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Biomarkers of cardiovascular disease risk in the neonatal population

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Review

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Abstract

The consistently high prevalence of cardiovascular disease (CVD) has urged the need for punctual and effective prevention. Extended research on this specific area has demonstrated the influence of fetal and neonatal periods on the risk of developing CVD in adulthood. Thus, the role of traditional and novel biological markers to the effective screening of CVD among the neonatal population is widely investigated. The objective of the present narrative review is to examine those neonatal biomarkers that may play a role in the development of CVD, to exhibit scientific data that appertain to their association with various perinatal conditions leading to CVD predisposition, and their potential role on prediction and prevention strategies. Multiple biomarkers, traditional and novel, have been mined across the studied literature. Adiposity, insulin resistance, altered lipid profile, inflammation, and endothelial dysfunction seem among the headliners of CVD. Even though various novel molecules have been studied, their clinical utility remains controversial. Therefore, it is quite important for the scientific community to find elements with strong predictive value and practical clinical use.

Introduction

Despite the remarkable progress on the promotion of cardiovascular health, cardiovascular disease (CVD) remains the principal cause of death worldwide.[1] Although CVD does not become clinically apparent from infancy, wide research is carried out in order to bear testament to the hypothesis that intrauterine growth and perinatal characteristics strongly affect the risk of developing CVD in adulthood.[2] Thus, increased appreciation of the above statements has prompted the need for new putative biomarkers that would facilitate an effective screening and primary prevention strategies.[2]

The intrauterine environment provides a foundation on which hypertension, insulin resistance (IR), or increased adiposity and metabolic syndrome may develop in offspring throughout their life.[3] In 1987, Barker et al. established a direct association of deficient fetal growth with hypertension and CVD in adulthood.[4] Preterm birth, small for gestation (SGA) infants (birth weight less than the 10th percentile for their gestational age and sex), large for gestation (LGA) infants (birth weight greater than the 90th percentile for their gestational age and sex), and intrauterine growth-restricted (IUGR) pregnancies (fetuses that do not achieve the expected in utero growth due to genetic or environmental incidents)[5] have been associated with increased risk of developing several morbidities later in life including CVD.[3,6]

Since CVD is a general condition comprised of a variety of components affecting the heart or the vascular system, one can come across more than one definition and a difficulty for a clear consensus. The risk of developing CVD in adulthood strongly coincides with developing one or more of the following conditions including hypertension, increased body mass index (BMI), IR, dyslipidemia, inflammation, atherosclerosis, and arterial stiffness.[2,7] Other studies make use of scores based on the existing literature in order to make a gross assessment of these components studied in the first years of life that can predict the development of CVD in adulthood.[7,8]

Concerning the pediatric population, uncertainty prevails in understanding the role of the different risk factors and biomarkers associated with the primary prevention of CVD.[2,7] In the neonatal population, various biomarkers associated with CVD in adults have been studied. However, because of the limited data for this population until adulthood, there is great heterogeneity in the literature and lack of direct association between specific biomarkers and CVD events such as stroke, myocardial infarction, and chronic kidney disease.[2,3,8]

Therefore, the aim of the present narrative review is focused on performing an overview of the literature concerning those biomarkers in the neonatal population and to observe their expression across various perinatal states that are already known to contribute to the

development of CVD in later life (prematurity, altered birth weight, IUGR, etc.)[3,6] and their potential predictive role and contribution for prevention strategies.

Methods

Search strategy

We adhered to the PICO (Population, Intervention or Exposure, Comparison, Outcome) Research guidelines, regarding the characteristics of the population and biomarkers to be examined, the implementation of the study, and the extraction of the outcomes. We searched for studies that investigated biomarkers in neonatal samples, possibly representative and/or predictive of the development of CVD in later life published from August 1997 through October 2021. The included studies covered a spectrum of neonatal conditions such as born at term, preterm, appropriate for gestational age (AGA), SGA, LGA, very low birth weight, extremely low birth weight (ELBW), IUGR. Our search was based on the following databases: PubMed, ResearchGate and was based on the following medical subject headings and keywords: "neonates", "infants", "newborn" and, with Boolean operator 'AND' "CVD", "CVD risk", "biomarkers", "predictive". Additionally, all references of the selected studies were searched to make sure no study was missed.

Selection of articles

Data were extracted independently by two reviewers (A.L. and D.R.). Of the 5,912 identified articles, eligible were the ones including human samples, published in the English language, and containing neonatal evidence regarding biomarkers with a potential association to CVD, as per the above-mentioned definitions. We included articles, studying biomarkers from cord and venous samples. Prospective, retrospective, longitudinal, and cross-sectional studies were included. Studies not containing raw data such as review, or opinion articles did not meet the inclusion criteria. Articles containing nonhuman or non-neonatal study groups, studies not containing any analysis of molecules or any association of the studied biomarkers with components of CVD were not included. Ultimately forty-eight articles met the inclusion criteria for the present review. The two authors independently assessed the title, abstract, and full text of the selected articles and data were extracted independently (Fig. 1).

CVD biomarkers in neonatal population

A biomarker's clinical value is defined by evidence from prospective studies, in a wide sample of the population, by standardization of the measurements, low variability, reproducibility, and low cost. Ascertaining an association between a biomarker in infancy and a CVD outcome in later life provides the power of a biomarker's predictive value. This review demonstrates various biomarkers (Table 1) that correlate with characteristics of CVD such as blood pressure, endothelial function, aortic intima-media thickness (aIMT), carotid IMT (cIMT), and alterations in cardiac ultrasound.

