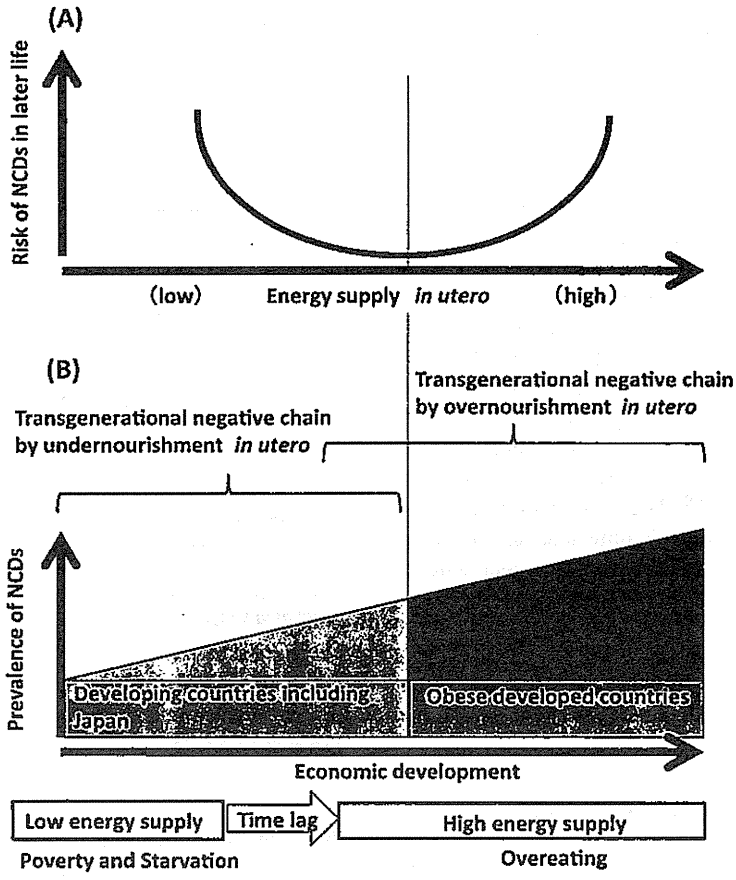

Figure 2. Energy supply *in utero* and the risk of NCDs in later life (A). The prevalence of NCDs in both developing and developed countries may be associated with differences in energy supply *in utero* (B).

elderly Japanese populations argues against the simple and major contribution of a Western lifestyle with a calorie-rich diet in favor of a presumed increase in the number of individuals with the '*thrifty phenotype*' due to undernourishment *in utero*. Kubota et al.[36] reported that the mean energy intake in Japanese pregnant women was less than 1,600 kilocalories/day throughout pregnancy, which corresponds to 30% (second trimester) and 37% (third trimester) fewer calories than what is recommended by the Ministry of Health, Labour and Welfare Japan (Figure 3). This suggests that considerable numbers of relatively undernourished Japanese fetuses exist due to a shortage in maternal energy intake. This distinct nutritional imbalance in Japanese pregnant women may have led to the '*thrifty phenotype*' in a large number of Japanese people, contributing, at least partly, to the development of obesity and or type 2 diabetes with less caloric intake.[35] Therefore, the nutritional conditions of Japanese fetuses are distinct from those in other developed countries, in which fetuses are typically supplied with excess energy from their mothers.

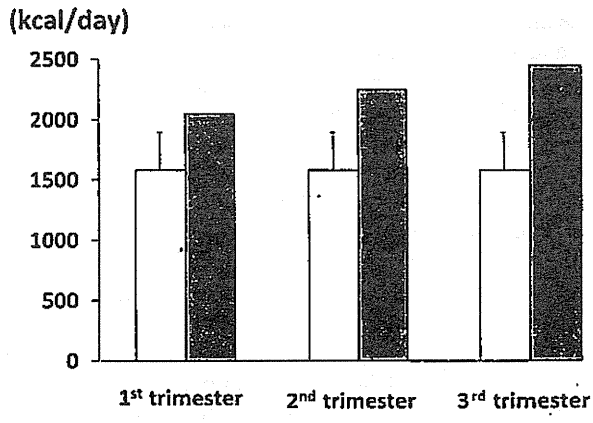

Figure 3. Mean energy intake of Japanese pregnant women in Hamamatsu city (white bars) and recommended energy intake by the Health, Labour and Welfare Ministry of Japan (gray bars).[36]
Error bars indicate standard deviations.

'Hypothalamic-adipose (HA) axis' hypothesis concerning 'thrifty phenotype'

The mechanisms underlying the '*thrifty phenotype*' have not yet been elucidated in detail; however, large numbers of animal models have provided evidence to support its involvement in calorie-rich countries.[37,38] Hales and Barker proposed that the permanently reduced secretion of insulin from pancreatic β-cells is critically involved in the development of an adult '*thrifty phenotype*' concomitant with insulin resistance.[24] Newsome et al.[39] conclusively proposed a relationship between low birth weight and disorders in glucose and insulin metabolism in adulthood by a systematic review of the literature. However, the early-programmed reduced secretion of insulin does not coincide with the initial induction of obesity in later life because adipocytes require an appropriate amount of insulin to store lipids. Therefore, the fetal insulin hypothesis cannot fully explain the primary risk of obesity proposed by the '*thrifty phenotype*' hypothesis.

Since the '*mismatch*' of the '*thrifty phenotype*' with an abundant energy supply may result in excess energy storage in the body, reasonably in adipose tissue, it is plausible that obesity is the most acceptable outcome of exposing '*thrifty phenotype*' offspring to a calorie-rich diet. Moreover, obesity is a major risk factor for NCDs.[40] Therefore, in this review, we focused on the developmental origins of obesity in relation to the '*thrifty phenotype*', particularly in the context of the central regulation of energy metabolism, and introduced our '*hypothalamic-adipose (HA) axis*' hypothesis as a candidate mechanism for explaining the acquisition of the '*thrifty phenotype*'.

Obesity is closely associated with the regulation of food intake and energy expenditure, which are centrally regulated by the hypothalamus, the control center for energy metabolism. The adipocyte-derived hormone, leptin, is known to affect the hypothalamus, leading to a decrease in food intake and increase in energy expenditure.[41,42] Disruptions in the production and circulating levels of leptin have been shown to play an important role in the development of metabolic syndrome in adulthood.[41] Evidence obtained in animal studies supported undernourishment *in utero* causing low hypothalamic sensitivity to circulating leptin, thereby linking undernourishment *in utero* to the risk of obesity in later life.[43] Moreover, maternal caloric restriction did not exacerbate obesity in leptin-deficient *ob/ob* mice, suggesting that leptin is a key factor in the developmental origins of obesity.[44] We previously revealed that undernourishment *in utero* resulted in blunted responses in food intake by and lower body weights in adult mice treated with leptin, concomitant with low signal transduction responses in the hypothalamus, relative to normally nourished controls.[45] We also showed that chemical damage to the arcuate nucleus (ARC) of the hypothalamus canceled out the accelerated development of obesity in adult mouse offspring that were undernourished *in utero*.[45] Since the ARC, which centrally regulates energy expenditure,[46] has been proposed to be the main target of leptin, permanent changes in hypothalamic responsiveness to circulating leptin appear to be the main regulatory system in the developmental risk of adult obesity, at least in our mouse animal model of undernourishment *in utero*.

