Clinica Chimica Acta 429 (2014) 106–110

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/clinchim

Metabolomics in diabetes

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ARTICLE INFO

Article history:
Received 25 August 2013
Received in revised form 25 November 2013
Accepted 30 November 2013
Available online 7 December 2013

Keywords:
Metabolomics
Diabetes
Biomarkers
Metabolites
Diagnosis

ABSTRACT

Characterization of metabolic changes is key to early detection, treatment, and understanding molecular mechanisms of diabetes. Diabetes represents one of the most important global health problems. Approximately 90% of diabetics have type 2 diabetes. Identification of effective screening markers is critical for early treatment and intervention that can delay and/or prevent complications associated with this chronic disease. Fortunately, metabolomics has introduced new insights into the pathology of diabetes as well as to predict disease onset and revealed new biomarkers to improve diagnostics in a range of diseases. Small-molecule metabolites have an important role in biological systems and represent attractive candidates to understand T2D phenotypes. Characteristic patterns of metabolites can be revealed that broaden our understanding of T2D disorder. This technique-driven review aims to demystify the mechanisms of T2D, to provide updates on the applications of metabolomics in addressing T2D with a focus on metabolites based biomarker discovery.

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1. Introduction

Typical civilization diseases, particularly type 2 diabetes (T2D), represent one of the most significant global health problems because they are associated with a large economic burden on the health systems of many countries [1]. WHO predicted an estimated future number of 366 million affected individuals in 2030, which would be equivalent to a diabetes prevalence of 5% [2]. Diabetes mellitus is a chronic disease that is characterised by high blood glucose levels, which may be due either to the progressive failure of pancreatic b-cell function and consequently a lack of insulin production or to development of insulin resistance and subsequently the loss of b-cell function [3,4]. Approximately 90% of patients with diabetes have T2D. Improvement of risk prediction for T2D is crucial to the identification of high-risk individuals who could benefit from targeted preventive measures. Also, the burden of T2D is growing worldwide and a more desperate need for better tools to detect, diagnose and monitor the disease.

Gold standard method for identifying patients with T2D is the oral glucose tolerance test [5]. However, this test is not widely used as a risk assessment tool because it is inconvenient, time-consuming, cost and has a poor specificity. Fasting plasma glucose and haemoglobin A1c (HbA1c) are more widely used and less expensive, but they do not predict diabetes onset as accurately as an oral glucose tolerance test [6]. An additional shortcoming is its lack of sensitivity, resulting in late disease discovery and consequently the development of complications at the time of diagnosis. To overcome this problem, researchers are hunting for new biomarkers that could be used to diagnose the earlier condition and single out individuals who are most likely to benefit

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0009-8981/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.cca.2013.11.037

from aggressive treatment [7]. Therefore, more sensitive markers for early detection of T2D disease are urgently needed, particularly, highly sensitive and specific biomarkers as primary indicators are relatively more useful. Biomarkers are conventionally defined as 'biological molecules that represent health and disease states.' [8]. They can be "direct" endpoints of the disease itself, or "indirect" or surrogate endpoints. Metabolomics technologies bring a wealth of opportunity to develop new biomarkers [9]. Metabolomics platform has made it possible to acquire high-throughput profiles of potential biomarkers [10].

Emerging metabolomics technologies have been widely applied, aiming at the discovery of candidate biomarkers for disease staging, prediction of recurrence and prognosis, and treatment selection [11]. The general procedure in which metabolomics was used for diagnosis and biomarker discovery is shown in Fig. 1. Metabolomics offers potential advantages that classic diagnose approaches do not, based on following discovery of a suite clinically relevant biomarker that are simultaneously affected by the T2D [12,13]. It may help in understanding the mechanism of T2D occurrence and progression on the metabolic level and providing information for the identification of early marker metabolites for T2D. Thus, in this mini-paper, particular attention will be paid to the past successes in applications of state-of-the-art technology on metabolomics to contribute to low-molecular-weight metabolites discovery in T2D research.

2. Metabolomics technologies

Metabolomics has been increasingly applied to diagnosing diseases, measuring the response to treatment, discovering biomarkers, identifying perturbed pathways [14–16]. Additionally, metabolomics can be seen as bridging the gap between genotype and phenotype, and identifying novel changes in specific metabolites. Technological developments are the driving force behind advances in scientific knowledge. There are two major high-throughput tools consisting of mass spectrometry (MS) and nuclear magnetic resonance (NMR) spectroscopy used in metabolomics study [17]. Both methods enable the comprehensive investigation of metabolic profiles and can provide complementary snapshots of the metabolome of body fluids [18]. Advantages of NMR spectroscopy include the nondestructive nature of the analysis, the robust and reproducible measurements and the minimal preparation requirements, as no separation or ionisation steps are necessary [19]. NMR analysis usually does not require any pretreatment, and enables the identification of complex unidentified metabolites [20]. MS is the most frequently used technique in metabolic studies with their high level of sensitivity, and often combined with other suitable methods for the analytical separation of compounds [21,22]. Because no single analytical method can accommodate the chemical diversity of the entire metabolome, therefore, a multiplatform approach may provide a more comprehensive understanding of metabolic alterations, and broaden the "window" of important metabolic variations [23,24].