Adipokines

Of the different pathways leading to CVD, adiposity imbalance seems to play a central role. Adipose tissue produces several bioactive proteins known as adipokines, which play a crucial role in the pathogenesis of obesity, inflammation, abnormal lipid and glucose metabolism, angiogenesis, and dysregulated cardiovascular health in general.[2,7]

Adiponectin

Adiponectin is a protein with an inverse association with IR, metabolic syndrome, and CVD. It possibly has fetal origins as it presented a slight though not significant increase between birth and four days postpartum.[9] Concerning the neonatal population, lower adiponectin levels were noticed in cord samples of IUGR,[10] SGA (term and preterm), and ELBW-AGA newborns compared to control groups.[11] Adiponectin seems an important determinant of fetal growth and neonatal body composition and there is a possible interaction between adiponectin's molecular weight isoforms and gender. Specifically, for female neonates, high-molecular-weight adiponectin appeared as one of the main determinants of adiposity and fetal growth velocity, whereas in males, fetal growth and adiposity appeared affected by low-molecular-weight adiponectin.[12] Females also presented with significantly higher levels of total and high molecular-weight adiponectin compared to males.[13] Cord adiponectin presented a linear association with weight, length, and subscapular z-scores at 6 months of age, in offspring of obese mothers. Also, a decrease in cord adiponectin levels was found in infants of diabetic mothers (IDMs)[14] The reduced adiponectin levels in these groups could be an expression of fetal programming, possibly affected also by the maternal compartment, that is related to altered adiposity and IR in later life and of a possible contribution of adiponectin in the pathogenesis of IR.[10-14]

Leptin

Leptin is a satiety factor with a central role in the regulation of appetite and metabolism.[10,15] In neonates it possibly correlates with GA and birth weight. Cord leptin displayed a significant decrease in neonatal samples during the first week of life.[9,16] Concerning intrauterine growth, leptin presented no significant differences between IUGR and controls. However, a negative correlation was observed between adropin, a liver-secreted factor involved in several metabolic pathways, and leptin in cord samples of IUGR neonates.[10] Cord leptin levels were related to measures of neonatal growth, body composition, and catch-up growth. Also, they were negatively associated with infant mid-upper arm circumference z-scores and positively associated, with birth weight, with increased odds of catch-down growth at 6 months of age and with the Ponderal Index.[12-14] Additionally, leptin also appeared as a strong predictor of decreased septal strain in infants of obese or diabetic mothers.[17] Following the dynamic changes in leptin levels from birth to childhood, three distinct patterns were identified: "low stable," "high-decreasing," and "intermediate-increasing." Most of the adiposity measures and biomarkers presented with their greatest values in the third group, while high-density lipoprotein cholesterol (HDL-C) was decreased in this group. Furthermore, the "intermediate-increasing" trajectory was related to altered parameters of obesity, such as BMI z-score, waist circumference, total fat mass index, higher insulin, inflammation, and lower HDL-C compared to the low-stable trajectory. Association with higher leptin levels at early adolescence, presented the intermediate-increasing and high-decreasing trajectories.[15] Leptin levels appear to correlate with body composition, adiposity, and energy balance, and elevated leptin levels have been associated with obesity-related inflammation biomarkers. Thus, the alterations in leptin levels throughout the first years of life could predict subsequent cardiometabolic outcomes.[10,15]

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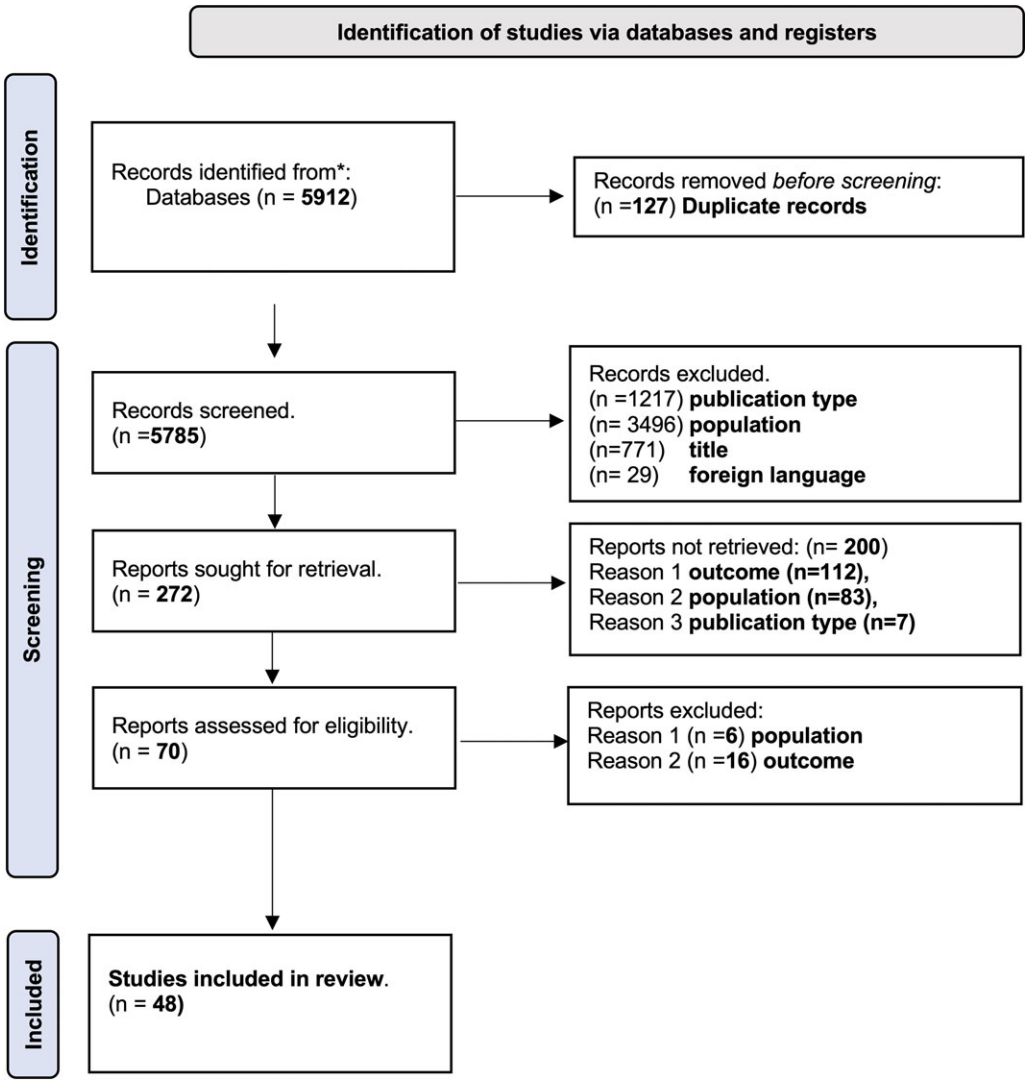

