homeostasis or reflect a metabolic link to diabetes type 1 related comorbidities, i.e. dyslipidemia and oxidative stress.

In Rydosz, Artur: "A Negative Correlation Between Blood Glucose and Acetone Measured in Healthy and Type 1 Diabetes Mellitus Patient Breath", JOURNAL OF DIABETES SCIENCE AND TECHNOLOGY, vol. 9, no. 4, 17 February 2015 (2015-02-17), pages 881-884, XP055856949, US ISSN: 1932-2968, DOl: 10.1177/1932296815572366 a negative correlation between an acetone concentration in exhaled breath and a blood glucose level is reported.

In Van den Velde, S. et al.: "GC-MS analysis of breath odor compounds in liver patients", JOURNAL OF CHROMATOGRAPHY B, ELSEVIER, AMSTERDAM, NL, vol. 875, no. 2, 15 November 2008 (2008-11-15), pages 344-348, XP025879919, ISSN: 1570-0232, DOl: 10. 1016/J .JCHROMB.2008.08.031 a decreased concentration of Indole in a subject's exhaled breath was identified as sign for a liver disease.

An example of a device for non-invasive blood glucose monitoring is a skin surface sampling system as described in U.S. Patent 10,143,447 B2 entitled "Skin surface sampling system". This system utilizes an elongated collection tube with a sampling head positioned on one end in contact with the patient's skin. A liquid supply absorbs volatile organic compounds (VOC) and semi-volatile organic compounds (SVOC) from the surface of the skin and collects the mixed liquid in a sample collection device. The system is operated by positioning the sampling head on the skin surface and then flushing the liquid supply through a set of channel grooves in the sampling head that direct the mixed liquid to the collection tube. Although providing a potentially non-invasive form of blood glucose level monitoring, the system requires a liquid capture system.

Despite of the advantages and the progress achieved by the above-mentioned developments, some significant technical challenges remain regarding responsiveness and reliability. It is therefore an objective of the present invention to provide a fast responding and robust blood glucose monitoring method.

SUMMARY

This problem is solved by a method for non-invasively determining a subject's blood glucose level with the features of claim 1 and a non-invasive blood glucose level monitoring system configured to execute said method. Preferred examples, which might be realized in an isolated fashion or in any arbitrary combination, are listed in the dependent claims.

As used in the following, the terms "have", "comprise" or "include" or any arbitrary grammatical variations thereof are used in a non-exclusive way. Thus, these terms may both refer to a situation in which, besides the feature introduced by these terms, no further features are present in the entity described in this context and to a situation in which one or more further features are present. As an example, the expressions "A has B", "A comprises B" and "A includes B" may both refer to a situation in which, besides B, no other element is present in A (i.e. a situation in which A solely and exclusively consists of B) and to a situation in which, besides B, one or more further elements are present in entity A, such as element C, elements C and D or even further elements.

In the present disclosure, a method to determine a subject's blood glucose level non-invasively by analyzing an exhaled breath or another gaseous emanation from the subject is disclosed. The method comprises non-invasively detecting an amount of at least one volatile organic marker in the subject's exhaled breath or the subject's other gaseous emanation as marker data and determining the subject's blood glucose level based on the marker data. The volatile organic marker is selected from a group of markers for which the amount of the volatile organic marker is negatively correlated to the blood glucose level.

A volatile organic marker, also called volatile organic compound (VOC), is an organic chemical that has a high vapor pressure or rather a low boiling point. Thus, VOCs are volatile at rather low temperatures such as room temperature for example. The human body is a major source of VOCs that originate from different parts and processes within the body. So-called endogenous VOCs originate from metabolic processes within the body. An important organ involved in generating and transforming such endogenous VOCs is the liver. VOCs originating from the environment are called exogenous VOCs, e.g. entering the body via respiratory air, food intake or diffusion through skin or originating from the microbiome, e.g. of the digestive tract.

VOCs generated or absorbed in various parts of the body enter the bloodstream and pass into the exhaled breath by gas exchange in the lungs. VOCs from skin originate from secretion of eccrine, sebaceous or apocrine glands.

It is noted, that a VOC may as well represent a derivative of a compound of interest, i.e. a compound originating from an endogenous process, or a fragment of a compound of interest, said fragment being formed by cleavage of the molecule during the analytical process.

Different methods for detecting an amount of a VOC or of a multitude of VOCs in a sample of exhaled breath or of gaseous emanation are known. According to a first example, the volatile organic marker is detected via mass spectrometry, i.e. measuring the so-called mass-to-charge ratio (m/z) of the ionized compounds. In a further example, the compounds are detected using proton transfer reaction time of flight mass spectrometry (PTR-ToF-MS) which comprises chemical ionization of the sample's compounds based on proton transfer. Typically, $H_3O^+$ ions are used for protonation of VOCs with adequate proton affinity. The PTR-ToF-MS enables a direct analysis without sample preparation and with a high sensitivity as well as a fast response.

