Nutritional support for low birth weight infants: insights from animal studies

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Abstract

Infants born with low birth weights (<2500 g, LBW), accounting for about 15 % of newborns, have a high risk for postnatal growth failure and developing the metabolic syndromes such as type 2 diabetes, CVD and obesity later in life. Improper nutrition provision during critical stages, such as undernutrition during the fetal period or overnutrition during the neonatal period, has been an important mediator of these metabolic diseases. Considering the specific physiological status of LBW infants, nutritional intervention and optimisation during early life merit further attention. In this review, the physiological and metabolic defects of LBW infants were summarised from a nutritional perspective. Available strategies for nutritional interventions and optimisation of LBW infants, including patterns of nutrition supply, macronutrient proportion, supplementation of amino acids and their derivatives, fatty acids, nucleotides, vitamins, minerals as well as hormone and microbiota manipulators, were reviewed with an aim to provide new insights into the advancements of formulas and human-milk fortifiers.

According to the WHO, infants with a birth weight <2500 g, irrespective of gestation, are defined as low birth weight (LBW)[1]. Infants with LBW have high morbidity and mortality during the neonatal period as an outcome of intra-uterine growth restriction (IUGR) or preterm birth[2]. Although great efforts have been put into nutritional management and clinical support for pregnant women, LBW infants still account for about 15 % of newborns[3]. Among all of the environmental factors leading to the occurrence of IUGR, maternal under-nutrition has been recognised as the most important. Because of improper nutritional provision during the fetal period, a critical period according to the nutritional programming theory, LBW infants not only show growth failure during the neonatal period, but also lifelong metabolic disturbance[4–6]. Therefore, nutritional intervention of LBW infants during their neonatal stage has aroused great attention in recent years. Because of the ethical issues involved, animal models have been widely used to investigate the physiological differences between LBW offspring and normal ones as well as the nutritional support strategies[7].

In this review, we will focus on discussing the physiological differences related to provision and digestion of nutrients between LBW infants and normal infants. Furthermore, we provide information about the current nutritional support given to these LBW infants, with a focus on the neonatal stage.

Consequences of being born with low birth weights

Catch-up growth and risks for the metabolic syndromes

The occurrence of IUGR reflects that the infant probably experienced undernutrition during its development within the uterus. In this case, as a protective mechanism, the fetus prefers to allocate the limited nutrients to vital organs (e.g. the brain) for survival and development, at the expense of somatic growth. Therefore, the growth-hormone system is down-regulated, as indicated by the lower serum concentrations of insulin, insulin-like growth factor (IGF) and insulin-like growth factor-binding protein 3 (IGFBP-3)[8–10]. By using IUGR piglets as a model, Wang *et al.*[11] reported that IUGR piglets showed lower concentrations of insulin and IGF-I in the jejunal mucosa when compared with normal littermates. IGF and IGFBP-3 reflect the growth velocity in childhood, and several studies have reported that these two factors can be used as predictors

of catch-up growth of LBW infants during the neonatal period[12–14].

Normally, catch-up growth in LBW infants is achieved by overnutrition compensation, and it is postulated to erase the growth deficit generated during the fetal period[1]. However, given the fact that IUGR infants are born with lower concentrations of insulin, IGF-I and IGFBP-3, the sudden shift to a normal or overly compensatory diet after birth might increase these parameters during the first 3 months of life[14,15], which will lead to insulin resistance in tissues to prevent hypoglycaemia[1,16]. Therefore, catch-up growth actually reflects an insulin-resistance state[17]. Meanwhile, preferential abdominal fat deposition, excess circulating lipids and ectopic fat storage were observed in the catch-up growth infants, all of which have been implicated in the risk for developing obesity, type II diabetes (T2D), hypertension and CVD[18,19]. Studies with rodents showed that an accelerated postnatal growth induced excessive adiposity, increased adipocyte sizes and glucose intolerance[20–23]. Notably, some researchers stated that growth in different neonatal periods may have different effects on later T2D and CVD risks. It has been reported that catch-up growth that occurred during early infancy (the first 3 months) has a greater programming effect on adiposity and metabolism when compared with growth in later stages of infancy[1].

Furthermore, previous studies have suggested that small-at-birth people have higher fasting plasma cortisol concentrations in their adult lives and increased adrenal responsivity to adreno-corticotropic hormone stimulation, which can then reduce lean body mass and increase lipid accumulation[24–27]. As a consequence, the elevated cortisol levels may present a possible link between LBW and adult metabolic syndrome. During the neonatal period, cortisol might also play a role in limiting IGFBP-3 proteolysis and therefore reducing IGF bioavailability[28] and leading to growth failure in LBW children.