Fig. 1. Prisma flow diagram.

Additional adipokines

Aliquot adipokines studied include visfatin and adropin, which play an important part in the regulation of glycemic homeostasis. Adropin also seems to be a novel regulator of endothelial function. It attenuates metabolic distress syndromes associated with obesity and contributes to energy homeostasis and lipid metabolism. Cord blood adropin was found significantly lower in IUGR neonates and presented a negative correlation with leptin and a positive correlation with endothelin-1 levels.[10] Visfatin is an insulin-mimetic factor known to increase along with the development of obesity. Visfatin levels were found to increase along with hyperglycemia as well. Significant differences between preterm and ELBW infants were reported regarding visfatin, Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), and insulin levels. Visfatin levels were found significantly increased in ELBW infants compared to term and preterm, and in preterm SGA and AGA infants. Thus, visfatin can be used as an early IR indicator also in ELBW infants.[11]

Inflammation

Inflammation is present in many of the different pathways leading to CVD, including obesity, adiposity, blood pressure, and atherosclerosis.[2,7] Concerning the pediatric population wide research is necessary to identify those inflammatory markers that could be related to the early onset of CVD and predictive of its progression in adulthood.

High sensitivity C-reactive protein (hs-CRP)

Recent pediatric research demonstrated that elevated CRP levels are related to CVD from the first years of life. Thus, researchers investigated the contribution of hs-CRP, a sensitive marker of systemic inflammation, in the first days of life among neonates at risk of developing CVD. Term healthy infants presented a significant increase in CRP in 24 and 36 hours postpartum, with a peak at 24 hours.[18] SGA neonates presented significantly higher levels of hs-CRP compared to AGA. No gender-specific differences were noticed. Further studies propose an association between cord hs-CRP and systolic blood pressure in children born SGA and a higher, though not significant aortic thickening in children born SGA.[19,20] Interestingly, chorioamnionitis was associated with a significant increase in hs-CRP in the immediate postnatal period.[21] In addition, no increase in hs-CRP was reported in IUGR fetuses or infants from gestational diabetes mellites (GDM) pregnancies.[22,23] Lastly, hs-CRP levels were significantly higher in South Asian neonates compared to Caucasian, in a frame of a general impaired metabolic profile characterized by hyperinsulinemia, dyslipidemia,

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Table 1. Frequently studied CVD biomarkers, traditional and novel

Biomarkers*	Study population	Result	Reference values
Adiponectin[10-12]	IUGR, SGA, ELBW	↓ levels	6–55.8 μg/ml[78]
Leptin[10,12,14,15,17]	IUGR, AGA and infants of obese mothers or with DM	Relation with body composition, adiposity and energy balance, inflammation	0.87–11.86 ng/ml[79] (10^{th}–90^{th} percentile)
Hs-CRP[19-24]	SGA, S. Asian, Chorioamnionitis	↓ lower levels, relation with ↑SBP, ↑ aIMT	0.3–6.1 mg/l 0–15 d[55] 0.1–1.0 mg/l 15 d–15 y
IL-6, TNF-a[14,23,26,27]	AGA, IUGR, SGA, GDM	Inverse association with neonatal body composition IL-6 ↑ in SGA and GDM	IL-6: 2–10.2 pg/ml[80] (2.5^{th}–97.5^{th} percentile) TNF-a: 2–2.52 pg/ml[81]
Homocysteine[29-31]	AGA, SGA, IUGR, Pre-eclampsia	No significant differences among SGA, IUGR, AGA ↑ in pre-eclamptic pregnancies	4.2–12.8 mol/L [82] (5^{th}–95^{th} percentile)
Insulin/HOMA-IR[11,12,14,17,23]	SGA, ELBW, Preterm, obese Mothers with DM, GDM	↑ and association with cardiac function and fetal growth	Insulin: 2.42–13 μU/ml[34] (5th–90th percentile) HOMA-IR: 0.52–2.89[34] (5th–90th percentile)
TG[24,26,28,38]	SGA, IUGR, GDM, family history of premature CAD	↑ levels	Acceptable: <75 mg/dl[83] Borderline: 75–99 mg/dl High: >100 mg/dl
HDL-C[24,26,38]	SGA, GDM	↓ and dysfunctional in SGA	15–42 mg/dl[55]
LDL-C[29,38]	SGA, Pre-eclampsia	↑ and more sensitive to oxidation in SGA ↑ in Pre-eclampsia	Acceptable: <110 mg/dl[83] Borderline: 110–129 mg/dl High > 130 mg/dl
PCSK9[42,43]	AGA, IUGR, SGA	↓ 35% in IUGR ↑ in females ↓ in male SGA compared to male AGA neonates	154.6–202.5 ng/ml[42]

SGA; small for gestation, AGA; appropriate for gestation, IUGR; intrauterine growth restriction, DM; diabetes mellites, Hs-CRP; high sensitivity C-reactive protein, SBP; systolic blood pressure, aIMT; aortic intima media thickness, IL-6; interleukin 6, TNF-a; tumor necrosis factor a, GDM; gestational diabetes mellites, HOMA-IR; homeostasis model assessment-estimated insulin resistance, ELBW; extremely low birth weight, TG; triglycerides, HDL-C; high density lipoprotein cholesterol; LDL; low density lipoprotein, PCSK9; Proprotein Convertase Subtilisin/Kexin-Type 9
*References on biomarker's correspond to the findings of the included studies.

and higher E-selectin levels in South Asian subjects.[24] The results suggest a possible association of the inflammatory status across perinatal conditions already correlated to CVD.

