristic bi-phase LT's differencs 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) in Example 2;

detecting characteristic mono-, 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, and for 1153 cm^{-1} at 10 and 15 minutes under OGTT (20 g) with reference to Table 2 (column 4) in Example 2; and/or

detecting characteristic mono- 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) in Example 2.

3. The method of Claim 1, wherein the pattern of individual metabolic response for prediabetic subject is further comprising:

detecting characteristic GV dynamics of glucose peak levels at 1030 - 1041 cm^{-1} similar to those at 1118 cm^{-1} according to Figure 8 f;

detecting predominant glucose peak position at 1037-1041 cm^{-1} within 1030 - 1041 cm^{-1} according to Figure 8 f and/or Figure 11 a;

detecting predominant right-shifted mean positions of the peak at 1118 cm^{-1} within 1120-1022 cm^{-1} according to Figure 11 c;

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

detecting 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) in Example 7.

4. The method of Claim 1, wherein the pattern of individual metabolic response for diabetic subject is further comprising:

detecting 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 dose-dependent and well-differentiated between intaken doses of glucose from starting to the ending point of the test;

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

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

detecting 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/or Figure 11 c;

detecting 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 prediabetic subjects as shown in Figure 7 a-c, Figure 9 a-d and/or Figure 11 a-d;

detecting characteristic monophasic, bi-phasic and three-phasic 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, and for 1153 cm^{-1} at 15 and 25 minutes under OGTT (5 g) with reference to Table 3 (column 3) in Example 2;

detecting characteristic monophasic and bi-phasic LT's changes 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) in Example 3; and/or

detecting characteristic monophasic LT's changes for 1030-1041 cm^{-1} at 0 minutes, for 1080 cm^{-1} at 0 minutes, for 1118 cm^{-1} at 0 minutes, and for 1153 cm^{-1} at 30 minutes under OGTT (75 g) with reference to Table 7 (column 4) in Example 7.

5. A HATR-FTIR spectrometer for use in a method of diagnosing disorders of glucose metabolism, such as impaired glucose tolerance and diabetes mellitus, by recognizing the pattern on the latency time (LT), its characteristics and its calculated differences with CBG on a subject under Oral Glucose Tolerance Test (OGTT) with different doses (low, medium, high), wherein the method comprises the steps of:

(i) induction of glucose excursions in the blood glucose, influenced by consumption of pure glucose *per os* at the different doses of 5 g, 20 g and/or 75 g in the subject;

(ii) gathering non-invasive glucose spectral measurements at assigned 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} by HATR-FTIR spectroscopy at pre-determined time intervals in the subject under the test, wherein glucose-specific peaks at 1030 cm^{-1} and 1041 cm^{-1} are always bounded with predominant detection of one of these in the mid-IR spectra;

(iii) calculation of the LT for each assigned glucose-specific peak by HATR-FTIR spectroscopy, wherein said latency time is the time interval from the time-point of induction of glucose excursions in the interstitial fluid of skin tissue till the time-point of maximum detected levels of said glucose-specific peaks by HATR-FTIR spectroscopy at 1030 - 1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1};

(iv) comparing the LT for each assigned glucose-specific peak by HATR-FTIR spectroscopy at the different doses for said subject with the LT obtained in capillary blood glucose (CBG) at the different doses in the same subject under the test, wherein said LT in CBG is the time interval from the time-point of induction of glucose excursions in the blood glucose till the time-point of maximum detected levels of said reference CBG measurements;

(v) pattern data recognition on the LT differences and its characteristics between the estimated LT for each glucose-specific peak measurement at 1030-1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1} by HATR-FTIR spectroscopy in comparison with the estimated LT for CBG to be specific for healthy, prediabetic or diabetic subjects.

6. The HATR-FTIR spectrometer of Claim 5, when the LT's differences for said subject obtained under OGTT with 75 g have the pattern of the time duration within 5-50 minutes with characteristic single- and/or two-phase detection at 1030-1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1} by HATR-FTIR spectroscopy as shown in Table 2 (column 5), Table 4 (column 2) and/or Table 7 (column 2), as compared with the LT's differences under OGTT with 75 g for diabetic subject with characteristic LT's differences of the shortest time duration within 0-30 minutes with characteristic mono-phase detection at 1030-1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1} by HATR-FTIR spectroscopy as shown in Table 3 (column 5), Table 4 (column 3) and/or Table 7 (column 4), determines the subject as a healthy subject.