Serum leptin levels markedly increase in normal mouse neonates during the lactation period, and this is referred to as the '*leptin surge*'[47] (Figure 4A). However, previous studies reported that leptin did not affect feeding or thermogenesis in neonatal mice[48] or rats.[49] Bouret et al.[50] reported that the neurotrophic action of leptin in the mouse hypothalamus only operated during the neonatal period. We[44,45] and others[51,52] proposed that undernourishment *in utero* changed the timing and/or plasma levels of leptin in the '*leptin surge*' during the period of lactation and modified the development of neuronal circuitries in the hypothalamus, resulting in permanently low hypothalamic responses to circulating leptin and thereby increasing the risk of obesity (Figure 4B). However, changes in the '*leptin surge*' during the neonatal period and its permanent effects on adulthood

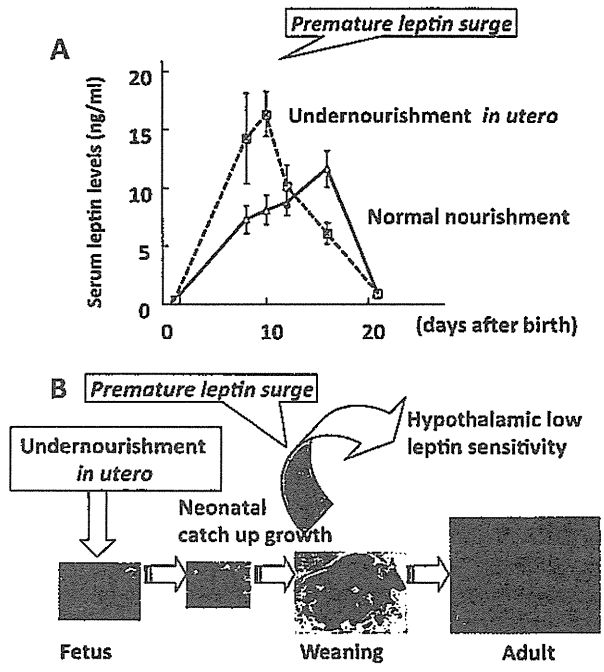

Figure 4. The *'Hypothalamic-adipose (HA) axis'* hypothesis as a possible mechanism underlying acquisition of the *'thrifty phenotype'*.[32,45]

remain controversial. We previously demonstrated that a 30% restriction in maternal caloric intake (70% of *ad libitum* intake) in the latter half of pregnancy caused earlier and greater deviations in the '*leptin surge*' in neonates, which we described as a '*premature leptin surge*'[45] (Figure 4A). To examine the relationship between the '*premature leptin surge*' and the risk of adult obesity, we administrated leptin to normally-nourished male mice aged 5 to 10 days and found that these pups subsequently developed a similar obesity-prone phenotype and low hypothalamic sensitivity to leptin as pups undernourished *in utero*, concomitant with similar changes in the development of neuronal circuitries in the hypothalamus.[45] These findings suggested a distinct role for the '*premature leptin surge*' as a programming signal from adipose tissue to the hypothalamus. De Moura et al.[52] also reported that the treatment of neonatal rats with leptin, either from 0 to 10 days of age or in the last 10 days of the lactation period, led to obesity and high leptin concentrations in later life.

On the other hand, Delahaye et al.[51] reported that a 50% restriction in caloric intake by rats from pregnancy to the lactation period markedly decreased the '*leptin surge*'. Vickers et al.[53] administered leptin to rat neonates from 3 to 10 days and found no phenotypic changes in normally nourished pups, but protection against obesity in pups undernourished *in utero*. To the best of our knowledge, there is currently no clear explanation for this discrepancy and we speculate the presence of multifactorial '*critical windows*' in exposure of the hypothalamus to the '*leptin surge*' during the lactation period with respect to timing, duration, dosage of the leptin treatment in each experimental protocol, gender differences, and species differences even between rats and mice. Nevertheless, changes in plasma leptin concentrations during the lactation period induced by fetal undernourishment, although still contentious, appear to be a key modulator of permanent hypothalamic energy regulation, leading to the development of the obesity-prone adult phenotype. Based on our findings, we proposed the important contribution of the '*HA axis*' hypothesis to the developmental origins of obesity (Figure 4B).

'Hypothalamic-pituitary-adrenal (HPA) axis' hypothesis and NCDs

The hypothalamus is not only the center of energy metabolism, but also a central regulator of stress responses that down-regulate the secretion of glucocorticoids from the adrenal glands, i.e., the hypothalamic-pituitary-adrenal (HPA) axis. A shift to an elevated stress response has been closely linked with the risk of NCDs.[54–57] The findings of previous clinical and molecular studies

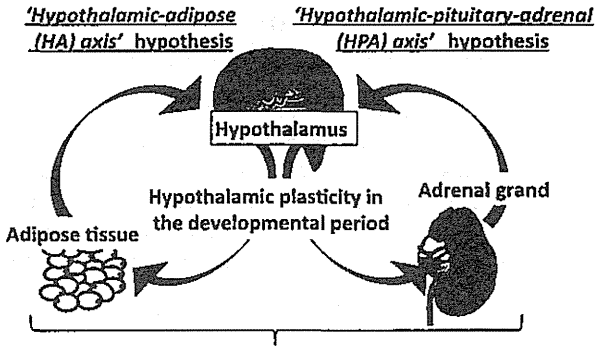

Figure 5. Hypothalamic plasticity in early life and developmental risk of NCDs in later life.[32]

demonstrated that elevated levels of adrenal hormones caused the accumulation of fat in visceral adipose tissues as well as associated metabolic abnormalities.[58,59] Human and animal studies indicated that prenatal stress caused the permanent hyper-reactivity of the HPA axis to be causatively associated with an elevated risk of NCDs; namely, the '*HPA axis*' hypothesis[60–68] (Figure 5).

Morphological and functional hypothalamic plasticity during the early developmental period has been suggested to play a key role in the '*HPA axis*' and '*HA axis*' hypotheses (Figure 5); therefore, the hypothalamus appears to be a promising target organ in the search for new early interventions that will reduce the prevalence of NCDs.