Additional inflammation markers

Additional elements of the inflammatory process, such as the cytokines IL-6 and TNF-a, the selectins and intercellular adhesion molecule (ICAM) families, seem important in CVD though less investigated. Both IL-6 and TNF-a appear to associate with IR, adiposity, and other CVD risk factors. In term healthy newborns cord IL-6 levels were significantly lower than in 24 and 48 hours postpartum reaching a peak during the first 24 hours.[25] The levels of IL-6 and TNF-a were negatively associated with neonatal birth weight z-scores, and even though they may contribute to the development of neonatal adiposity in utero, an inverse association with neonatal body composition was found.[14] IL-6 and TNF-a tended to increase in a group of IUGR neonates, and IL-6 values were higher in SGA neonates and neonates from GDM pregnancies.[23,26,27] These higher inflammatory cytokine concentrations are suggestive of triggering the proinflammatory response in these populations.

Inflammation and endothelial dysfunction

E-selectin, ICAM-1, *vascular cell adhesion molecule-1* (VCAM-1)

Concerning markers of endothelial dysfunction, such as E-selectin, ICAM-1, and VCAM-1 in the pediatric population, the number of relevant studies is very limited. E-Selectin appeared significantly higher in South Asian neonates, whereas ICAM-1 and VCAM-1 did not differ compared to Caucasian ones. Hyperinsulinemia, dyslipidemia, and higher CRP levels were also present in South Asian subjects.[24] In children with a family history of premature coronary artery diseases, there were positive correlations between total cholesterol (TC) and VCAM-1 and TC and ICAM-1.[28] Additionally, when the levels of serum ICAM-1 were studied among twins one of which being IUGR no significant differences were noticed.[27] Yet, the levels of serum ICAM-1 were statistically higher in infants of GDM pregnancies and VCAM-1 was significantly higher in infants of GDM pregnancies and placental atherosclerosis.[23] Consequently, alterations on specific markers of endothelial dysfunction demonstrate the early onset of vascular stress as a result of exposure to an atherogenic environment.

Homocysteine (tHcys)

Homocysteine is considered a cardiovascular risk biomarker in adults. It exerts several toxic effects, including injury on the vascular endothelial cells.[29,30] It appeared at no significant differences among SGA, IUGR, and control fetuses.[30] However, studies have shown that maternal alleles affect neonatal homocysteinemia and that maternal levels of tHcys seemed the most powerful independent predictor of cord tHcys.[29,31] Furthermore, significantly higher concentrations of tHcys and fibrinogen were noticed among newborns of pre-eclamptic pregnancies compared to controls, suggesting the intrauterine origin of CVD risk in this population.[29]

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Insulin resistance

The role of insulin in the development of cardiovascular pathology remains controversial. Extended research in adults provides evidence that IR is the result of various intracellular events associated with oxidative stress, adipocyte dysfunction, and the release of various adipokines.[7] Thus, it is important to validate those elements that can predict IR development from an early postnatal period.

Insulin

In term neonates, there is a hormonal and metabolic adaptation in the perinatal period, whereas, in preterm, abnormalities of glucose homeostasis are customary. Insulin and HOMA-IR appeared increased in ELBW and SGA infants. Additionally, IR increased across rising levels of prematurity and SGA status.[11] Yet, among IUGR who made a catch-up growth and those who did not, no significant differences were noticed concerning insulin and HOMA-IR,[32] which appeared to increase in newborns of mothers with GDM or obesity and pregestational DM.[17,23] Additionally, infants of obese mothers with pregestational type 2 DM showed impaired cardiac function at one month of age in the absence of septal hypertrophy, which is associated with altered maternal and infant lipid and glucose metabolism.[23] Cord insulin levels also associated with maternal fasting glucose, neonatal birth weight z-scores, measures of body composition, and cord lysophosphatidylcholines. Consequently, fetal growth in the first two trimesters possibly associates with insulin levels.[12,33] Maternal and neonatal obesogenic alleles significantly affected neonatal insulin and HOMA-IR values, while there are polymorphisms that affect neonatal glucose homeostasis elements, such as insulin, in an opposite manner.[31] In addition, insulin levels were significantly higher in South Asian neonates compared to Caucasian.[24]