7. The HATR-FTIR spectrometer of Claim 5, when the LT's differences for said subject obtained under OGTT with 75 g have the pattern of the time duration 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} by HATR-FTIR spectroscopy as shown in Table 7 (column 3), as compared with the LT's differences under OGTT with 75 g for diabetic subject with characteristic LT's differences of the time duration within 0-30 minutes with characteristic mono-phase detection at 1030-1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1} by HATR-FTIR spectroscopy as shown in Table 7 (column 4), determines the subject as a prediabetic subject.

8. The HATR-FTIR spectrometer of Claim 5, when the LT's differences for said subject obtained under OGTT with 75 g have the pattern of the time duration within 0-30 minutes with characteristic predominant mono-phase detection at 1030-1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1} by HATR-FTIR spectroscopy as shown in Table 7 (column 4), as compared with the LT's differences under OGTT with 75 g for prediabetic subject with 0-55 minutes with characteristic multi-phase cascade detection at 1030-1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1} by HATR-FTIR spectroscopy as shown in Table 7 (column 3) or as compared with the LT differences of the time duration within 5-50 minutes with characteristic single- and/or two-phase detection at 1030-1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1} by HATR-FTIR spectroscopy as shown in Table 7 (column 2), determines the subject as a diabetic subject.

9. A HATR-FTIR spectrometer for use in a method of screening disorders of glucose metabolism, such as impaired glucose tolerance and diabetes mellitus, by recognizing the pattern on the latency time (LT), its characteristics and its calculated

differences with CBG on a subject under Oral Glucose Tolerance Test (OGTT) with different doses (low, medium, high), wherein the method comprises the steps of:

(i) induction of glucose excursions in the blood glucose, influenced by consumption of pure glucose *per os* at the different doses of 5 g, 20 g and/or 75 g in the subject;

(ii) gathering non-invasive glucose spectral measurements at assigned 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} by HATR-FTIR spectroscopy at pre-determined time intervals in the subject under the test, wherein glucose-specific peaks at 1030 cm^{-1} and 1041 cm^{-1} are always bounded with predominant detection of one of these in the mid-IR spectra;

(iii) calculation of the LT for each assigned glucose-specific peak by HATR-FTIR spectroscopy, wherein said latency time is the time interval from the time-point of induction of glucose excursions in the interstitial fluid of skin tissue till the time-point of maximum detected levels of said glucose-specific peaks by HATR-FTIR spectroscopy at 1030 - 1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1};

(iv) comparing the LT for each assigned glucose-specific peak by HATR-FTIR spectroscopy at the different doses for said subject with the LT obtained in capillary blood glucose (CBG) at the different doses in the same subject under the test, wherein said LT in CBG is the time interval from the time-point of induction of glucose excursions in the blood glucose till the time-point of maximum detected levels of said reference CBG measurements;

(v) pattern data recognition on the LT differences and its characteristics between the estimated LT for each glucose-specific peak measurement at 1030-1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1} by HATR-FTIR spectroscopy in comparison with the estimated LT for CBG to be specific for healthy, prediabetic or diabetic subjects.

10. The HATR-FTIR spectrometer of Claim 9, when the LT differences obtained at the different glucose doses of 5 g, 20 g and 75 g for said subject have the pattern as shown in Table 2 as compared with the LT differences obtained at the different glucose doses of 5 g, 20 g and 75 g for the diabetic subject as shown in Table 3, determine said subject as a healthy subject.

11. The HATR-FTIR spectrometer of Claim 9, when the LT differences obtained at the different glucose doses of 5 g, 20 g and 75 g for said subject have the pattern as shown in Table 7 (column 3) as compared with the LT differences obtained at the different glucose doses of 5 g, 20 g and 75 g for the healthy subject as shown in Table 2 or for the diabetic subject as shown in Table 3, determine said subject as a subject having prediabetes.

12. The HATR-FTIR spectrometer of Claim 9, when the LT differences obtained at the different glucose doses of 5 g, 20 g and 75 g for said subject have the pattern as shown in Table 3 as compared with the LT differences obtained at the different glucose doses of 5 g, 20 g and 75 g for the healthy subject as shown in Table 2, determine said subject as a subject having diabetes mellitus.

