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Review

Prematurity at birth and increased cardiovascular risk: is a metabolomic approach the right solution?

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Abstract

In recent decades, steady progress in the field of physiopathology and the use of increasingly sophisticated technological procedures have resulted in an increase in the survival rates of babies born preterm. However, some of these individuals, although surviving, may at times be faced with severe consequences. Some conditions may be manifested at an early age (particularly dysmorphisms as well as neurological and ophthalmological conditions), whilst others (namely renal and cardiovascular events), evolve gradually and are manifested only years later. In a number of reports in literature it has been demonstrated how prematurity and consequent low weight at birth are risk factors for developing hypercholesterolemia, arterial hypertension, obesity, type 2 diabetes, QTc interval prolongation at basal electrocardiogram, early endothelial dysfunction, structural and functional cardiac modifications, and increased death rates from coronary heart disease. Even some drugs used in the neonatal management of preterm babies may have a detrimental effect on their future cardiac function.

The aim of this narrative review was to overview the up to know few reports about metabolomics (a new and promising technique which allows the systematic study of the complete set of metabolites in a biological sample) applied to the identification of a possible future cardiovascular system involvement in subjects born preterm.

An outlook of the requirements for future researches has been also discussed.

Keywords

Prematurity, metabolomics, cardiovascular risk, prevention, therapy.

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Introduction

In recent decades, steady progress in the field of physiopathology and the use of increasingly sophisticated technological procedures have resulted in an increase in the survival rates of babies born preterm [1]. However, some of these individuals, although surviving, may at times be faced with severe consequences. Some conditions may be manifested at an early age (particularly dysmorphisms as well as neurological and ophthalmological conditions), whilst others (namely renal and cardiovascular events), usually evolve gradually and are manifested only years later [2-11].

Data present in literature underline how low gestational age and reduced foetal growth contribute towards an increased cardiovascular in preterm neonates [7]. For example, a research based on about 15,000 men and women born in Hertfordshire (England) during 1911-30, demonstrated that death rates from coronary heart disease fell progressively across the range of birth weight [12]. In a more recent study carried out in Finland on a cohort of 4,630 men born from 1934-1944, the inverse correlation between the onset of cardiovascular events and prematurity/weight at birth has been confirmed [13].

An association between prematurity/low weight at birth and hypercholesterolaemia in adulthood had been sporadically reported as well.

In this respect, a systematic review of all research works published about this matter was undertaken. In particular, 79 studies involving 74,122 subjects were taken into account in this analysis. The results obtained reported an increase corresponding to 1.39 mg/dl (0.036 mmol/l) of serum total cholesterol per kg of weight reduction at birth (95% CI 1.81 to 0.97 mg/dl; 95% CI 0.047 to 0.025 mmol/l). However, it should be emphasized that the reverse correlation detected between low weight at birth and total cholesterol was observed in studies recruiting only a limited number of patients. Ultimately, this correlation seems to be scarcely implicated in the management of major cardiovascular events during the adult period of life [14].

Reduced embryonic-foetal development, resulting in low birth weight, may lead to a reduced nephron endowment, hypertension and renal diseases in adulthood. In multiple animal models, it has been demonstrated an association between preterm birth and hypertension, mediated, at least in part, by an associated congenital nephron deficit. Nephron numbers were found to be lower, and glomeruli tended to be larger, especially in rats born with an extreme prematurity. An increase in glomerular size is consistent with hyperfiltration necessitated by a reduction in total filtration surface area, which suggests a congenital nephron deficit. Hyperfiltration manifests clinically as microalbuminuria, lower urinary sodium excretion, higher tissue sodium content, and accelerated loss of renal function, the prevalence of which are higher specially among adults born with lower gestational age. In addition, studies examining the effect of low birth weight on the activity of the renin-angiotensin system have found that renin and angiotensin activity and renal messenger RNA levels are reduced in preterm animals, possibly consistent with a degree of volume expansion secondary to sodium retention. Taken together, these findings may be an independent factor determining susceptibility to essential hypertension in humans [15].