Accumulation of NCD risk by 'catch-up growth'

A systematic review revealed that small babies were more predisposed to adult obesity if they showed rapid '*catch-up growth*' soon after birth[69] (Figure 1). Regarding the critical period of '*catch-up growth*', previous studies suggested the possible importance of the first few weeks of postnatal life[70,71] or the period until two years of age;[69] whereas others showed that low birth weight children who grew excessively in later childhood were also at a higher risk of adult obesity.[21,72] Botton et al.[73] showed that neonates with a faster weight gain velocity during the first three months showed a greater weight gain velocity after three years of age, leading to a larger fat mass in adolescence (Figure 6). These findings suggested that the interaction between prenatal low energy supply and subsequent rapid '*catch up growth*' soon after birth, presumably being equal to a rapid encounter with a postnatal high-energy supply, appeared to increase the risk of obesity and its associated metabolic disorders[31,38,74–76] (Figure 1).

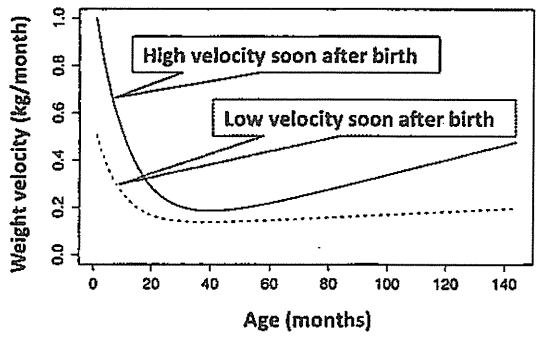

Figure 6. Predicted transition of weight growth velocity (modified from the figure by Botton et al.)[73]

'Catch-up-related adipose tissue remodeling' hypothesis concerning accumulation of NCD risk by 'catch-up growth'

To the best of our knowledge, a consensus has not yet been reached regarding how '*catch-up growth*' soon after birth increases the risk of adult obesity caused by undernourishment *in utero*, or how it permanently modulates the metabolic characteristics of the '*thrifty phenotype*' acquired by undernourishment *in utero*. We recently focused on the possible involvement of adipose tissue remodeling in the aggravation of obesity-related metabolic disorders by '*catch-up growth*' during the lactation period.

The fat body of drosophila evolved into three different organs, i.e., adipose tissue, liver, and blood cells of mammals, over a period of 60 million years, during which the reciprocal regulation of their functions developed.[77] Recent studies identified various changes in the intercellular spaces between ballooning adipocytes due to increased lipid storage, particularly those associated with the chronic infiltration of immune competent cells, especially inflammatory macrophages, leading to the concomitant impairment of glucose and/or lipid metabolism.[78–80] We recently developed a mouse animal model of undernourishment *in utero* by maternal caloric restriction, in which the rate of '*catch-up growth*' during the lactation period positively correlated with

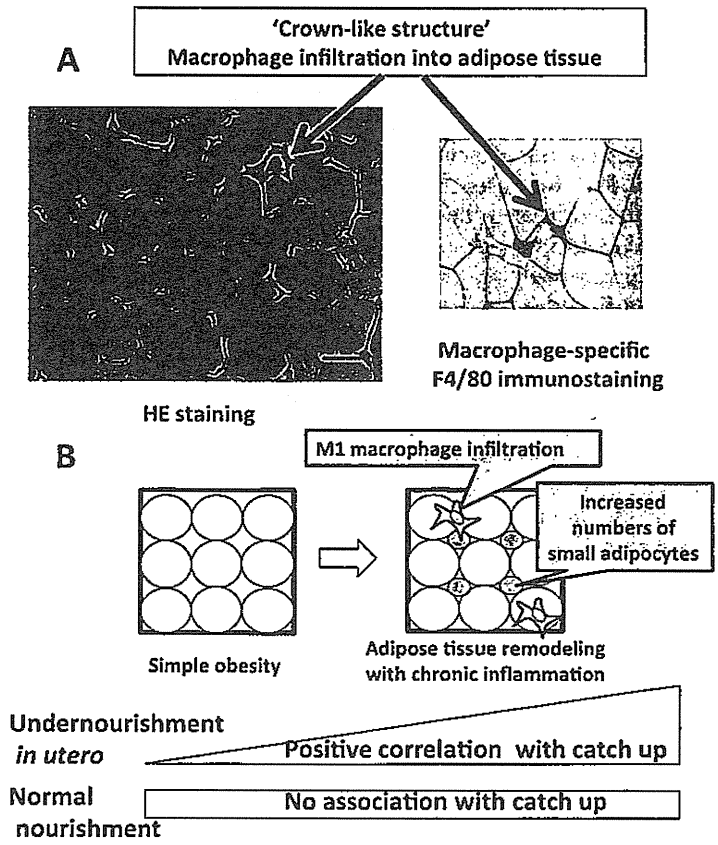

Figure 7. '*Catch-up-related adipose tissue remodeling*' hypothesis for increased risk of obesity and associated metabolic disorders by '*catch-up growth*'.[81,84]

body weight gain, fat mass gain, and blood glucose levels under a high fat diet.[81] Using this animal model, we demonstrated that the rate of '*catch-up growth*' after undernourishment *in utero* positively correlated with the infiltration of M1 macrophages (Figure 7A) as well as the expression of inflammatory cytokines in adult adipose tissue collected from mice on a high fat diet.[81] These findings indicated that rapid growth during the lactation period, attributed to a rich-energy supply following low-energy supply *in utero*, appeared to induce chronic inflammation in adult adipose tissue[81] (Figure 7A, B). Fetal undernourishment also increased the number of not only large, but also small ballooning adipocytes in adult adipose tissue obtained from mice on a high fat diet.[81] Nishimura et al.[82] proposed that small adipocytes, which are adipogenic/angiogenic cell clusters including adipocyte precursor cells, play a major role in adipocyte hyperplasia, and are prominent during the development of obesity; therefore, the concept of '*adipose tissue remodeling*' was proposed as a critical pathological mechanism underlying the exacerbation of obesity itself and its related metabolic disorders.[79,83] We previously reported that the rate of '*catch-up growth*' during the lactation period positively correlated with the relative rate of small adipocytes in adult adipose tissue collected from animals on a high fat diet,[81] suggesting that '*catch-up growth*' induced '*adipose tissue remodeling*' (Figure 7B). These findings indicated that a sudden change in nutritional conditions from a low energy supply *in utero* to a calorie-rich neonatal life, leading to '*catch-up growth*', is a key phenomenon exaggerating '*adipose tissue remodeling*' based on chronic inflammation in later life (Figure 7B). Therefore, we proposed the '*catch-up-related adipose tissue remodeling*' hypothesis[84] as a potential mechanism for the risk accumulation of NCDs by '*catch-up growth*'.