13. A HATR-FTIR spectrometer for use in a method of diagnosing disorders of glucose metabolism, such as impaired glucose tolerance and diabetes mellitus, by recognizing the pattern of GV (glycemic variability) dynamics and its characteristics at absorption wave numbers of 1030 cm^{-1}, 1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1} by HATR-FTIR spectroscopy on a subject under Oral Glucose Tolerance Test (OGTT) with different doses (low, medium, high) and/or post-prandially, wherein the method comprises the steps of:

(i) induction of glucose excursions in the blood glucose, influenced by consumption of pure glucose per os at the different doses or influenced by consumption of food in the subject;

(ii) gathering non-invasive glucose spectral measurements at assigned 5 glucose-specific peaks at 1030 cm^{-1}, 1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1} by HATR-FTIR spectroscopy at pre-determined time intervals in the subject under the test, wherein glucose-specific peaks at 1030 cm^{-1} and 1041 cm^{-1} are always bounded with predominant detection of one of these in the mid-IR spectra;

(iii) determination of each glucose value at 1030 - 1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1} by HATR-FTIR spectroscopy in dynamics at pre-determined time intervals in the subject from the starting time-point of induction of glucose excursions in the interstitial fluid of skin tissue under the test till the ending time-point of the performed test;

(iv) comparing the changes of each glucose value obtained in (iii) for said subject during and at the end of the performed test;

(v) determining the pattern on the dynamics of glycemic variability at each assigned glucose-specific peak at 1030-1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1} by HATR-FTIR spectroscopy to be specific for healthy, prediabetic or diabetic subjects.

14. The HATR-FTIR spectrometer of Claim 13, wherein the detected changes of each glucose value and the pattern recognition of GV dynamics at 1030 - 1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1} obtained at the different glucose doses *per os* and/or post-prandially for said subject as shown in Figure 5 a-c, Figure 8 c-d and Figure 11 a-d have the pattern of

comparative dose-independent and indifferentiated between intaken doses of glucose GV dynamics of glucose peak levels at 1030 - 1041 cm^{-1}, 1080 cm^{-1} and 1118 cm^{-1} according to Figure 5 a-c, and/or

predominant high glucose peak levels within 1030-1041 cm^{-1} over the other glucose peaks levels to Figure 8 c-e, and/or

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

predominant left-shifted mean positions of the peak at 1118 cm^{-1} according to Figure 5 c and/or Figure 7 a, and/or

predominant left-shifted mean peak position at 1153 cm^{-1} according to Figure 11 d; and/or

as compared with differences in the levels of glucose values and wavenumber shifts at 1030 - 1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and/or 1153 cm^{-1} for prediabetes and diabetes as shown in Figure 7 a-c, Figure 9 a-d and/or Figure 11 a-d, determine said subject as a healthy subject.

15. The HATR-FTIR spectrometer of Claim 13, wherein the changes of each glucose value and the pattern recognition of GV dynamics at 1030 - 1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1} obtained at the different glucose doses *per os* and/or post-prandially for said subject have the pattern of

characteristic GV dynamics of glucose peak levels at 1030 - 1041 cm^{-1} similar to those at 1118 cm^{-1} according to Figure 8 f, and/or

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

predominant right-shifted mean positions of the peak at 1118 cm^{-1} within 1120-1022 cm^{-1} according to Figure 11 c, and/or

detected characteristic differences in the levels of glucose values and wavenumber shifts at 1030 - 1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1}, and/or 1153 cm^{-1}

as compared with characteristic differences for healthy and diabetic subjects as shown in Figure 11 a-d, determine said subject as a subject having prediabetes.

16. The HATR-FTIR spectrometer of Claim 13, wherein the changes of each glucose value and the pattern recognition of GV dynamics at 1030 - 1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1} obtained at the different glucose doses *per os* and/or post-prandially for said subject as shown in Figure 6 a-c, Figure 7 a-c, Figure 8 a-b and/or Figure 11 a-d, have the pattern of

characteristic comparative dose-dependent and well-differentiated between intaken doses of glucose GV dynamics of glucose peak levels at 1030 - 1041 cm^{-1}, 1080 cm^{-1} and 1118 cm^{-1} according to Figure 6 a-c, and/or

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

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

detected 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/or Figure 11 a-d,

as compared with the changes of each glucose value and the pattern recognition of GV dynamics at 1030 cm^{-1}, 1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1} for the healthy subject as shown in Figure 5 a-c and 8 c-d, determine said subject as a subject having diabetes mellitus.