3. Metabolomic features of T2D

T2D is characterized by insulin resistance and impaired beta-cell function but currently it is difficult to determine the precise pathophysiology in T2D patients. Insulin secretion from pancreatic β-cells is controlled by complex metabolic and energetic changes provoked by exposure to metabolic fuels. Perturbations in these processes lead to impaired insulin secretion, the ultimate cause of T2D. To increase our understanding of stimulus-secretion coupling and metabolic processes potentially involved in the pathogenesis of T2D, a comprehensive investigation of the metabolic response will be performed [25]. Metabolomics technologies have the potential for providing novel biomarkers of disease and drug efficacy, and are increasingly being incorporated into biomarker exploration studies [26]. More specifically, metabolomics has a global and non-invasive analysis of biomarkers that are indicators of pathogenic process, or response to therapeutic intervention, thereby helping to monitor treatment response [27]. Recently, panels of multiple biomarkers reflecting T2D pathologies have been developed. A variety of biomarkers representing various pathophysiological pathways of insulin resistance, have also been investigated [28].

The number of T2D patients has recently been increasing worldwide. Thus, the discovery of potential T2D biomarkers, leading to the early detection and/or prevention of diabetes mellitus, is strongly required. The term biomarker was defined by the National Institutes of Health as a "characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention". These include lipids, sugars, nucleotides, amino acids, organic acids, and many other low-molecular-weight compounds [29]. These small molecular metabolites could yield important information about a person's health or disease,

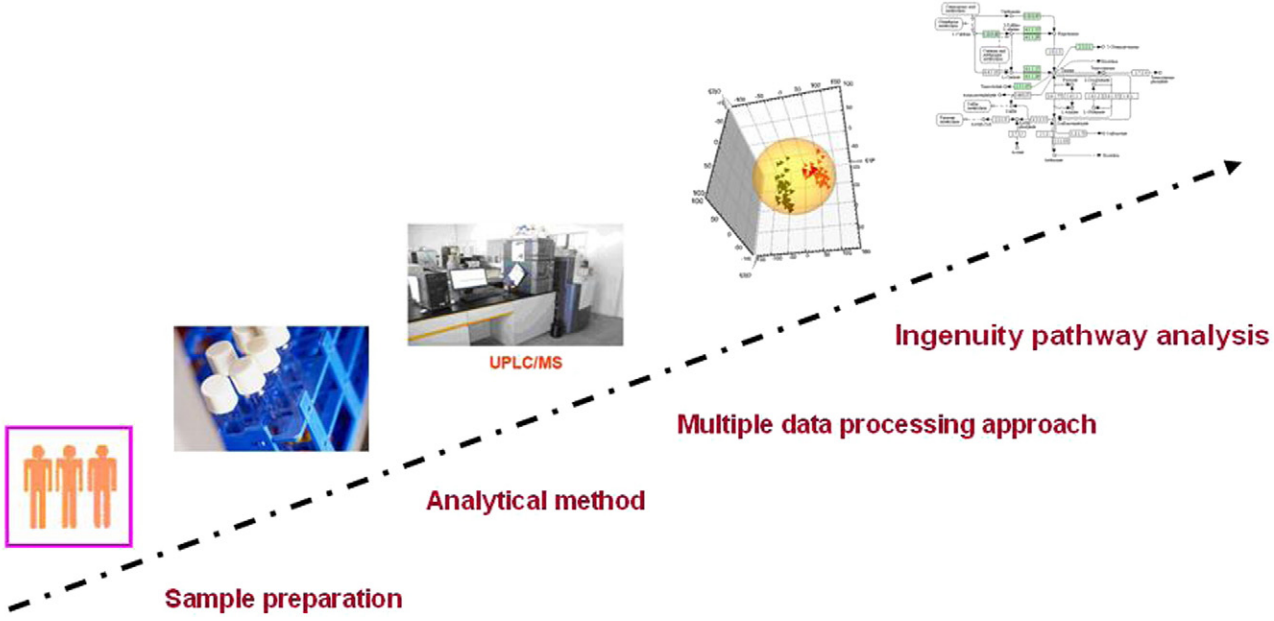

Fig. 1. The general procedures in metabolomic can be used for biomarker discovery.

some of which may be molecular targets for therapeutic intervention [30]. Metabolomics in diabetes has provided researchers much knowledge and the opportunity to gain new insights into metabolic pathways and pathophysiological mechanisms. Several potential metabolic biomarkers and related metabolic pathways have been identified and are currently being investigated and validated in T2D patients, such as 3-hydroxybutyrate with ketogenisis and altered bile acids [31]. Furthermore, metabolomics studies conducted on human subjects between diabetic patients and healthy controls revealed many important altered metabolic pathways and metabolic variations. Metabolomics increased our knowledge of the dysregulated metabolic pathways associated with progression of diseases and provided potentially new therapeutic strategies targeting these dysregulated pathways, though our understanding about the distinct and complete metabolic footprints of T2D [32].