Alternative detection methods to detect a volatile organic marker in real-time are Selected Ion Flow Tube Mass Spectrometry (SIFT-MS) or secondary electrospray ionization high-resolution mass spectrometry (SESI-HRMS).

The sample of exhaled breath is captured using a mouthpiece, a nasal cannula, a handheld breath analyzer or any other device suitable to capture at least a fraction of the exhaled breath.

To detect an amount of one or more volatile organic marker from other gaseous emanation a sample of the secretion of one or more parts of the body is captured, e.g. from the head, chest, back, armpit, waist, arm or genital area.

It is understood that the detected amount of each volatile organic marker comprises a single value or a multitude of values over time wherein each value represents a single measurement or an average over two or more measurements. It is also understood that the amount of the volatile organic marker is

either determined in absolute values or in relative values, e.g. determining an amount of change of the marker concentration.

The person's blood glucose level may be determined from the detected amount of one or more volatile organic markers in the exhaled breath or other emanation due to the correlation between said entities. It is understood that the correlation provides for values of blood glucose derived from absolute or relative values of the volatile organic marker concentration in the person's breath.

According to an example, the marker data is normalized based on a reference signal, e.g. derived from ambient air or from another marker in the same sample of exhaled breath or from another sample of the person's breath or other emanation. In a further example the set-up to perform the method is taught and/or trained based on individual metabolic processes, e.g. creating individual profiles for a person/patient. For example, the training involves selecting the volatile organic marker from a group of volatile organic markers also comprising derivatives or fragments of endogenous compounds.

Surprisingly, a negative correlation between the volatile organic marker amount and the blood glucose level has proven to be particularly beneficial for the reliability, responsiveness and sensitivity of the method.

The negative correlation may only be achieved by compounds that do have a functional role in the insulin response. The amount of such compounds, i.e. markers, in breath or other emanation are essentially independent of external influences or individual characteristics of the patient.

According to an example of the disclosure, the volatile organic marker is one of indole ($C_8H_7N$), a partly saturated derivative of indole, a fully saturated derivative of indole and a true fraction of indole.

Thus, in one aspect, the present disclosure provides a method to determine a subject's blood glucose level non-invasively by analyzing an exhaled breath or another gaseous emanation from the subject, comprising:

- non-invasively detecting an amount of at least one volatile organic marker in the subject's exhaled breath or the subject's other gaseous emanation as marker data;
- determining the subject's blood glucose level based on the marker data;
- wherein the volatile organic marker is selected from a group of markers for which the amount of the volatile organic marker is negatively correlated to the blood glucose level;

**characterized in that**

the volatile organic marker is one of indole (C8H7N), a partly saturated derivative of indole, fully saturated derivative of indole and a true fraction of indole.

Indole is an aromatic heterocyclic organic compound with formula $C_8H_7N$. It is widely distributed in the natural environment and can be produced by a variety of bacteria, such as E. coli, which are usually present in the human intestine. Furthermore, indole is the most abundant metabolite produced from

Fragments of indole are for example benzene $C_6H_6$ with a mass-to-charge ration of m/z = 79.055 after protonation with $H^+$ and $C_7H_8$ with a mass-to-charge ration of m/z = 93.069 after protonation.

According to another example, the method further comprises to detect at least one additional volatile organic marker non-invasively in the exhaled breath or the other gaseous emanation from the subject as additional marker data and to determine the subject's blood glucose level based on the marker data and the additional marker data, wherein the amount of the additional volatile organic marker and the blood glucose level are a positively correlated.

Pursuant to alternative examples, the additional volatile organic marker is one or more of carbon dioxide, nitric oxide, formaldehyde, propanol, propanoic acid, acetone, acetic acid, butanol, butyric acid, phenol and caprolactam. Alternatively, the additional volatile organic marker is a fragment or a derivative of one or more of carbon dioxide, nitric oxide, formaldehyde, propanol, propanoic acid, acetone, acetic acid, butanol, butyric acid, phenol and caprolactam. Although the additional marker data may not be as accurate and reliable they do provide additional information. In an example, additional marker data of a specific additional volatile organic marker is used to indicate hypo- or hyperglycemia additionally to the determination of the blood glucose level.

According to a further example the method further comprises to detect non-invasively an amount of at least one volatile organic marker in the subject's exhaled breath as well as in the subject's other gaseous emanation as marker data. Either it is detected the amount of the same volatile organic markers or of different volatile organic markers in the breath and the other gaseous emanation respectively.

According to another example, the method comprises the following steps: continuously monitoring the subject's breathing over a period of time and non-invasively detecting the amount of the at least one volatile organic marker in the continuously monitored subject's breathing over time as the maker data. Furthermore, temporal alterations of an amount of at least one control marker is detected non-invasively in the continuously monitored subject's breathing over time as control marker data. A temporal correlation between the marker data and the control marker data is determined and at least one segment of the marker data over time that corresponds to a temporal period of exhalation

is selected based on the temporal correlation. The subject's blood glucose level is determined based on the selected segment of the marker data. Pursuant to alternative examples the control marker is one of $O_2$, CO, $CO_2$, NO, $N_2$, and $H_2O$.