Glucose

Hyperglycemia is directly associated with vascular disease. It is the first mediator of diabetic endothelial dysfunction, leading to impaired vascular health.[23] Glucose in term AGA neonates ranges from 3.9 to 6.7 mmol/l (70.2–120.6 mg/dl) (5^{th}–90^{th} percentile).[34] Its concentrations rise at two days postpartum at approximately 70mg/dl.[35] In contrast with the previous parameters glucose levels did not significantly differ among term, preterm, ELBW infants or the SGA, AGA subgroups. Similarly, glucose levels did not significantly differ among South Asian and Caucasian neonates. No significant differences were noticed among newborns of obese diabetic mothers, newborns of obese non-diabetic mothers and controls as well. Additionally, glucose itself did not seem to be involved in the impaired cardiac function of newborns of obese diabetic mothers.[11,17,24] Yet other studies demonstrated significantly elevated glucose levels in SGA neonates.[26] Glucose presented with significantly negative associations with birth weight z score, percentage of body fat and the state of LGA among children born to Indigenous and Non-Indigenous Australian women or obese pregnant women.[33,36] Cord glucose levels were significantly lower in IUGR neonates who got a catch-up, however, no significant differences were observed regarding during the follow-up. Elevated glucose and triglyceride levels in cord and maternal samples are typical features of SGA used to predict type 2 diabetes and CVD.[32] Also glucose levels were significantly lower in GDM infants. Glucose along with other metabolic elements presented a direct association with the pathophysiology of GDM.[23] Lastly, maternal fat mass and obesity alleles seemed to affect glucose much more than neonatal alleles and several parameters linked to glucose homeostasis did.[31]

C-peptide

The connecting peptide, or C-peptide, represents pancreatic beta-cell function. In the context of diabetes or hypoglycemia, C-peptide can be used to distinguish between different conditions with similar clinical features. Studies have demonstrated a positive association of cord C-peptide with maternal fasting glucose, cord lysophoshatidilocholines, neonatal birth weight z-scores, measures of body composition, LGA, and neonatal fat; however, there were no associations with infant anthropometry at six months of age.[33,36] Significantly higher C-peptide concentrations were noticed in infants of obese diabetic mothers. Also, C-peptide belongs to those infant parameters that correlate with septal segmental longitudinal strain.[17] Thus, C-peptide seems to be a strong mediator of the association between maternal BMI and each neonatal outcome across the glucose tolerance spectrum of normal glucose tolerance, GDM, and type 2 diabetes.[36]

Insulin-like growth factors I, II (IGF-I, II)

Insulin-like growth factors are molecules with a possible role in DM in the adults. In neonates, their contribution to the development of CVD is a field quite underexplored. However, IGF-I was raised in cord blood of offspring born to obese women because of maternal dysglycemia.[33] IGF-1 and IGF-BP3 levels were found similar in the umbilical cord, at 9 months and 12 months in IUGR infants. It is stated that the normalization of insulin levels and IGF growth factor usually occurs during the first three months of postnatal life.[32] Studies also have shown that at six months of age cord IGF-I was linearly associated with Lysophoshatidilocholines, infant weight z-scores, BMI z-score, and mid-upper arm circumference z-score. Also, it was positively associated with increased odds of catch-down growth, suggesting possible participation in fetal glucose homeostasis and fetal growth.[33]

Lipid profile

Although CVD based on atherosclerosis manifests in adulthood, there is mounting evidence that atherosclerosis begins in the first stages of life and progresses to measurable vascular changes in adulthood.[2] Lipid levels in infants (aged < 6 months) before and after 4 weeks of life presented a slight though not significant increase in TC and LDL-C and a significant increase in triglycerides and decrease in HDL-C.[37] Lipid metabolism is widely explored including both traditional and novel biomarkers associated with CVD risk.

IUGR neonates appeared with higher levels of triglycerides and oxidized low-density lipoproteins (LDLs), molecules that associate with IR and atherogenesis.[27,32] Triglyceride concentrations were elevated in umbilical cord and in all lipoprotein fractions in SGA infants. Similarly, SGA infants appeared with low levels of HDL-C in total cholesterol. A similar altered lipid profile was demonstrated among South Asian neonates. Furthermore, LDL, very-low-density lipoprotein (VLDL), and HDL_3 from SGA neonates were enriched with triglycerides, same as the characteristics of patients with diabetes and metabolic syndrome and could be indicative of systemic inflammation and CVD. LDL from the SGA group presented higher sensitivity to oxidation and was easily taken up into macrophages, suggesting stronger proatherosclerotic properties. HDL-C from SGA neonates appeared dysfunctional with lower expression of anti-inflammatory apoA-I and increased

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expression of apoC-III. In summary, cord samples of SGA neonates presented atherogenic lipid profiles and impaired lipoprotein characteristics.[24,26,38] Other studies demonstrated the presence of large HDL-C subclasses enriched in apo-C-I in cord blood. These molecules appeared elevated in infants with lower birth weights and younger gestational ages and with significantly elevated total and large LDL cholesterol and LDL particle number, but lower total and VLDL triglycerides in contrast with SGA neonates.[38] Additionally, infants with a greater positive change in BMI z-score in the first 6 months presented a high proportion of saturated and low proportion of polyunsaturated plasma fatty acids (PUFA) at birth. Also, a tendency for a lower proportion of n-3 long-chain (LCPUFA) in infants with greater BMI z-score changes in the first 6 months was noticed. Thus, there is an indication that low levels of LCPUFA at birth correlate with a higher risk of obesity in later life.[39] Also differences appeared in lipids among term and preterm such as significantly higher total cholesterol, LDL, and various atherogenic indexes while no gender-based differences are reported.[40] Altered lipid profile was noticed in infants of GDM pregnancies, including significantly higher triglyceride and cholesterol levels and significantly lower HDL-C values. Alterations of neonatal HDL-C proteome associated with GDM, are accompanied by impaired cholesterol efflux capability and a trend to impaired anti-oxidative function. No sex differences were noticed in the HDL proteome. In the GDM group, HDL-C was also enriched with serum amyloid A1 protein and with apoE, while α-1-antitrypsin and atheroprotective apoM were reduced. Neonatal HDL–triglyceride levels were slightly increased, and a higher proportion of larger HDL-C molecules was noticed.[23,41] Altered lipid profiles were also present in newborns from preeclamptic pregnancies, with significantly higher LDL-C levels.[29] Even though in newborns with a family history of premature coronary artery disease no differences arose in terms of lipid metabolism in the age of 18-30 months, such children showed higher triglycerides, VLDL, and Lipoprotein(a). The same study also demonstrated gender-based differences including higher TC, LDL-C, HDL-C, and Apo A1 levels in female newborns.[28] Ultimately, data suggest a nonsignificant trend toward a proatherogenic lipid profile in chorioamnionitis-exposed infants. Such observations may indicate future cardiometabolic risk for infants exposed to inflammation in utero.[21]