Consistent with the animal data, many human studies have also revealed an inverse association between prematurity/low birth weight and blood pressures in infancy, childhood, and adulthood. In several studies, the relationship was more significant in girls than boys. In adolescence, this correlation is often lost, but some reports do still show a persistence in this link. In young adults, it has been found blood pressures tend to be higher in those who had been of preterm babies, even after correction for the impact of parental blood pressure, a possible confounder. Indeed correction for parental blood pressure did decrease, but did not eliminate, the strength of this inverse association. Barker et al. first reported the inverse association between hypertension in adult life and birth weight. Blood pressure does appear to "track" throughout age groups, and former preterm children with higher blood pressures become adults with higher blood pressures. The differences in blood pressure

between people of ELBW and normal birth weight also become amplified with age [16, 17].

A considerable body of scientific evidence has documented that the development of obesity, a well known cardiovascular adverse events risk factor, is influenced by the weight at birth: low weight at birth induces direct and future development of abdominal obesity [18]. This evidence is enclosed in the so called perinatal programming of the obesity, according to which previous conditions, even far in the past, could influence further laying and location of body fat. On the contrary, the hypothesis of thrifty phenotype has postulated a potential relationship between reduced foetal nutrition and an excess of postnatal feeding aimed at rapidly increasing the weight of neonates.

Indeed, not only prematurity and reduced uterine growth, but even the following modifications had a relevant influence on the future health state. The most unfavourable conditions to this regard were a low weight at birth combined with a rapid increase in weight during childhood [19].

The relationship between preterm birth, low weight, and development of type II diabetes remained unproven until the publication in 2008 of a systematic review on this matter. Thirty-one of 327 research studies were evaluated, for a total of 152,084 subjects. An inversely proportional relationship between prematurity and consequent low weight at birth and type II diabetes had been observed in 23 of these studies, despite the heterogeneity of the examined populations, which included numerous types of ethnicity. In the studies analyzed, the relationship between weight at birth and future development of diabetes was particularly significant when considering infants with a birth weight lower than 3 kg [20].

At electrocardiographic examination, it has been recently demonstrated a significant mean prolongation of QT interval corrected for heart rate (QTc) in young ex extremely preterm adults when compared to a group of ex-full term infants ($p < 0.00001$). Moreover, in 8.3% of the sample investigated QTc exceeded the upper limit of normal range, whilst the prevalence rate for prolonged QTc in the general population ranges from 0.01 to 0.05%. Furthermore, a strong correlation was observed between QTc and both gestational age and birth weight. A pathophysiological interpretation of these findings cannot fail to take into account the possible presence of a subclinical dysfunction, maybe induced by renal immaturity (i.e. a modified metabolic substrate, involving ionic channels responsible for cardiac repolarization), which may explain this electrocardiographic abnormality. It is known how prolonged QTc is a risk factor for developing life-dangerous ventricular arrhythmias [10].

Evidence about exercise capacity and physical activity in subjects born preterm is limited. Recent reports show a significant reduction in peak oxygen consumption during exercise performed on a cycle ergometer, probably reflecting a long term pathophysiological impact of preterm birth on cardiopulmonary function. Furthermore, ex-preterm young adults have a significantly poorer physical performance in comparison with their normal full term peers [21, 22].

Furthermore, endothelial dysfunction is the earliest clinically detectable stage of cardiovascular disease, preceding the formation of atherosclerotic plaques. The predictive power of endothelial dysfunction, related with the future development of adverse cardiovascular events and cardiac death, has also been showed. It has been demonstrated that endothelial function was significantly reduced in young adults previous extremely preterm subjects compared to a control group of healthy subjects born at term ($p < 0.0001$). Moreover, this function correlated significantly with gestational age ($r = 0.56$, $p < 0.0009$) and birth weight ($r = 0.63$, $p < 0.0001$). Taken together, these results suggest that prematurity at birth may underlie the onset of early circulatory dysfunction, maybe predictive of increased cardiovascular risk [11].

These findings may be explained by the fact that extreme prematurity at birth translates into a reduced production of nitric oxide and vasodilatory substances and/or increased release of vasoconstrictor compounds, such as asymmetric dimethylarginin (ADMA), whose blood levels have been afterwards studied in a group of young adults previously born preterm.

ADMA blood levels were reduced in ex-preterm subjects compared to healthy controls born at term ($p < 0.05$), and significantly correlated inversely with gestational age ($r = -0.61$, $p < 0.00001$) and birth weight ($r = -0.57$, $p < 0.0002$) [9].