17. A HATR-FTIR spectrometer for use in a method of screening of disorders of glucose metabolism, such as prediabetes and diabetes, by continuous glucose monitoring of individual metabolic response on a subject under Oral Glucose Tolerance Test (OGTT) with different doses (low, medium, high) and/or post-prandially, wherein the method comprises the steps of:

(i) induction of glucose excursions in the blood glucose, influenced by consumption of pure glucose per os at the different doses or influenced by consumption of food in the subject;

(ii) gathering non-invasive glucose spectral measurements at assigned 5 glucose-specific peaks at 1030 cm^{-1}, 1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1} by HATR-FTIR spectroscopy at pre-determined time intervals in the subject to be further used for qualitative and quantitative parametric evaluation of GV dynamics at 1030 cm^{-1}, 1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1} by HATR-FTIR spectroscopy during and at the end of the test in said subject to be specific for healthy, prediabetes or diabetes;

(iii) calculation of the LT for each glucose measurements at 1030 cm^{-1}, 1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1} by HATR-FTIR spectroscopy, wherein said latency time is the time interval from the time-point of induction of glucose excursions in the interstitial fluid of skin tissue till the time-point of maximum detected levels of said HATR-FTIR measurements at 1030 cm^{-1}, 1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1};

(iv) comparison of the LT for each assigned glucose-specific peak by HATR-FTIR spectroscopy at the different doses for said subject with the LT obtained in capillary blood glucose (CBG) at the different doses in the same subject under the same test to be further used for qualitative and quantitative parametric evaluation of the pattern of the LT differences to be specific for healthy, prediabetes or diabetes.

18. The HATR-FTIR spectrometer of Claim 17, wherein the pattern for qualitative and quantitative parametric evaluation of GV dynamics at 1030 cm^{-1}, 1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1} by HATR-FTIR spectroscopy of

comparative dose-independent and indifferentiated between intaken doses of glucose GV dynamics of glucose peak levels at 1030 - 1041 cm^{-1}, 1080 cm^{-1} and 1118 cm^{-1} according to Figure 5 a-c, and/or

predominant high glucose peak levels within 1030-1041 cm^{-1} over the other glucose peaks levels to Figure 8 c-e, and/or

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

predominant left-shifted mean positions of the peak at 1118 cm^{-1} according to Figure 5 c and/or Figure 7 a, and/or

predominant left-shifted mean peak position at 1153 cm^{-1} according to Figure 11 d; and/or

as compared with differences in the levels of glucose values and wavenumber shifts at 1030 - 1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and/or 1153 cm^{-1} for prediabetes and diabetes as shown in Figure 7 a-c, Figure 9 a-d and/or Figure 11 a-d, determine said subject as a healthy subject.

19. The HATR-FTIR spectrometer of Claim 17, wherein the pattern for qualitative and quantitative parametric evaluation of the LT differences of

detected characteristic bi-phase LT's differencs 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) in Example 2, and/or

detecting characteristic mono-, 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, and for 1153 cm^{-1} at 10 and 15 minutes under OGTT (20 g) with reference to Table 2 (column 4) in Example 2, and/or

detecting characteristic mono- 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) in Example 2,

determine said subject as a healthy subject.

20. The HATR-FTIR spectrometer of Claim 17, wherein the pattern for qualitative and quantitative parametric evaluation of GV dynamics at 1030 cm^{-1}, 1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1} by HATR-FTIR spectroscopy of

characteristic GV dynamics of glucose peak levels at 1030 - 1041 cm^{-1} similar to those at 1118 cm^{-1} according to Figure 8 f; and/or

detecting predominant glucose peak position at 1037-1041 cm^{-1} within 1030 - 1041 cm^{-1} according to Figure 8 f and/or Figure 11 a; and/or

detecting predominant right-shifted mean positions of the peak at 1118 cm^{-1} within 1120-1022 cm^{-1} according to Figure 11 c; and/or

detecting characteristic differences in the levels of glucose values and wavenumber shifts at 1030 - 1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and/or 1153 cm^{-1},

as compared with characteristic differences for healthy and diabetic subjects as shown in Figure 11 a-d, determine said subject as a subject with prediabetes.