According to an alternative example, the method further comprises to select at least one additional segment of the marker data over time based on the temporal correlation, wherein the additional segment corresponds to a temporal period of inhalation. A blank value is determined based on the additional segment and subtracted from the marker data before determining the subject's blood glucose level.

As breathing is a cyclic process, the control marker enables to monitor said chronological sequence and to distinguish periods of exhalation and periods of inhalation. The correlation of the control data with the marker data enables to select one or more segments of the marker data corresponding to a desired period of the breathing cycles. While the exhaled breath contains VOCs originating from endogenous processes, the gas sample derived from temporal periods correlated to inhalation provides background information and e.g. is used to derive a blank value.

In an alternative example to derive a blank value the method comprises to detect an amount of at least one volatile organic marker in a gaseous reference sample non-invasively as reference data, to determine a blank value based on the reference data and to subtract the blank value from the marker data before determining the subject's blood glucose level. Pursuant to a further example, the gaseous reference sample contains ambient air.

In another aspect, the present disclosure provides a non-invasive blood glucose level monitoring system for executing the method as described herein comprising:
- a volatile organic marker detecting system configured to detect an amount of the volatile organic marker in a sample as marker data,
- a vapor distribution member configured to bring a sample of exhaled breath or other gaseous emanation from a subject in contact with the volatile organic marker detecting system and
- a processing unit configured to determine the subject's blood glucose level based on the marker data.

These and other advantages, effects, features and objects of the inventive concept will become better understood from the description that follows.

CLAIMS

1. A method to determine a subject's blood glucose level non-invasively by analyzing an exhaled breath or another gaseous emanation from the subject, comprising:
- non-invasively detecting an amount of at least one volatile organic marker in the subject's exhaled breath or the subject's other gaseous emanation as marker data;
- determining the subject's blood glucose level based on the marker data;
- wherein the volatile organic marker is selected from a group of markers for which the amount of the volatile organic marker is negatively correlated to the blood glucose level;
**characterized in that**
the volatile organic marker is one of indole (C8H7N), a partly saturated derivative of indole, fully saturated derivative of indole and a true fraction of indole.

2. The method of claim 1, wherein the amount of the volatile organic marker is detected by mass spectrometry.

3. The method of any of the preceding claims ,wherein the method further comprises:
- non-invasively detecting at least one additional volatile organic marker in the exhaled breath or the other gaseous emanation from the subject as additional marker data,
- determining the subject's blood glucose level based on the marker data and the additional marker data
- wherein the additional volatile organic marker is selected from a group of markers for which the amount of the volatile organic marker is positively correlated to the blood glucose level .

4. The method of claim 3, wherein the additional volatile organic marker is one or more of carbon dioxide, nitric oxide, formaldehyde, propanol, propanoic acid, acetone, acetic acid, butanol, butyric acid, phenol and caprolactam.

5. The method of claim 3 or 4, wherein the additional volatile organic marker is a derivative or a fragment of one or more of carbon dioxide, nitric oxide, formaldehyde, propanol, propanoic acid, acetone, acetic acid, butanol, butyric acid, phenol and caprolactam.

6. The method of any of the preceding claims wherein the method further comprises:
- non-invasively detecting an amount of at least one volatile organic marker in the subject's exhaled breath as well as in the subject's other gaseous emanation as marker data.

7. The method of any of the preceding claims wherein the method comprises:
- continuously monitoring the subject's breathing over a period of time,
- non-invasively detecting the amount of the at least one volatile organic marker in the continuously monitored subject's breathing over time as the maker data,
- non-invasively detecting temporal alterations of an amount of at least one control marker in the continuously monitored subject's breathing over time as control marker data,
- determining a temporal correlation between the marker data and the control marker data,
- selecting at least one segment of the marker data over time corresponding to a temporal period of exhalation based on the temporal correlation and
- determining the subject's blood glucose level based on the selected segment of the marker data.

8. The method of claim 7 wherein the control marker is one of $O_2$, CO, $CO_2$, NO, $N_2$, and $H_2O$.

9. The method of claim 7 or 8 wherein the method comprises:
- selecting at least one additional segment of the marker data over time corresponding to a temporal period of inhalation based on the temporal correlation,
- determining a blank value based on the additional segment and
- subtracting the blank value from the marker data before determining the subject's blood glucose level.

10. The method of any of the preceding claims wherein the method comprises:
- non-invasively detecting an amount of at least one volatile organic marker in a gaseous reference sample as reference data,
- determining a blank value based on the reference data and
- subtracting the blank value from the marker data before determining the subject's blood glucose level.

11. A non-invasive blood glucose level monitoring system for executing the method of any of the preceding claims comprising:
- a volatile organic marker detecting system configured to detect an amount of the volatile organic marker in a sample as marker data,
- a vapor distribution member configured to bring a sample of exhaled breath or other gaseous emanation from a subject in contact with the volatile organic marker detecting system and

- a processing unit configured to determine the subject's blood glucose level based on the marker data.