4. Bringing metabolomics into T2D research

Advantages of metabolomics over other "omics", include its high sensitivity and its ability to enable the analysis of relatively few metabolites compared with the unwieldy number of corresponding genes or mRNA molecules. There is mounting evidence that metabolomics can provide important insight into biomarker discoveries and the pathogenic nature of various diseases and a great deal of research on diabetes has been conducted with clinical human subjects during the last decade [33,34]. Given that the overall health status of an individual is captured by his or her metabolic state, metabolomics promises to improve current, single metabolites-based clinical assessments by identifying metabolic signatures that embody global biochemical changes in disease. Metabolomic analytical platforms and informatics tools are being used to map potential biomarkers for T2D [35].

Application of metabolomics in T2D studies has rapidly evolved during the last decade and provides researchers the opportunity to gain new insights into metabolic profiling and pathophysiological mechanisms. Thus, several metabolites were identified to be related to T2D or insulin resistance and represent the basis for the identification of novel diabetes biomarkers [36]. The accumulation of information from novel metabolomics technologies comes with substantial hope and expectations that these approaches will yield novel insights into T2D disease processes and that these insights will eventually translate into clinical applications that will pave the way for current medical routine to the ideal of personalized medicine. High-definition MS has been carried out to obtain comprehensive metabolite profiling and pathways of large biological data sets [7]. MS tends to have much higher analytical sensitivity, enables broader surveys of the metabolome, and can be used to characterize metabolite data either in a targeted or nontargeted manner. Integration of metabolomics-based diagnostic principles into the T2D might be the direction to enable a revolution for future health care, also perhaps it is time to embrace the arrival of 'T2D-OMICS' era.

5. Biomarkers and metabolomics studies on T2D

Identification of early biomarkers for prediction and monitoring is needed for adequate screening diagnostics of diabetes. A number of marker metabolites for diagnosis and prognosis of T2D have been reported. Metabolite profiles of body fluids or tissues can be regarded as important indicators of physiological or pathological states, may provide a more comprehensive view of mechanisms in disease, and raise the possibility of identifying surrogate markers of T2D. Metabolomic discovery of biomarkers of T2D risk may reveal etiological pathways and help to identify individuals at risk. Floegel et al. had investigated the association between serum metabolites measured by targeted metabolomics in the European cases of T2D [37]. MS used to quantify several metabolites, including acylcarnitines, amino acids, hexose, and phospholipids, in serum samples, significantly improved T2D prediction. Surprisingly, metabolomics has revealed that branched-chain amino acids and related metabolites are more strongly associated with insulin resistance than many common lipid species [38]. The branched-chain amino acids-related signature is predictive of incident T2D and intervention outcomes and uniquely responsive to therapeutic interventions. Of note, Ha et al. reported that the receiver operating characteristic curve estimation suggested that decanoyl carnitine and lysoPC (C14:0) are the best metabolites for predicting the risk of developing T2D [39].

Phospholipids and their metabolisms are closely allied to nosogenesis and aggravation of T2D. Identification of molecular components of potential biomarkers was performed on ion trap-MS [40]. As a result, 18 compounds with significant regulation in patients compared with healthy controls were regarded as potential biomarkers for T2D. Among them, 2 novel biomarkers, i.e., PI C18:0/22:6 and SM dC18:0/20:2, can be used to discriminate healthy individuals and T2D cases. Urinary metabolomes were analyzed to enhance understanding of the metabolic indicators of T2D disease pathogenesis and progression [41]. Urinary compounds significantly increased in the T2D when compared with the normal group including glycine betaine, citric acid, kynurenic acid, glucose, and pipecolic acid. Wang et al. had investigated whether metabolite profiles could predict the development of diabetes [42]. Result showed that a combination of three amino acids could predict future diabetes. These findings underscore the potential role of amino acid metabolism in early T2D and suggest that amino acid profiles could aid in diabetes risk assessment.

