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Conceptual Paper

Metabolomics One of the New Medicine Languages

Safaa EL Meneza*

Professor of Pediatrics, Faculty of Medicine for Girls, Al-Azhar University, Egypt

***Corresponding Author:** Safaa EL Meneza, Professor of Pediatrics, Faculty of Medicine for Girls, Al-Azhar University, Egypt.

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The aim of this article is to introduce metabolomics as new field in clinical chemistry that may commence uprising in understanding the nature of diseases and hence therapy. It is important to direct attention of the neonatologist to understand this new omics technology to support their patients with ultimate diagnostic and treatment.

Metabolites are the end products of the processes that occur within a cell. The metabolome comprises all the metabolites in a biological cell, tissue or organism. The metabolome is defined as the complete set of small molecule endogenous metabolites, intermediates and metabolism products which are the end products of cellular processes found in an organism and biological system (cell, tissue, organ, biological fluid, or organism,) at a specific point in time.

Metabolomics is a relatively new field, with the term "metabolome" first being used in 1998. Metabolomics is one of those new omics sciences as genomics, transcriptomics and proteomics. The word origin is from the Greek change meaning change and nomos meaning a rule set or set of laws.

The study of metabolomics can be beneficial in understanding the entire physiological state of an organism, including biology of a living being organism, its genetic framework and interaction with environmental effects. It is based on the systematic study of the complete set of metabolites in a biological sample. Also, metabolomics can be defined as "the systematic quantitative measurement of the full dynamic multiparametric metabolic response of living systems to pathophysiological stimuli or genetic modification" in biologic samples.

Metabolomics with genomics, transcriptomics and proteomics studies, which are also known as multi-omics, can provide more comprehensive insights into biological processes.

Metabolomics researches focuses on the chemical processes undergone by metabolites. It involves the use of sophisticated analytical technologies as mass spectrometry, electron ionization, amphoteric pressure chemical ionization (APCI), electrospray ionization (ESI), high-performance liquid chromatography (HPLC), capillary electrophoresis, gas chromatography, nuclear magnetic resonance (NMR) to identify and quantify cellular metabolites, in addition to the extraction of relevant information so that the data can be interpreted and applied in a practical setting. nuclear magnetic resonance (NMR) spectroscopy and mass spectrometry (MS) are the techniques most often used for metabolome profiling. Metabolomics analysis need tools as cluster analysis, pathway mapping, comparative overlays and heat maps.

There are Targeted and no targeted approaches. Targeted assays can be highly sensitive and specific and reproducibly quantitative, especially when heavy isotopes are used to label substances and instrumental methods are narrowly focused. Nontargeted approaches, provide a broad portrait of metabolism. The methods of the nontargeted approach tend to be less rigorously quantitative. Nontargeted metabolomics of human urine can generate massive data sets that include not only classic mammalian metabolites from known biochemical pathways but also food additives, drugs and their metabolites, botanical compounds from the diet, products of fermentation by gut microbes, and substances with unknown identities.

Personalized medicine profits from extensive molecular phenotyping methods, like proteomics and metabolomics, as it delivered more understanding into gene function and can help to detect new prospects in diagnosis as biomarker to detect diseases and also in treatment of the diseases. Metabolomics provides a cohesive image of genomic, transcriptomic, and proteomic variation.

Metabolomics analysis of biofluids or tissues enables the parallel assessment of the levels of a broad range of metabolites. It allows to understand the interaction between gene expression and the environment and has been shown to have a great impact in investigation of physiological status, diagnosing diseases, measuring the response to treatment, discovering biomarkers, identifying perturbed pathways due to disease or treatment, functional genomics, pharmacology, toxicology, and nutrition through the variations in metabolite profile. This property is of a great clinical importance in view of the newer definitions of health and disease.

Efforts to detect metabolomics biomarkers (physiological or molecular changes) that are characteristic of common infectious diseases, cancers, and other disorders at low cost using noninvasive sampling, such as through urinalysis or analysis of exhaled breath, could lead to increased acceptance of screening programs.

Till now, there are about 21404 papers listed in PubMed, a few data are available in the newborn (297), obstetrics (241. If more information on perinatal/neonatal maturational processes and their metabolic background were available, the management of sick or preterm newborns might be improved. Currently, the use of metabolomics in neonatology is still in the pioneering phase. Up till now, the use of metabolomics in neonatology is still in the early stage. There are limited number of metabolites that are routinely measured in the biofluids of newborns by conventional analytical methods. Recent studies have evaluated how physiological variables or pathological conditions can affect metabolomics profiles of different biofluids in pediatric populations.