Overnourishment in utero and risk of NCDs in later life

The incidence of obesity has increased in developed countries, especially in North America, over the past several decades due to the oversupply of nutrients relative to the amount required for normal metabolism. This increase can be largely attributed to lifestyle patterns such as the excess consumption of energy-rich meals and decline in physical activity. However, an alternative explanation has been proposed for the increasing rates of obesity, i.e., a transgenerational negative chain of overnourishment *in utero* and/or the postnatal period (Figure 2). The DOHaD theory states that infants subjected to an early environment that is over-rich in nutrients are predisposed to obesity in later life (Figure 2).

Fetal exposure to diabetes or gestational diabetes during pregnancy has been reported to increase the risk of childhood and adult obesity, diabetes, metabolic syndrome, and cardiovascular diseases.[85,86] In a cohort study involving the Pima Indians, the majority of whom develop type 2 diabetes during childhood due to genetic causes, the risk of type 2 diabetes and obesity was higher in the fetuses of diabetic mothers.[87] Previous studies identified a relationship between maternal obesity and excessive weight gain during pregnancy and large-for-gestational-age infants.[88–91] Furthermore, the risk of childhood and adolescent obesity was found to be higher in these large-for-gestational-age infants.[88,91,92] Salsberry et al.[93] showed that maternal pre-pregnancy obesity was a significant risk factor for overweight adolescent offspring. Human and animal studies revealed that a high intrauterine energy supply consistently elevated the risk of NCDs in later life.[94–96] In developed countries, especially those in which obesity appears to be prevalent, the transgenerational risk of early exposure to an excess energy supply in the intrauterine environment has been proposed to play a crucial role in increasing the risk of NCDs in addition to overeating and reduced physical activity. Although mankind battled against starvation for millions of years, those in developed countries need to adapt to a continuous environment of satiation throughout life from *in utero*.

Since undernourishment *in utero* is also a risk factor for NCDs in later life, a 'U-shaped' curve was proposed for the relationship between nutritional conditions *in utero* and the risk of developing adult NCDs[3,25,26,31,38,97,98] (Figure 2). The rate of increase in the number of NCD patients in developing countries is markedly higher than that in developed countries;[3,98] therefore, overnourishment after birth may be a stronger risk factor for the development of adult NCDs in neonates undernourished *in utero* than the continuous exposure to overnourishment over the entire course of life, including the fetal period.

Candidates for early interventions in perinatal medicine

The core concepts of preemptive medicine are the early identification of high-risk individuals and early interventions specific to the risk background.[8,9,99] Although evidence for the preventive efficacy of early interventions against the continuing prevalence of NCDs as well as medical economic cost performance is limited, we proposed the following candidates as targets for early interventions in perinatal medicine (Figure 8). Nutritional interventions for lean and obese pregnant women, if effective, represent the most promising strategy[100,101] (Figure 8) due to the high

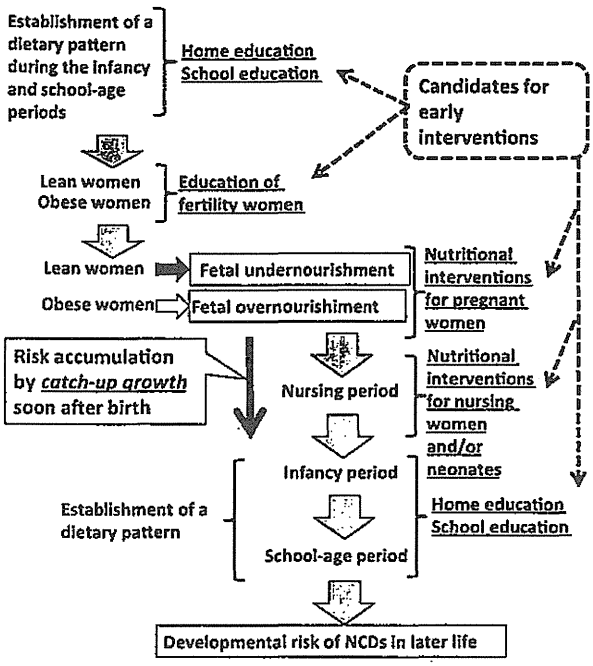

Figure 8. Candidates for early interventions in preemptive medicine from the standpoint of perinatal care.

risk of undernourishment and overnourishment *in utero*, respectively. Educational interventions concerning nutritional aspects for fertile women, including information on the transgenerational negative chain according to the DOHaD theory,[3,25,26,31,38,97,98] before conception may effectively reduce the incidence of lean and obese pregnant women (Figure 8). Considering the establishment of dietary patterns during infancy and school-age periods, and preparing and conducting home and school educational programs on lifestyle based on scientific evidence, especially lifelong benefits, while also taking into consideration the next generation, will be constructive (Figure 8).

Since '*catch-up growth*' has been reported to increase the risk of adult NCDs,[21,31,38,69–76] nutritional interventions for nursing women and/or neonates may be another target for early interventions (Figure 8). However, Houk et al.[102] demonstrated that children born small for gestational age without '*catch-up growth*' were at high risk of short stature in adulthood and should be referred for growth hormone treatment. Therefore, deciding the neonatal and infantile optimal growth patterns in view of differing genetic and epigenetic backgrounds due to environmental factors for the purpose of improving lifelong outcomes is difficult. Furthermore, establishing standard methods to achieve optimal growth in neonates and/or infants is challenging because numerous factors, including various unidentified ones, may be involved in their growth patterns. It is also important to respect the natural wishes of mothers to have normal children, especially if they were born small. The development of home and school educational programs concerning the importance of improving the lifestyles of children who experience '*catch-up growth*' would be beneficial (Figure 8).

Candidate biological samples for identifying biomarkers in perinatal medicine

The final goal of preemptive medicine is to delay or prevent the onset of NCDs by identifying high-risk individuals in early life and implementing early interventions specific to their risk types.[8,9,99] Barker et al.[103] first proposed that low birth weight newborns (i.e., those weighing less than 2,500 g) were at high risk of developing cardiovascular diseases in later life. According to the 'U-shaped' curve observation[3,25,26,31,38,97,98] (Figure 2), macrosomia is also a risk factor for NCDs.[104] The rates of low birth weight and macrosomia in Japan were reported to be 9.6% and 0.5%, respectively.[105] In contrast, the rate of macrosomia in the United States was 10%.[106] Thus, birth weight varies greatly by region and historical transition. Furthermore, because of the considerable contribution of genetic background and other factors, such as preterm deliveries, multiple pregnancies, maternal complications, fetal complications, and placental deficiencies, small and large babies are not always solely the result of undernourishment and overnourishment *in utero*, respectively. Therefore, the simple assessment of birth weight is not sufficiently specific for clear identification of high-risk individuals.