As a further evidence that preterm birth is a new risk factor for cardiovascular event, in a recently published research it has been demonstrated how young adults who were born preterm have adverse structural alterations in their heart that could put them at risk of cardiac problems. The study – which employed cardiac magnetic resonance imaging – was the first of its kind to demonstrate that those born preterm had significantly increased left ventricular

mass ($p < 0.001$), with greater prematurity associated with greater mass. Preterm-born subjects also had short left ventricles with small internal diameters and a displaced apex. Ejection fraction was preserved, but both longitudinal systolic and diastolic function, as well as rotational movement, were significantly reduced among the premature individuals [23].

Even some drugs used in the neonatal management of preterm babies may have a detrimental effect on the future cardiac and vascular functions [24-28].

In conclusion, all the above stated observations suggest that preterm birth condition may underlie the development of potential future adverse cardiovascular events.

Metabolomics as a new tool to identify prematurity at birth-related cardiovascular risk

Metabolomics, also called the 'new clinical biochemistry', is a novel technique based on nuclear magnetic resonance spectroscopy and mass spectrometry, combined with separation techniques as gas or liquid chromatography, which allows the systematic study of the complete set of metabolites in a biological sample (e.g. urine, blood, exhaled breath condensate). The metabolome is considered the most predictive phenotype and is capable of considering epigenetic differences. It is so close to the phenotype that it can be considered the phenotype itself. In the last three years about 5,000 papers have been listed in PubMed about metabolomics [29]. Reports about metabolomics applied to the study of the cardiovascular system were fewer, and the majority of them involved adult patients [30].

However, the use of metabolomics appears to be a promising tool in identifying preterm newborns at increased risk for developing cardiovascular diseases in their future life. The management of preterm babies might improve if more information on perinatal/neonatal maturational cardiovascular processes and their metabolic background were available [31].

In this respect, a metabolomic study has been performed with the aim to characterize the physiological and biochemical responses to prematurity in comparison with born at term controls. Urine metabolic profiles between these two groups were different and it was made possible to identify the molecules responsible for such differences (such as myo-inositol, sarcosine, creatine and creatinine).

These different metabolic patterns are the same known to be involved in the metabolic syndrome, which increases the risk of developing cardiovascular disease and diabetes In particular the role of myo-inositol has been emphasized [32].

Animal models have been applied to study the relationship between prematurity at birth and diabetes/metabolic syndrome as well. Atherton and colleagues applied 1H-nuclear magnetic resonance spectroscopy and mass spectrometry to study peroxisome proliferators activated receptors (PPARs) subtype α in preterm null mutant mice. PPARs subtype α partly regulates genes encoding mitochondrial, microsomal and peroxisomal β-fatty oxidation in the liver. When hearts and other tissues of these mice were analysed, perturbations in glycolysis, tricarboxylic acid cycle and gluconeogenesis were observed. All these profound systemic changes in metabolism have been shown to predict future diabetes development [33].

In a recent pilot study, 1H-nuclear magnetic resonance urinary metabolomics approach at birth has been used in predicting the presence of patent ductus arteriosus in a small sample of neonates ($n = 14$), including four infants born at term, four preterm without patent ductus arteriosus, and six preterm with patent ductus arteriosus.

In this respect, urinary metabolomics at birth was able to distinguish these three subgroups at day 4 of life [34]. By a practical point of view, these metabolomic promising findings suggest that the prediction and monitoring of a persistent patent ductus arteriosus may be facilitated, and so the unnecessary and unethical prophylaxis with anti-inflammatory drugs could be avoided [26].

The metabolic profile in 1H-nuclear magnetic resonance spectra of plasma taken immediately after birth from umbilical vein and artery blood were recorded for preterm with a very low birth weight and normo-ponderal full-term neonates [35]. Clear distinctions were observed. Decreased levels of lipoproteins, glucose, pyruvate, and albumin-lysyl, as well as increased levels of glutamine were characteristic of cord blood (both arterial and venous) from very low birth weight infants, along with a decrease in levels of several amino acids in arterial cord blood. A lower level of lysyl groups of albumin is indicative of a degree of oxidative stress. It has recently been suggested that prematurity at birth is associated with a level of relative hypoxia with the addition of reperfusion and oxidative stress. The existing evidence support the view that oxidative stress may play a crucial role in cardiac and vascular abnormalities in different types of cardiovascular diseases, including hypertension, atherosclerosis,

ischemic heart disease, cardiomyopathies, and congestive heart failure [35, 36].