Protein convertase subtilisin/Kexin type-9

Protein convertase subtilisin/Kexin type-9 (PCSK9) plays a key role in lipoprotein metabolism. It is a targeted CVD biomarker in adults. It appeared as an independent predictor of LDL concentrations in IUGR and controls.[42,43] PCSK9 levels in IUGR were 35% lower than in the control group. This persisted when subgrouping into early and late-onset IUGR. Furthermore, LDL receptor was significantly upregulated in IUGR. Gender wise, highest PCSK9 levels presented in control males born before 34 weeks of gestation.[42] Further data showed that PCSK9 levels of female infants were significantly higher than in males and they correlated with TC and LDL-C. These indicate that PCSK9 is an important regulator of LDL through fetal life. PCSK9 levels were found significantly lower in male SGA neonates than in male AGA, while PCSK9 levels between SGA and AGA female infants presented with no significant differences. Also, male SGA infants presented the lowest serum LDL-C values, among the four studied groups, suggesting a possible influence of PCSK9 on LDL levels concerning these populations. The evidence regarding the relationship between serum PCSK9 levels at birth and the development of dyslipidemia during adulthood is sparse and thus further research is required to assess the predictive power and clinical relevance of this upcoming CVD risk biomarker.[43]

Biomarkers of myocardial function

Troponins (Tns)

Three subunit proteins (troponin C, I, and T) are involved in the actin–myosin interaction in muscle cells. Tns are increased in several forms of cardiomyopathy, such as hypertrophic cardiomyopathy or left ventricular hypertrophy.[44] High-sensitive TnI (hsTnI) and hsTnT follow a similar pattern reaching a peak during the first month of life, with a fast decrease during the first six months and a slow-paced decrease until achieving a plateau at adolescence.[45]

Troponin I (TnI)

TnI is a biomarker of myocardial injury (Table 2). HsTnI, presented with no differences among maternal and fetal levels and there was an independent regulation of hsTnI between mother and fetus.[44] Yet, Cardiac TnI (cTnI) was found significantly elevated in IDMs. In fact, IDMs group with respiratory distress had significantly higher levels of cTnI. CTnI also correlated positively with interventricular septum thickness, intraventricular dimensions, and posterior wall diameter in IDMs. No sex-based differences are reported for cTnI.[46] Further data demonstrate higher levels of cTnI, in term IUGR and SGA fetuses, that presented with echocardiographic signs of systolic and diastolic dysfunction with increased myocardial performance index (MPI) and decreased mitral annular plane systolic excursion.[30]

Also, preeclamptic and/or fetal growth-restricted pregnancies presented with indications of fetal cardiac remodeling and cardiac dysfunction manifested by increased MPI and cord TnI concentrations.[47] Thus, cTnI constitutes a valuable predictor of hypertrophic cardiomyopathy and/or left ventricular dysfunction.[46]

Troponin T (TnT)

Serum cardiac troponin T (cTnT) is considered as a good marker of myocardial injury in conditions such as perinatal asphyxia. CTnT levels are higher in premature infants with respiratory distress syndrome, in macrosomic infants, and infants from pregnancies with GDM and pregestational DM I, II.[48,49] At the same time, cTnT levels presented an inverse correlation between cTnT and echocardiographic markers of myocardial function and stroke volume. No gender-based influences were noticed.[48] Elevated cTnT values were found in fetuses with a reversed end-diastolic flow (AREDV) in the umbilical artery. AREDV in the umbilical arteries and ductus venosus pulsatility index for veins were characterized as independent variables associated with abnormal cTnT levels. Severe cardiac compromise, with increased systemic venous pressure, and a rise in right ventricular afterload in the cases of the third group are demonstrated by myocardial damage and elevated fetal cTnT.[50] A possible diagnostic value of cTnT in young children with suspected myocardial injury is supported by studies that pointed out neonatal high levels of cTnT in accordance with congestive heart failure[51] (Table 2).

Natriuretic peptides

BNP, NTpBNP. Brain natriuretic peptide (BNP) and biologically inactive n-terminal pro brain natriuretic peptide (NTpBNP) are structurally related. They are released by the stressed myocardium in response to volume and pressure loading.[22] In a group of full-term AGA neonates, NTproBNP presented a peak in the first 24

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Table 2. CVD biomarkers of myocardial function

Biomarkers*	Study population	Result	Reference values
Cardiac TnI[44]	IUGR, SGA, maternal DM, Pre-eclampsia	↑ infants of diabetic mothers with respiratory distress ↑ IUGR, SGA with US signs of myocardial damage ↑ Pre-eclampsia and/or fetal growth restriction	2.15–31.72 pg/ml84 (5th–95th percentile)
Cardiac TnT[48-51]	Preterm Infants, Macrosomic infants, Infants with signs of myocardial damage	↑ prematurity and respiratory distress ↑ in macrosomic infants from GDM or DM I, II ↑ in infants with signs of myocardial damage	0.018–0.097 μg/l[85] (75^{th} –99^{th} percentile)
BNP, NTpBNP[22,30,44,47-49]	IUGR, Pre-eclampsia, Respiratory distress	↑ in IUGR with signs of cardiac dysfunction ↑ Pre-eclampsia with fetal growth restriction NTpBNP ↑ in respiratory distress, macrosomic and/or from diabetic mothers	BNP: 10–76.85 pg/ml[84] (5^{th}–95^{th} percentile) NTproBNP: 369.62–2233.15 pg/ml[84] (5^{th}–95^{th} percentile)