Disease detection using mass spectrometry (MS) has been used the diagnosis and monitoring of inborn errors of metabolism as phenylketonuria and in evaluating patients with neuroendocrine tumors, such as pheochromocytoma and neuroblastoma.

Metabolomics role in disease prevention and treatment as obesity and associated diseases, including diabetes mellitus, cardiovascular disease, and kidney disease were proven. There was distinct patterns, in form of high levels of aromatic amino acids and the three branched-chain amino acids (leucine, isoleucine, and valine) in obese patients due to excess protein consumption, genetic variation in catabolic enzymes, and altered metabolism of gut microbes that correlate with increased risk of type II diabetes and death from cardiovascular disease.

Metabolomics has provided more understanding of drug action and identify biochemical pathways that expand the image regarding drug action and toxicity. This pharmacometabolomics, aided the understanding the metabolic responses to drugs and in turn stimulated new lines of investigation. Metabolomics identified that acetaminophen metabolites were responsible for liver damage associated with acetaminophen overdose. It also has role in understanding biochemical mechanisms of disease as the scientific value of metabolomics in mechanistic biochemistry becoming clear. Metabolite outlines showed amplified information of delicate changes in complex cellular machinery, it was valuable in study of cancer mechanisms.

Metabolomics appears to be a new, very useful tool in diagnostic information in neonatal Medicine. Metabolome is one of the prognostic phenotypes. It relies upon simple, noninvasive techniques. The most commonly used biological samples for metabolomics studies are urine, blood plasma or serum. Urine characteristics and being simple non-invasive methods render it particularly suited for metabolomics analysis even in small babies.

There are several applications of metabolomics in neonatology, include: gestational age, prematurity ,postnatal age, monitoring of postnatal metabolic maturation over time, type of delivery, zygosity, perinatal asphyxia, intrauterine growth restriction, prenatal inflammation and brain injury, respiratory, cardiovascular malformation and dysfunction, renal diseases; nephropathies, nephrotoxicity, metabolic diseases; inborn errors of metabolism, sepsis, necrotizing enterocolitis and antibiotic treatment; nutritional studies on maternal milk and formula, pharma-metabolomics, bronchopulmonary dysplasia, and long-term diseases. Also, the fields of pharma-metabolomics and nutri- metabolomics are important in neonatology. It can be predictive and preventive. Together with genomics, transcriptomics and proteomics, metabolomics appears to be a promising tool in neonatology for the monitoring of postnatal metabolic maturation, the identification of early biomarkers for predicting of outcome, the diagnosis and monitoring of various diseases, as well as therapeutics and drug development and the "tailored" management of neonatal disorders. It may aid in personalized neonatal medicine.

In depth studies showed that premature newborns were characterized by a stronger signature of varying metabolites, suggestive of disturbances in nucleotide metabolism, lung surfactants

biosynthesis and renal function, along with enhancement of tricarboxylic acid (TCA) cycle activity, fatty acids oxidation, and oxidative stress. Also study the difference between normal and diseased kidney trough 1H- NMR in urine sample showed VIP variables, hippurate, tryptophan, phenylalanine, malate, tyrosine, hydroxybutyrate, N –acetyl glutamate, tryptophan, proline.

There were different metabolic patterns between IUGR infants and control. The discriminants in the urine metabolic profiles derived essentially from significant differences in certain metabolites such as: myo-inositol, sarcosine, creatine and creatinine. Metabolomics was used too to find biomarkers for preterm birth in fetal, maternal, and newborn biofluids.

Furthermore, the response to hypothermia treatment of newborn infants with hypoxic ischemic encephalopathy was studied by analysis of H1-NMR metabolites, revealed increase in lactic acid and taurine with accumulation of mannitol in urine of dead cases. Studies showed unique metabolic profile of the patients affected by sepsis compared to non-affected ones. Metabolomics also guides for detection of preterm exposed to histological chorioamnionitis. Detection of fungal infection and monitoring of antifungal treatment was possible through the metabolomics. The increase of gluconic acid was marker for NEC.

The five top metabolites till now are glycine, choline, betaine, inositol/myoinositol and gluconate, they used as biomarker for early detection of IUGR, sepsis, NEC, BPD.

These new data provide more information about perinatal and neonatal maturation processes and metabolic background, subsequently will improve the care and health of the newborn infants [1-11].

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