Substantial efforts have been made over the past few decades to identify effective biomarkers for use in clinical practice that can identify individuals at high risk of developing NCDs.[107–112] The application of "omics" technologies to biological samples has identified hundreds to thousands of biomarker candidates; however, only a small number of these have been translated into clinical diagnostics for patient care and/or early interventions for premorbid patients.[111,112] Gupta et al.[112] primarily attributed this to disease heterogeneity and pre-analytical variabilities associated with the identification of biomarkers, and also, in developing countries, to economic crises, a lack of awareness and education, the paucity of biorepositories, enormous diversity in socio-epidemiological backgrounds, ethnicity, lifestyles, diet, exposure to various environmental risk factors and infectious agents, and ethical and social issues.

We propose the following biological samples for use in identifying biomarkers in individuals at high risk of

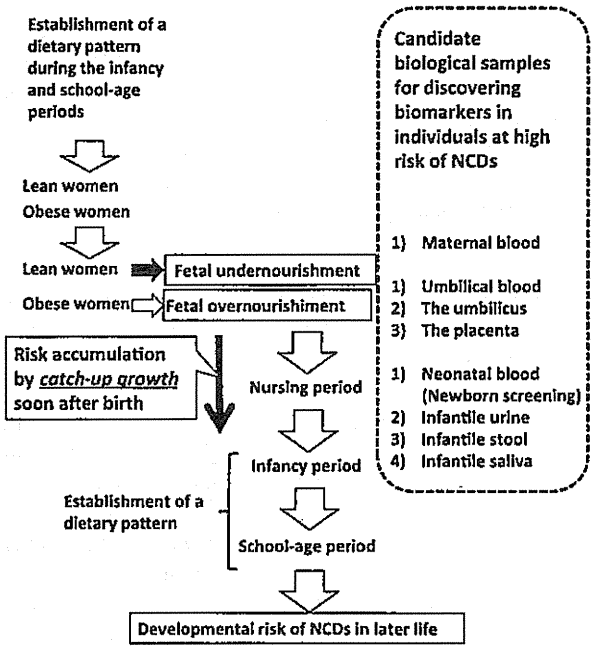

Figure 9. Candidate biological samples for the identification of biomarkers from the standpoint of perinatal care.

developing NCDs from the standpoint of perinatal care (Figure 9): 1) blood samples from pregnant women (cell-free fetal DNA),[113,114] 2) umbilical blood, 3) the umbilicus (pure fetal origin tissue), 4) the placenta (mostly fetal origin tissue, but including maternal origin tissue, especially in the basal plate of the placenta), 5) neonatal blood obtained at a newborn screening, such as Guthrie newborn screening,[115] 6) infantile urine, 7) infantile stools, and 8) infantile saliva.

Inexpensive and simple standard methodologies using stable biological samples that are easy to access need to be established in order to identify individuals at high risk of developing NCDs using newly identified biomarkers because the prevalence of NCDs is a heavy burden not only in developed, but also in developing countries. The road from the identification of effective biomarkers, authorization, and governmental approval to their translation into clinical settings appears to be long and difficult; however, the rewards may be significant not only for individuals, but also for society because lowering the morbidity of NCDs will reduce medical expenses and social security costs and ensure an effective workforce in the future.

Conclusions

The morbidity of NCDs has increased rapidly in both developing and developed countries, leading to substantial increases in health care and social security costs. In view of the pathogenesis of NCDs based on the DOHaD theory, the perinatal care of fetuses as well as neonates has an important impact on the risk of NCDs in adulthood. The importance of perinatal care is expected to be reconsidered from the perspective of preemptive medicine.

Acknowledgments

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Conflict of interest

None.

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Adults with Congenital Heart Disease

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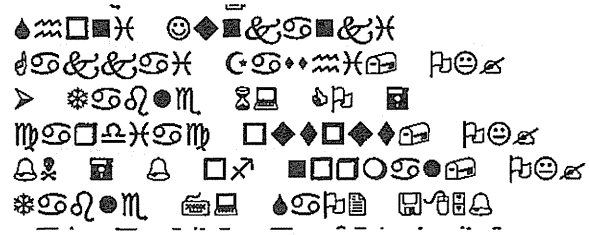

Abstract

Improvements in the surgical care of pediatric patients with congenital heart disease (CHD) have resulted in a growing population of adult CHD (aCHD) patients. These adults are developing a host of new issues and complications that many adult cardiologists have not been trained to recognize and treat. Additionally, some of this cohort are facing stressors, such as pregnancy, that are new to pediatric cardiologists. Fortunately, research in the natural history of adults with CHD, their psychosocial issues, and treatment of aCHD is taking place. This chapter explores the unique issues associated with this special CHD population, which the next generation of adult cardiologists will need to understand.

Improvements in the quality and level of care in the fields of pediatric cardiology and cardiovascular surgery have resulted in the survival and increased life expectancy of patients with congenital heart disease (CHD). Today, 85–90% of those born with CHD grow up to become adults. Even though surgical treatment has made survival to adulthood possible for CHD patients, it is seldom curative. Unoperated and postoperative patients with moderate to complex lesions require lifelong surveillance. Postoperative residua, sequelae and long-term surgical complications (see table 1 for definitions) vary in severity and require regular medical attention by experienced cardiologists (tables 1, 2). Because of this, a number of specialized centers have been established in the last 3–4 decades, first in Europe and North America, and then in East Asia, to respond to this need. This evolving field of adult congenital heart disease will now include board-certified specialists as one of the internal medicine subspecialties in North America, and, possibly, the trend will spread into other international regions.

Frequency of Adult Congenital Heart Disease

Data from large referral centers in Europe and North America revealed that the number of adult CHD (aCHD) patients continues to increase due

Table 1. Residua, sequelae, and late complications

Residua	Lesions which existed before surgery and left over after surgery or getting worse with age (i.e. left-axis deviation or mitral regurgitation)
Sequelae	Lesions which inevitably happen as a results of surgery (pulmonary regurgitation after ToF repair or surgical scar)
Complications	Lesions that happen unexpectedly due to surgery (nerve palsy)
Late complications	Complications that occur (un)expectedly in (un)operated lesions with age (heart failure, sudden death, arrhythmias, thrombosis, or cyanotic organ damage)

Table 2. Exacerbating factors in adults with CHD

Residua, sequelae, complications after initial cardiac surgery, reoperation
Catheter intervention, ablation
Noncardiac surgery
Reproductive issues, inheritance
Arrhythmia, cardiac failure, sudden death
Multisystem systemic disorders in cyanotic CHD
Infective endocarditis
Influence of aging and metabolic syndrome
Smoking, alcohol abuse
Exercise, recreational sports
Travel by aircraft, driving license
Psychosocial considerations
Health and life insurance, disability benefits
Liver disease (hepatitis, liver cirrhosis, hepatic cancer)

to the success of medical and surgical care of pediatric patients [1, 2]. As a consequence of advanced treatment, the proportion of aCHD patients surviving outnumbers children with CHD in many countries of the Western World. In the Asia-Pacific region, however, available data are limited to only a few countries and the proportion of adults with CHD varies from country to country: from 75% in Singapore, 51% in Japan, 32% in Thailand, 22–26% in Korea to 20% in Taiwan [3, 4].