21. The HATR-FTIR spectrometer of Claim 17, wherein the pattern for qualitative and quantitative parametric evaluation of the LT differences of

detecting 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) in Example 7,

determine said subject as a subject with prediabetes.

22. The HATR-FTIR spectrometer of Claim 17, wherein the pattern for qualitative and quantitative parametric evaluation of GV dynamics at 1030 cm^{-1}, 1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1} by HATR-FTIR spectroscopy of

detected 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 dose-dependent and well-differentiated between intaken doses of glucose from starting to the ending point of the test; and/or

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

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

detected 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/or Figure 11 c; and/or

detected 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/or Figure 11 a-d; and/or

determine said subject as a subject with diabetes.

23. The HATR-FTIR spectrometer of Claim 17, wherein the pattern for qualitative and quantitative parametric evaluation of the LT differences of

detected characteristic monophasic, bi-phasic and three-phasic 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, and for 1153 cm^{-1} at 15 and 25 minutes under OGTT (5 g) with reference to Table 3 (column 3) in Example 2; and/or

detected characteristic monophasic and bi-phasic LT's changes 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) in Example 3; and/or

detected characteristic monophasic LT's changes for 1030-1041 cm^{-1} at 0 minutes, for 1080 cm^{-1} at 0 minutes, for 1118 cm^{-1} at 0 minutes, and for 1153 cm^{-1} at 30 minutes under OGTT (75 g) with reference to Table 7 (column 4) in Example 7,

determine said subject as a subject with diabetes.

24. Glucose molecule species with absorption wave numbers at about 1030 cm^{-1}, 1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1} in a subject under Oral Glucose Tolerance Test (OGTT) with different doses (low, medium, high) for use in a method of diagnosing prediabetes and diabetes mellitus in the subject, comprising:

(i) induction of glucose excursions in the blood glucose, influenced by consumption of pure glucose at the different doses in the subject;

(ii) detection of glucose molecule species with absorption wave numbers at about 1030 cm^{-1}, 1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1} at the different glucose doses by HATR-FTIR spectroscopy.

25. The glucose molecule species of claim 25, when the glucose molecule species at about 1030 cm^{-1}, 1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1} having the pattern of LT differences as shown in Table 3 as compared with the healthy subject are detected, determine the subject as a subject having diabetes mellitus.

26. The glucose molecule species of claim 25, when the glucose molecule species at about 1030 cm^{-1}, 1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1} having the pattern of LT differences as shown in Table 7 as compared with the healthy subject are detected, determine the subject as a subject having prediabetes.

27. The glucose molecule species of any of Claims 25-27, wherein the different doses (low, medium, high) are 5g, 20g, 75g.

28. Glucose molecule species with absorption wave numbers at about 1030 cm^{-1}, 1041 cm^{-1}, 1080cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1} for use in a method of screening of disorders of glucose metabolism such as prediabetes and diabetes in a subject, comprising:

(i) induction of glucose excursions in the blood glucose, influenced by consumption of pure glucose in the subject;

(ii) detection of glucose molecule species with absorption wave numbers at about 1030 cm^{-1}, 1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1} by HATR-FTIR spectroscopy.

29. The glucose molecule species of claims 28 or 29, when the glucose molecule species at about 1030 cm^{-1}, 1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1} having the pattern of LT differences as shown in Table 7 column 3 as compared with the healthy subject are detected, determine the subject as a subject having prediabetes.

30. The glucose molecule species of claims 28 or 29, when the glucose molecule species at about 1030 cm^{-1}, 1041 cm^{-1}, 1080 cm^{-1}, 1118 cm^{-1} and 1153 cm^{-1} having the pattern of LT differences as shown in Table 7 column 4 as compared with the healthy subject are detected, determine the subject as a subject having diabetes mellitus.

ABSTRACT

Provided is a method for monitoring individual metabolic response that involve calculation of the lag/latency times (LT) for the peak levels of measured a variety of glucose molecule values by HATR-FTIR (horizontally attenuated total reflection Fourier transform infrared) spectroscopy and the LT for the peak level of CBG (capillary blood glucose), with subsequent calculation of the LT differences between them. Obtained meaningful time-dependent and dose-dependent glucose molecule peak values and their LT's 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.