Glutamine levels were elevated in both the venous and arterial cord blood plasma of preterm neonates born with an extremely low birth weight: the reason for this is not clear. It is noteworthy, however, that glutamine is the most abundant amino acid in blood and is involved in multiple pathways including the biosynthesis of purines and pyrimidines, the supply of energy to neonatal gut, and to other rapidly dividing cells. As preterm birth is associated with significant stress, it has been hypothesized that the increase of glutamine reflects a dramatic surge in glutamine biosynthesis and placental transfer in order to cover the need of the stressed preterm infant. Increased rates of glutamine production have been reported in preterm infants , and higher levels of glutamine were observed in the amniotic fluid of malformed fetuses, including those with congenital heart diseases [35].

Furthermore, for the first time these results showed that, because of its characteristics and simple non-invasive mode of collection, also cord plasma is particularly suitable for metabolomic analysis.

Maternal diabetes mellitus significantly affects the foetal heart. Hypertrophic cardiomyopathy observed in the infants from diabetic mothers is characterized by thickening of the interventricular septum, and to a lesser extent the ventricular free walls. It is observed in infants of diabetic mothers without a reasonable metabolic control. Fortunately, most affected infants are clinically asymptomatic and have resolution of the hypertrophy within months, presumably as there is no further exposure to the abnormal intrauterine milieu. The development of hypertrophic cardiomyopathy is believed to occur as a consequence of both fetal hyperinsulinaemia and the normally increased expression and affinity of insulin receptors which leads to the proliferation and hypertrophy of cardiac myocytes [37].

In an exploratory nuclear magnetic resonance metabolomic study of second trimester maternal urine from diabetic women, higher 3-hydroxyisovalerate and 2-hydroxyisobutyrate levels have been shown, probably due to altered biotin status and amino acid and/or gut metabolisms (the latter possibly related to higher body mass index values). Other urinary changes suggest choline and nucleotide metabolic alterations, whereas lower plasma betaine and TMAO levels have been found. In the light of the above, metabolomics of maternal biofluids enables the non invasive detection of metabolic changes associated to prenatal disorders, thus unveiling potential disorders biomarkers [38].

In a recent study, it has been demonstrated how the metabolomic technique is able to predict a subclinical pathological process in the kidney of young adults born preterm with en extremely low birth weight (< 1,000 g). The latter also have increased systolic blood pressures ($p > 0.05$) in comparison with controls born at term with a normal weight [39].

Based on these premises, even if metabolomics is still in its pioneering phase, it has assumed a crescent role in the identification of cardiovascular disorders in the neonatal metabolic profile, determined by the interconnection of the different processes. A combination of factors including genotype, physiological or pathological conditions, nutrition, and environment are all capable of producing an effect on the biochemical composition of biological fluids, thus providing important information on metabolic abnormalities implicated in a number of diseases, including cardiovascular pathologies [30, 40].

Contemporary medicine is strongly influenced, if not obsessed, by healthcare protocols. These are often necessary in countries with more developed healthcare systems, where reference points can be used in the defensive medicine field. Actually, by definition, protocols do not take into account (or take into slight account) the individuality of each patient, a situation that requires a diagnostic and, more importantly, a personalized and tailor-made therapeutic approach. Pharmacogenomics and pharmacometabolomics, for example, are ready or nearly so to allow a personalization of therapy [41].

The sensitivity shown by metabolomic platforms in detecting subtle cardiovascular abnormalities well before any change detectable with clinical measures, represents a very promising basis for the application of metabolomics in subjects born preterm. Scientists should thus aim to fully exploit the possibilities afforded by this method in order to identify biomarkers capable of improving the detection, and outcome of cardiovascular system involvement as a consequence of prematurity at birth. Technological advancements in mass spectrometry and nuclear magnetic resonance, together with the advent of new bioinformatic tools will contribute towards overcoming the current limits of metabolomics (i.e. complexity and cost-effectiveness). Indeed, the association of metabolomics to prematurity may enhance the evaluation of new therapeutic options in clinical trials, furthermore contributing towards

identifying patients at risk of manifesting adverse effects during treatment, predicting therapeutic response, and achieving the implementation of new tools focused on establishing an increasingly patient-oriented treatment.

Declaration of interest

The Authors declare that there is no conflict of interest.

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