A metabolomics approach was used to identify candidate biomarkers of T2D and revealed significant metabolic variation, such as glycosylated hemoglobin levels, fasting glucose and insulin [43]. Three metabolites (glycine, lysophosphatidylcholine and acetylcarnitine) were identified and significantly altered levels and may help in developing novel strategies to prevent T2D. Understanding the biochemical networks that underlie metabolic homeostasis and how they associate with insulin action will help unravel diabetes etiology. Fiehn et al. had examined differences in plasma concentrations of metabolites in fasted obese T2D vs. obese non-diabetic African-American women [44]. It reflects a close link between abnormalities in glucose homeostasis, amino acid catabolism, and efficiency of fuel combustion in the tricarboxylic acid cycle. In a study, NMR-based metabolomic analysis in conjunction with multivariate statistics was applied to examine the urinary metabolic changes in T2D [45]. It demonstrated profound changes in nucleotide metabolism, including that of N-methylnicotinamide and N-methyl-2-pyridone-5-carboxamide, which may provide unique biomarkers for following T2D progression.

Suhre et al.'s study depicts the promising potential of metabolomics in diabetes research by identification of a series novel and deregulated metabolites that associate with T2D [46]. Key perturbations of metabolic pathways were linked to kidney dysfunction, lipid metabolism, and interaction with the gut microflora (bile acids). Zhao et al. had investigated pathogenesis and pathogenic process of T2D by NMR-based metabonomics [47]. Principal components analysis on urine samples indicates markedly elevated levels of creatine/creatinine, dimethylamine, and acetoacetate, with concomitantly declined levels of citrate, 2-ketoglurarate, lactate, hippurate, and succinate compared with control rats, respectively. In a work, a metabonomic study was performed to determine metabolic variations associated with T2D patients [48]. Significantly altered serum metabolites in T2D subjects include increased valine, maltose, glutamate, urate, butanoate and long-chain fatty acid, and decreased glucuronolactone, lysine and lactate. The development of both glucose intolerances and insulin resistances is closely correlated with the progressive changes of human serum metabolome [49]. It provides useful information to bridge the gaps in understanding the metabolic alterations associated with the progression of glucose intolerances and insulin resistance status. Comprehensive GC × GC-TOF/MS coupled with pattern recognition methods were applied to analyze plasma from T2D patients,

and carried out to discover metabolites [50]. Five potential biomarkers including glucose, 2-hydroxyisobutyric acid, linoleic acid, palmitic acid and phosphate were identified. These potential biomarkers in plasma, e.g. palmitic acid, linoleic acid and 2-hydroxybutyric acid might be helpful in the diagnosis or further study of diabetes mellitus. Here, Zhang et al. explored the differences in metabolite concentrations between T2D patients and healthy volunteers [12]. Biomarkers reflected the biochemical events associated with early stages of T2D. These urinary differential metabolites were identified involving several key metabolic pathways such as taurine and hypotaurine metabolism; cysteine and methionine metabolism; valine, leucine, and isoleucine biosynthesis metabolism, etc. It provides new insight into pathophysiologic mechanisms and may enhance the understanding of its cause of disease. Analyzing metabolic differences between unperturbed and perturbed systems, such as healthy volunteers and patients with a disease, can lead to insights into the underlying pathology [51,52]. In this review we take a closer look at the metabolomics used within the field of T2D. Furthermore, we highlight the most interesting metabolomics publications and discuss these in detail; additional studies are mentioned as a reference for the interested reader.

6. Conclusions and future perspectives

Metabolomics has the potential to generate novel noninvasive diagnostic tests, based on biomarkers of disease, which are simple and cost effective yet retain high sensitivity and specificity characteristics. An early diagnosis of the disease or the identification of those at risk has the potential of allowing more effective prevention programs and better treatment of the disease. T2D, called the burden of the twenty-first century, is growing with an epidemic rate. There is still a lack of reliable biomarkers indicative of metabolic alterations, highlighting the need for the development of early diagnostic and prognostic markers for T2D. A deeper understanding of global perturbations in biochemical pathways could provide valuable insights about mechanisms of disease, prognostic, and diagnostic biomarkers. High-throughput metabolomics have provided insightful information on T2D disease development and onset prediction, and has revolutionized T2D research. Valuable information regarding T2D development, therapy and diagnosis can now be obtained with microliter sample volumes. Any findings associated with relevance to T2D, once passed to the clinical level, will be eventually combined with other diagnosis approaches to hopefully reach the 100% detection level for high-risk patients.

Competing interests

The authors have declared that they have no competing interests.

Acknowledgments

This work was supported by grants from the Key Program of Natural Science Foundation of State (Grant No. 90709019, 81173500, 81373930, 81302905, 81102556, 81202639), National Key Technology Research and Development Program of the Ministry of Science and Technology of China (Grant No. 2011BAI03B03, 2011BAI03B06, 2011BAI03B08), Key Science and Technology Program of Heilongjiang Province, China (Grant No. GC06C501, GA08C303, GA06C30101), Foundation of Heilongjiang University of Chinese Medicine (Grant no. 201209), National Key Subject of Drug Innovation (Grant No. 2009ZX09502-005).

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