Treatment Facilities and Human Resources

With few exceptions, however, reparative surgery is followed by residua and sequelae that require long-term if not life-long surveillance [5]. Because of the complexities inherent in the comprehensive care of these patients, specialized tertiary-care facilities emerged in the late 1970s in North America and Europe [6, 7]. The comprehensive care by multidisciplinary teams, including adult and pediatric cardiologists, cardiac surgeons, specialized nurses, and other cardiac and noncardiac consultants, has made the care of aCHD patients with moderate-to-severe CHD unique. Centers have emerged within teaching hospitals having preexisting pediatric cardiology units with capabilities in multi-imaging modalities and surgical treatment to care for aCHD. Availability of other cardiovascular specialists (vascular medicine, electrophysiology, and imaging), obstetricians-gynecologists, psychiatrists, infectious disease specialists, hematologists, nephrologists, rheumatologists, clinical geneticists, pulmonologists, and specialized nurses is also important to address other issues associated with CHD. However, there appears to be a significant shortfall in tertiary-care provisions for aCHD, which will require further planning and resource allocation [8]. As aCHD has high rates of health care utilization, particularly aCHD with moderate-severe lesions, appropriate resource allocation is required to serve this growing population. Patients with severe CHD had higher adjusted rates of outpatient cardiologist care, emergency department utilization, hospitalization, and days in critical care compared to patients with other CHD types [8].

Regarding cardiac providers for aCHD, proper transition from pediatric cardiologists and cardiovascular surgeons to aCHD specialists and/or cardiologists that are well trained in the field of aCHD is necessary [9]. Other than some areas in North America and Europe, this system has not been developed. In many parts of the world, such as the Asia-Pacific area, pediatric cardiologists are still principal caregivers for aCHD.

Table 3. Cardiac failure, especially RV failure in aCHD: background morphology and physiology

RV failure – subpulmonary and systemic
Systemic RV failure with/without atrioventricular valve regurgitation
Complete transposition of the great arteries after atrial switch
Congenital corrected transposition of the great arteries
Single RV
Subpulmonary RV failure
Left-right shunt (atrial septal defect)
Tricuspid regurgitation (Ebstein's disease, ToF after repair)
Pulmonary stenosis, pulmonary hypertension, Eisenmenger's syndrome
Pulmonary regurgitation (ToF after repair)
LV failure
Pressure overload
Coarctation of the aorta, aortic stenosis
Volume overload
Aortic regurgitation (bicuspid aortic valve, ToF or cyanotic CHD with pulmonary atresia or stenosis)
Left-to-right shunting (ventricular septal defect, patent ductus arteriosus)
Mitral regurgitation

Current Status and Future Prospects of Adult Congenital Heart Disease

In postoperative patients with CHD, even if the procedure is performed at the proper time and without complication, disease-specific and/or operative procedure-specific anatomical and functional abnormalities can progress. These abnormalities are classified as residua, sequelae, and complications (table 1) [5]. Residua are observed before surgery and continue postoperatively, such as right-ventricular (RV) outflow stenosis in repaired tetralogy of Fallot (ToF). Sequelae occur after surgery, such as pulmonary regurgitation in repaired ToF. An example of a complication is unexpected nerve palsy secondary to a surgical procedure. In moderate and severe CHD, there are residua and sequelae specific to the type of CHD. With few exceptions, reparative surgery is not curative and requires long-term surveillance. Residua and sequelae may progress in severity with age and induce late complications, such as arrhythmias, cardiac failure, thromboembolism due to RV failure, sudden death, reoperation, cardiac intervention, and ablation. There are many other obstacles that further complicate aCHD (table 2), including pregnancy and delivery, noncardiac surgery, hepatitis, psychosocial problems such as depression, cognitive abnormalities, health insurance coverage problems, and extracardiac complications inherent in the comprehensive care of these patients, making close follow-up and proper management mandatory. The most common cause of death is postoperative arrhythmia [10].

Common Problems and Specific Pathophysiological Issues in Adult Congenital Heart Disease

Cardiac Failure

Chronic heart failure is widespread in aCHD, with RV failure being most common. Table 3 outlines the morphology and physiology of heart failure in aCHD. Potential pathogenetic factors for cardiac failure in aCHD are shown in table 4. Chronotropic incompetence and exercise intolerance are present even in asymptomatic patients. Volume/pressure overload, neurohormonal activation, impaired autonomic nervous function, and operative scar formation in aCHD may all play a contributory role in congestive heart failure (CHF) and may be followed by arrhythmias and sudden cardiac death (SCD). Additionally, atrial/ventricular chamber dilatation, fibrosis, and

Table 4. Possible pathogenetic factors for heart failure in aCHD

Cyanosis
Pressure/volume overload
Residua and sequelae after repair
Poor intraoperative myocardial preservation
Artificial material (large ventricular patch)
Ventricular incisions/scar
Arrhythmias (brady- and tachyarrhythmias)
Abnormal ventriculoarterial coupling (decreased aortic stiffness)
Abnormal ventricular-ventricular interaction
Myocardial ischemia (LV hypertrophy, abnormal coronary supply)

dysfunction may also be risk factors for cardiac failure. In considering therapy for cardiac failure or coexisting arrhythmias, care must be taken for the underlying hemodynamic substrate in each CHD, particularly repairable ones that might favor a surgical or catheter-based approach to treatment. Typical aCHD substrates for CHF, arrhythmias, and SCD are: severe aortic stenosis and/or aortic regurgitation (superimposed coarctation of the aorta), Ebstein's disease, congenital corrected transposition of the great arteries, ToF after repair, extracardiac conduit repair (Rastelli procedure), complete transposition of the great arteries after Mustard or Senning operation, single-ventricle physiology, Fontan surgery, and unrepaired or palliated cyanotic CHD.

Management of CHF in aCHD includes medication, cardiac resynchronization therapy (CRT), reoperation and cardiac/cardiopulmonary transplantation with or without intracardiac repair. Reoperation combined with arrhythmia surgery, such as in reoperation of repaired ToF with subsequent extracardiac conduit repair, is popular in the aCHD field, and this concept is generally different from patients with acquired heart disease in that reoperation can be rare other than patients with valve surgery. In patients with repaired ToF with sustained ventricular tachycardia (VT) and a history of syncope, reoperation with cryoablation of VT is recommended in order to stabilize hemodynamics and reduce the incidence of recurrent VT. Cardioverter defibrillator implantation is indicated if the patients have no severe residual lesions that can be repaired [11].