TnI; Troponin I, IUGR; intrauterine growth restriction, SGA; small for gestation, DM; diabetes mellites, US; ultrasound, TnT; Troponin T, GDM; gestational diabetes mellites, BNP; brain natriuretic peptide, NTpBNP; N terminal pro BNP.
*References on biomarker's correspond to the findings of the included studies.

hours postpartum.[52] They presented an inverse association with gestational age, and they were significantly higher in IUGR fetuses with early signs of impaired cardiac function.[22] Also, a significant correlation with uterine artery mean performance index z-score, arterial cord pH, and an adverse perinatal outcome was present. BNP levels have shown a progressive increase across severity groups with a significant increase in IUGR cases.[22,30,44] They were also found raised among cases of IUGR and preeclampsia as well.[47] NTpBNP concentrations presented higher among infants with respiratory distress, macrosomic infants, or IDMs. Also, NTpBNP correlated significantly with left atrial to aortic root ratio, indicating its value as a marker of ventricular volume loading.[48,49] Therefore, these molecules could have a role in effective screening in circumstances where echocardiography means are limited (Table 2).

Additional markers of myocardial function. Heart fatty acid-binding protein (H-FABP) is a novel biochemical marker with a high sensitivity to detect myocardial cell damage. H-FABP concentrations were significantly higher in IUGR fetuses at stage 3 together with a significant linear increment across severity stages.[22] Other biomarkers such as Midregional pro-adrenomedullin (MRproADM), mid regional-pro atrial natriuretic peptide (MRproANP), and copeptin, Fetal MRproANP was inversely correlated with gestational age, possibly as a physiological response to the requirements during the progress of the pregnancy. Fetal copeptin was increased in association to labor, and fetal MRproADM was not affected by GA.[44]

Additional potential markers of CVD

Vitamin D

Interestingly, there is a possible relationship between insufficient vitamin D concentrations and the pathogenesis of early atherosclerotic CVD.[53,54] 25-dihydroxy vitamin D (25OHD) concentrations range from 17 to 34 ng/ml.[55] 25OHD levels in cord blood and are inversely associated with childhood systolic and diastolic blood pressure. Additionally, neonates with sufficient levels of 25OHD had a significantly lower aIMT than the other 25OHD deficiency groups, suggesting that vitamin D deficiency may induce atherosclerotic changes in vascular structure in term healthy infants.[53,54] These formulate a possible protective role of this molecule against CVD risk.

Other potential CVD biomarkers

Placental 11b-hydroxysteroid dehydrogenase 2 (11b-HSD2) has been negatively correlated with HOMA-IR and fasting insulin and presented a negative association with SBP in one year of age. At the same age, cord cortisol presented a single negative correlation with skinfold thickness which could positively contribute to metabolic health in postnatal life. Cord cortisol and 11b-HSD2 values were unaffected from male or female sex.[56] Further data revealed higher Osteoprotegerin and lower Receptor activator of nuclear factor kappa-B ligand levels in newborns of pre-eclamptic pregnancies. Preeclampsia appeared as an important determinant of osteoprotegerin levels and an independent predictor of increased neonatal blood pressure. Osteoprotegerin levels were also significantly associated with increased diastolic blood pressure.[57] Concerning serum minerals, neonates within the highest quartile for Mg displayed higher levels of LDL and homocysteine. Newborns with a high Ca/Mg ratio showed low levels of insulin.[58] Urinary proteomics revealed that among the most abundant proteins in preterm were retinol-binding protein, plasma protease C1 inhibitor, antithrombin-III, and angiotensinogen. These upregulated elements are suggestive of higher CVD risk.[59] Prematurity was also associated with hypoproteinemia mediated impaired cardiovascular function and an "anti-angiogenic" status established by the downregulation of proangiogenic factors, angio-MiRs (inter alia MiR-125, MiR-126, MiR-145, MiR-150, or MiR155) and the upregulation of angiostatic factors endostatin and thrombospondin-2.[60,61] Serum proteomics have shown that the state of IUGR alters the expression of proteins such as lysophospholipid acyltransferase MBOAT7, serotransferrins, apolipoprotein E, apolipoprotein A-I, SERPIN1, with a known contribution to CVD pathways such as apoptosis, diabetes, dyslipidemia, inflammation, and arterial hypertension.[62] Concerning IUGR, renin, and angiotensin I levels were significantly elevated as well as systolic blood pressure and prolonged mean left ventricular isovolumic relaxation time.[63] Concerning the peptidome profile of fetal GDM-induced macrosomia, various upregulated peptides play a key role in the regulation of lipids.[64] Downregulation of BCL2 genes and miR-181a molecules with a role in obesity, anti-inflammatory, and antioxidant pathways in infants of GDM

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pregnancies could pose as potential biomarkers for childhood obesity.[65] Further findings suggest an upregulated expression of the cardiac biomarkers cardiotrophin 1 and titin in LGA infants and especially in the GDM subgroup.[66] Ultimately oxidant/antioxidant balance is disturbed in favor of oxidants in IDMs presenting with significantly higher total antioxidant capacity, total oxidant status, and oxidative stress index. The extent of oxidative stress is directly associated to the severity of myocardial and hematological involvement in IDMs in the first days of life.[67]