As the pathophysiology and symptoms of cardiac failure, such as exercise intolerance, cardiac dysfunction, and neurohormonal abnormalities, are very similar between patients with CHD and acquired heart disease, management strategies for CHF in acquired heart disease, such as treatment with angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and β-blockers, can be applied to aCHD patients. These medications have been shown to work in patients with left-ventricular (LV) failure; however, no evidence for efficacy in RV failure exists [11–15]. Regarding CRT, there are several reports on its usefulness for aCHD. CRT can work in CHD and cardiac failure, but experience is still limited and specific conditions such as RV failure, complete right bundle branch block (not left bundle branch block) and coronary vein abnormalities could possibly make CRT difficult [16]. Other future possibilities include cardiac transplantation and artificial heart. Further experience for managing cardiac failure in aCHD is necessary.

Arrhythmias

Arrhythmia and SCD in aCHD is a big issue. Repaired ToF patients with severe pulmonary valve regurgitation associated with RV dysfunction are prone to SCD following VT. Measurement of QRS duration, RV size by MRI, and inducible VT by electrophysiological study are advocated and have been proven to be useful for the prediction of SCD in repaired ToF patients [17]. Reoperation with cryoablation for VT is effective for the prevention of these crucial events. Cardioverter defibrillators are also used for primary and secondary prevention of sudden death, but inappropriate firing and a high frequency of complications are still observed in some cases [18]. Supraventricular tachyarrhythmias such as atrial flutter or atrial fibrillation are common in aCHD patients long after repair. Antiarrhythmic medication and catheter ablation including the catheter maze procedure (creating atrial scar tissue that interrupts abnormal electrical impulses) have been successful, but there is no consensus regarding the

Table 5. Defect type and treatment options in PAH patients

Type of defect	Treatment
Small restrictive defects (ASD <2 cm, VSD <1 cm) with normal PVR (<3 WU) and net left-right shunting	No contraindication for closure
Large nonrestrictive defects (ASD >2 cm, VSD >1 cm) in cyanotic patients with elevated PVR and shunt reversal (right to left)	Closure contraindicated Treat with advanced therapies for PAH
Moderately restrictive defect in patients who have not undergone closure and have mild/moderately elevated PVR (3–6 WU) but no cyanosis	Treat with advanced therapies Rule out desaturation with exercise Serial right-heart catheterizations with vasodilator and exercise testing Consider closure or partial closure (with fenestration) if on treatment: PVR <3 WU No desaturation with exercise Q_p:Q_s between 1.6:1 and 2:1 PAH reversible with vasodilator therapy PAP <2/3 systemic BP, PVR <2/3 SVR Tolerates temporary occlusion in catheterization laboratory
Defects previously closed in childhood, now with elevated PVR and evidence of irreversible PAH	Treat with advanced therapies for PAH

ASD = Atrial septal defect; BP = blood pressure; PAP = pulmonary artery pressure; Q_p:Q_s = pulmonary:systemic blood flow; SVR = systemic vascular resistance; VSD = ventricular septal defect; WU = Wood's units.

management of atrial fibrillation in aCHD. In addition to warfarin, there are new oral anticoagulants available for atrial fibrillation in Fontan patients and patients with other disorders, but their efficacy is still under review. New guidelines are needed for these latest anticoagulants, and for the role of catheter and surgical cryoablation in aCHD.

Pulmonary Hypertension

Pulmonary arterial hypertension (PAH) in CHD develops as a result of vascular remodeling secondary to increased pulmonary blood flow, increased pulmonary vasculature pressure due to left-to-right shunting, and increased sheer stress. Despite significant advances in pediatric cardiology and surgery, about 3–10% of adults with CHD will develop PAH [19, 20].

There are no clear guidelines for the treatment of PAH-CHD. However, the data available seem to demonstrate that with the advancement of PAH-targeted therapies, the quality of life, exercise capacity, and outcomes in these patients are improving [21–24]. Targeted therapies for PAH may be useful in select patients with a combined medical-surgical approach (table 5).

Correcting a defect on the wrong patient could lead to progression of pulmonary hypertension, RV failure, and a worse prognosis than prior to repair [22]. An adult with cyanosis at rest or with exertion should probably not undergo closure of a septal defect, as this is a sign of advanced PAH-CHD and reversal of shunting, and patients being considered for surgery should get a right-heart catheterization to measure hemodynamics. In aCHD, pulmonary vascular resistance (PVR) and the pulmonary to systemic blood flow ration (Qp/Qs) are important indicators of severity of disease and reversibility with surgery. High pulmonary pressures due to high Qp/Qs, with a normal or low PVR, are poten-

Table 6. Physiological changes during pregnancy and delivery

Hemodynamic changes (similar reaction during exercise)
Pregnancy
Increased blood volume: 140–150% of normal
Increased cardiac output: 140–150% of normal
Dilatation of peripheral arteries
Labor
Increase in blood volume: 500 ml/contraction
Blood loss during delivery: 500–900 ml
Venous return after delivery: 500 ml
Return to normal hemodynamics within 1 month
Hypercoagulability, anemia (relative)
Tachypnea
Increased cortisol and estrogen levels
Autonomic nerve dysfunction (increased heart rate)
Histologic changes in aortic media (elastic fiber fragmentation, aortic dilatation)

Table 7. Risk factors (high) for pregnancies in women with CHD

Pulmonary hypertension (Eisenmenger's syndrome)
LV out- and/or inflow stenosis
Severe aortic stenosis (pressure gradient >80 mm Hg)
Severe mitral stenosis
Cardiac failure (NYHA class III or IV, ejection fraction <35%)
Marfan's syndrome (aortic root >40 mm), CHD with dilated aortic root (>45 mm)
Mechanical valve
Cyanotic CHD with or without pulmonary hypertension (SaO_2 <85%)
Fontan-type circulation
Systemic RV with decreased function
Complete transposition of the great arteries after atrial switch
Congenital corrected transposition of the great arteries

tially reversible. On the other hand, high pulmonary pressures secondary to a high PVR could be a contraindication to surgery. A recent extensive review suggested that PVR values <6 Wood's units can be considered operable, although these numbers should be used as a guide and not an absolute [22]. In patients that are borderline operable, the best strategy is to treat with targeted therapy and then reevaluate. Patients with the Eisenmenger syndrome (PVR and remodeling secondary to chronic elevation in pulmonary pressures) could possibly be treated with targeted medical therapy, especially pulmonary vasodilators [24]. Residual defects can be present years after the initial operation and can be the cause of PAH-CHD decades later [20].