Pregnancy conditions impact CVD biomarkers

As for the maternal compartment during pregnancy, preeclampsia and GDM seem to significantly affect CVD biomarkers of the neonate and the cardiovascular health of the offspring in later life. Preeclampsia can lead to prematurity and growth restriction, conditions already associated with CVD and has been associated with hypertension in adolescence.[68,69] The CVD effects of preeclamptic pregnancies on the neonate are further supported by metabolomics which reveal alterations in molecules involved in kidney function, in the metabolism of lipids and in vascular health. These include molecules such as creatinine, uric acid, N4-acetylcytidine, pseudouridine, carnitine, and sphingolipid metabolism, respectively.[70] Offspring of GDM pregnancies display deviant triglyceride and lipoprotein constituents and a possible predisposition for obesity as well as increased cord VEGF levels indicative of altered development of the vascular system.[71,72] SGA infants of GDM pregnancies presented increased levels of LDL-C, growth hormone, and fibrinogen and decreased levels of HDL-C and ApoA suggesting diminished antioxidative particle properties and a proneness of developing IR in the future.[73] IDMs have also showed greater intraventricular dimensions, thickening of the right ventricular wall, and impaired systolic and diastolic function of the myocardium even in cases with good glycemic control.[74,75]

Biomarkers' contribution on CVD

Appreciating the concept of a potential CVD biomarker, especially in the neonatal period, requires understanding of its role to CVD as a molecule. Adipokine imbalance affects lipid and glucose metabolism, satiety, inflammation, vascular health, and blood pressure.[2,7] Adiponectin has anti-inflammatory and insulin-sensitizing properties, and leptin affects energy balance, adiposity accumulation, and appetite, acting in the level of hypothalamus.[10,11,76] Inflammation affects the atherosclerotic process. CRP relates with complement binding, increase of adhesion molecules and thrombotic factors, and decrease of vasodilating molecules. Data also indicate a possible association of the intrauterine inflammatory status with sympathetic system hyperactivity and stress response in childhood.[7,20] IL-6 and TNF-a derive from adipose tissue, stimulating CRP production from the liver. TNF-a stimulates the production of molecules such as ICAM-1 that favor the adhesion of leucocytes to the endothelium, promoting atherosclerosis.[7] Homocysteine exerts several toxic effects, including injury on the vascular endothelial cells. The fetal endothelium may be more vulnerable; therefore, moderate increase of tHcys could lead to endothelial damage.[29,30] Vitamin D benefits vascular homeostasis by attenuating oxidative stress and vasoconstriction.[54] A possible association of Vitamin D with β-cell function and IR is being investigated.[77] Dysregulation of adiposity and oxidative stress promote IR. IR stimulates vascular pathology through various biochemical pathways, thrombotic factors, mitogenesis, and the release of molecules such as endothelin-1, and platelet-derived growth factor.[7] Hyperglycemia promotes the production of reactive oxygen species, and glycation products and attenuates the vasodilating properties of insulin mediating endothelial damage.[23] Lipid imbalance can result in a continuous inflammatory process of the vascular wall in accordance with altered immune response and genetic factors, leading to CVD.[2] PCSK9 mediates the increase of circulating LDL through promoting the degradation of the LDL receptor in hepatocytes. Troponins restrain the ATPase activity of actomyosin, leading to muscle relaxation. They increase in heart conditions following insufficient oxygen or blood supply to the heart muscle.[44] BNP derives from the ventricles increasing in response to volume overload, hypoxia, and subclinical diastolic dysfunction.[22] These infantile aberrations possibly include atherosclerotic and cardiovascular consequences in the future.

Reaching clinical relevance

Even though the number of molecules associated to the various aspects of CVD is very wide, very few have reached everyday clinical practice regarding the neonatal population. Optimization of cardiovascular health in younger ages requires better understanding of the role and the pathophysiological mechanisms of each possible biomarker, as in this age spectrum CVD is subclinical and our current diagnostic methods are not able to detect it. Some biomarkers are studied more frequently in terms of biological function leaving the field for novel ones quite unexplored. Thus, the need for longitudinal rather than for cross-sectional assessment is well appreciated. Biomarkers should be assessed early and repeatedly and should be linked to future already calibrated risk factors and characteristics of CVD. Those parameters should provide clinical utility. In this frame, establishment of age and gender-based reference values for each biomarker becomes essential. Very few biomarkers were identified with established percentile or reference ranges and are reported in Tables 1 and 2. From the studied literature, not all studies investigated the influence of gender on the biomarkers. Further research on this field in the future would support the tendency of a more personalized approach of health and disease. However, due to the limited data available in the neonatal population, and the long-term nature of the follow-up needed, the cost–benefit ratio and safety parameters become primary considerations. Therefore, for most of the biomarkers studied in this population, the transition from laboratory or clinical research to everyday clinical practice poses a considerable challenge.

Conclusions

Further research is carried out in order to investigate these pathophysiological processes, risk factors, and biomarkers, which contribute to different aspects of CVD and have the potential to aid in its prediction, identification, and assessment. Crucial seems the role of adiposity imbalance with adiponectin and leptin contributing to IR, body composition, lipid profile, and obesity. Also, inflammation seems a strong mediator of CVD, associated with prematurity, and birth weight. It can lead to CVD through different pathways such as sympathetic system hyperactivity and stress response during childhood, impaired vascular health, vasoconstriction, IR, and adiposity. Altered lipid metabolism can lead to a chronic inflammatory process of the arterial wall and seems to correlate with fetal growth, birth weight, body composition, and maternal metabolic characteristics. Female sex appears to associate with a more atheroprotective cardiometabolic profile. However,

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more research is needed for the establishment of the possible gender specificity of the fetal and neonatal cardiometabolic environment or the possible benefits of gender-specific approaches on treatments in the future. Gestational age, GDM, preeclampsia, and fetal growth seem to also affect parameters of myocardial function that could serve as early estimates of myocardial health. Considering the long-term CVD risk assessment, plenty of novel biomarkers are being studied and new methods such as proteomics or genomics are being introduced enabling biomedical community to customize preventive practices according to the relative risk for CVD.

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