Pregnancy and Delivery

Half of the aCHD patients are female and many will face pregnancy in their lifetime, which results in hemodynamic and other physiologic changes (table 6). Cardiac disease is the leading cause of maternal death in some countries, and most pregnant women with cardiac disease have CHD. The number of such patients at risk for child bearing is expected to grow [25]. Women with PAH, severe LV outflow tract stenosis, cyanotic CHD, aortic root dilatation, cardiac dysfunction, and mechanical valves carry a high risk for pregnancy-related morbidity (table 7). The most frequent complications in these patients during pregnancy and delivery are CHF or arrhythmia followed by thrombosis. Risk stratifica-

tion for pregnant patients with CHD is related to the functional status of the patient and lesion specificity [26]. Timely prepregnancy counseling should be offered to all women with CHD to prevent avoidable pregnancy-related risks [27]. Adequate care during pregnancy, delivery, and the postpartum period requires a multidisciplinary team approach with cardiologists, obstetricians, and anesthesiologists, especially in women with moderate or severe risks. Successful pregnancy is feasible for most women with CHD with mild-to-moderate severity when appropriate counseling and optimal care are provided. Registration systems on pregnancy and delivery in cardiac disease, including aCHD, have been initiated in Europe and Japan [28]. In Asian and underdeveloped countries, rheumatic heart disease is still common, so proper management planning during pregnancy for women with this disorder is also important.

Psychosocial Issues

Most aCHD patients with proper therapy will have a longer life span and may experience psychological stressors associated with chronic disease. Consequently, many studies are now focusing not only on medical support, but also on their psychosocial features and their quality of life. These studies are conducted by means of questionnaires or interview surveys, such as semistructured interviews or structured clinical interviews. The results regarding the psychosocial state of patients compared to controls are inconsistent in emotional and social functioning, depression, anxiety, and mood disorders [29–32]. However, adult patients with cyanosis after the Fontan procedure are at higher risk for depressive symptoms [33]. Additionally, there have been inconsistent results when evaluating self-esteem in patients with aCHD [34, 35].

The reasons for these inconsistent findings could be explained by differences in sample size (including low response rates), recruiting sources (e.g. the sample is not from a homogeneous group), study methods, and sociocultural background (e.g. the health care system and mental health treatment [35]) in different countries. In a Japanese study [34], aCHD patients often have psychosocial difficulties, which influence the patients' mental health, social problem solving, independence, and self-esteem.

Table 8. Factors for low incidence of atherosclerosis in cyanotic aCHD

Cyanotic aCHD patients have low levels of low-/high-density lipoprotein and total cholesterol, which persist after surgical elimination of cyanosis
Increased nitric oxide levels
Increased serum bilirubin levels
Low platelet counts

Possibility of Acquired Cardiovascular Disease

In spite of the theoretical risk of atherosclerosis in patients with aCHD due to various risk factors, cyanotic CHD is noted to have a minimal incidence of coronary artery disease (CAD) [28, 36–39]. Perloff [36] found that atherosclerosis was absent on coronary angiography of 49 cyanotic patients with CHD in their early 40s. A more recent series, describing 250 patients with CHD who underwent selective coronary angiography for reasons other than suspected CAD in the United Kingdom, revealed that the prevalence of significant CAD (9.2%) was similar to the general population: no patient younger than 40 years had significant CAD, and none of the cyanotic patients had significant CAD [40]. In general, cyanotic CHD is a preventive factor for cardiovascular disease [36] (table 8).

Cardiovascular risk may also vary by type of CHD (table 9) [41]. Specific conditions in which the coronary arteries are directly affected or altered surgically may confer a greater risk for premature atherosclerotic CAD. Coronary artery re-implantation at the time of arterial switch repair in transposition of the great arteries has been shown to result in abnormal coronary flow, and intracoronary ultrasound reveals that some patients develop intimal proliferation, a precursor to atherosclerosis [42]. Left-sided obstructive lesions may also be associated with CAD. Coarctation of the aorta, even after repair, is commonly associated with systemic hypertension; aortic stenosis can be associated with LV hypertrophy and

Table 9. Clinical manifestations of cardiovascular disease (CVD) in aCHD

aCHD patients have a similar prevalence of risk factors for CVD as the general population
Cyanotic aCHD patients have a lower incidence of CVD
Acyanotic aCHD patients have a similar prevalence of CVD as the general population
Increased risk of coronary atherosclerosis is observed in congenital coronary artery anomalies, complete transposition of the great arteries after arterial switch, and coarctation of the aorta
Aortopathy may be an additional risk factor for CVD
Prevention of CVD is even more important in young adults with CHD

diastolic dysfunction, known risk factors for adult-onset cardiovascular morbidity and mortality [43].

According to a recently published paper, 141/12,124 (1%) of aCHD patients had CAD, which is lower than the prevalence of CAD in the general population, most likely due to the young age of adults in this study; however, 109 of these 141 (77%) experienced coronary artery interventions [44]. The most frequent background CHD in this study were atrial septal defects, bicuspid aortic valve, ToF and coarctation of the aorta, and 82% of these patients had traditional risk factors for CAD, such as hypertension, hyperlipidemia, diabetes mellitus, or obesity [44]. Surprisingly, 7 of the patients had the Eisenmenger syndrome, and all of these patients had at least one of the traditional risk factors for CAD [44].

aCHD patients have a similar prevalence of traditional risk factors for CAD as the general population, and noncyanotic aCHD patients have a similar prevalence of CAD as the general population. However, patients with cyanotic aCHD, even after repair, have a lower incidence of CAD. In cyanotic patients with risks such hypertension, dyslipidemia, diabetes mellitus, and the metabolic syndrome, atherosclerosis is still possible [40, 44–47].

Aortopathy

Bicuspid aortic valve and/or coarctation of the aorta are consistently associated with medial wall abnormalities in the ascending aorta, which are prevalent in a variety of CHD types, such as single ventricle, persistent truncus arteriosus, transposition of the great arteries, hypoplastic left-heart syndrome and ToF, and may predispose to dilatation, aneurysm, rupture, and aortic regurgitation [48, 49]. This dilatation can develop in CHD patients even without a stenotic region of the aorta. CHD patients who exhibit ongoing dilatation of the aortic root and reduced aortic elasticity may have wall abnormalities intrinsic to the aortic root [50]. The paradigm in aortic dilatation has shifted from the idea of so-called poststenotic dilatation to primary intrinsic aortopathy. The effects of aortic dilatation and increased stiffness can induce aortic regurgitation, LV hypertrophy, reduced coronary artery flow, and LV failure. This aortic pathophysiological abnormality has been labeled as a new clinical entity: 'aortopathy'. These patients should be followed for progression of aortic root dilatation. Also, we should evaluate therapies that prevent this dilatation and stiffness, such as β-blockers/angiotensin-converting-enzyme inhibitors or angiotensin II receptor antagonists.

Conclusion

Formal education and training systems for CHD practitioners are still lacking in developing countries such as Asia. Collaborative work and support of addressing the shortage of adult cardiologists knowledgeable in CHD is necessary. Further expansion of this population and the need for the evolution of specialized care facilities for pediatric cardiology and aCHD can be anticipated throughout the world. Training and education focused on the trainees who represent the next generation of pediatric and adult cardiologists will allow them to assume responsibility for this patient population.

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