Digestive function deficiency

Recently, by using different experimental models, it has been reported that LBW offspring such as LBW fetuses, neonates, children or young adults have a higher incidence of short- and long-term dysfunctions in several vital organs, as indicated in Table 1. For example, evidence has shown abnormal brain volumes[29] and muscle fibre distributions[40] of young LBW adults, lower bone quality of preterm children[41] as well as smaller thymic size of IUGR human fetuses[42]. Besides lower tissue weight, dysregulated expressions of proteins were observed in the liver, skeletal muscle and small intestine of newborn IUGR pigs[31].

Among these organs, the gastrointestinal tract (GIT) is of paramount importance in postnatal nutrient acquisition. The epithelial barrier of the GIT is involved in the first steps of postnatal immune system maturation, providing protection against food antigens and invasion of environmental micro-organisms[33,45]. Most studies on the effect of LBW on GIT health were carried out in animal models, especially on piglets. LBW piglets normally show impaired gastrointestinal development, which further imposes limitations on postnatal body growth and development of other organs[33]. Compared with normal-birth weight (NBW) newborns,

LBW piglets show a reduced small intestinal weight and a reduced small intestine:body weight ratio up to 21 d of age[46]. The reduced ratio of intestinal weight:length in these LBW piglets indicates a thinner intestinal wall[32,47]. Differences in intestinal architecture between IUGR and NBW neonates were widely documented, indicating that the intestinal absorptive surface was smaller in IUGR piglets during the early days of life, as evidenced by the reduced ratio of intestinal villus height:crypt depth[33,34,45,48–50]. This reduction of exchange surface is crucial because of its role in processing dietary nutrients into available molecules and regulating the flux of antigenic material[50]. Further proteome analysis of the jejunum of LBW piglets revealed that the expression of key proteins involved in major biological processes such as absorption, digestion and transport of nutrients, cell apoptosis, nutrient metabolism, cellular redox homoeostasis and stress response were affected by birth weight during the first 21 d of life[46,47,50]. Moreover, He et al.[34] have reported that IUGR piglets have a distinct metabolic status compared with NBW piglets at 21 d of age, with changes related to lipogenesis, lipid oxidation, energy supply and utilisation, amino acid and protein metabolism, and antioxidant ability.

Gut bacterial colonisation of LBW piglets is also altered during the early days of life[45]. For example, preterm LBW infants had reduced population levels of strict anaerobes such as Bifidobacterium and Bacteroides, and had a high prevalence of Staphylococcus, Enterobacteriaceae, Enterococcaceae and other lactic acid bacteria including the genus Lactobacillus in a low-diversity bacterial ecosystem[51–53]. In summary, these results all suggest that LBW newborns are associated with both immediate and long-term altered intestinal adaptation during the neonatal period.

Possible nutritional interventions for improving growth and health of low birth weight infants

Appropriate patterns of nutrient delivery

Parenteral nutrition. During the initial days or weeks of life, GIT impairment in LBW infants usually induces an inability to tolerate enteral feedings, which can be referred to as 'feeding intolerance', as indicated by increased gastric residuals, abdominal distension and/or emesis[54]. In this case, parenteral nutrition (PN), supplying essential nutrients either by a central or peripheral intravenous injection[55,56], is considered a useful strategy to avoid feeding intolerance until full enteral nutrition (EN) can be adopted. PN should be started either immediately after birth or within the first 2 h of life[57]. In addition, Valentine et al.[58] reported that when PN started within the first 24 h of life, these small infants had shorter durations of PN administration and achieved full enteral feedings earlier compared with those that started PN more than 24 h after birth. The early use of PN has been shown to reduce postnatal growth failure and mortality, prevent N imbalance, prevent essential fatty acid and trace mineral deficiency, and improve growth and neurodevelopmental outcomes[59], without the associated short-term metabolic or clinical side effects[60]. In early intravenous nutrition for very low birth weight (VLBW; birth weight <1500 g) infants, the recommended administrations of amino acids, glucose and lipids are 2·5–3·5, 12–18 and 3 g/kg per d, respectively.

Table 1. Examples of epidemiological and animal studies that reveal alterations in vital organs of low birth weight (LBW) offspring compared with normal ones

Compartments observed	Outcomes	Developmental stage	Experimental Model	References
Brain	Reduced volumes of grey and white matter and ventricular dilatation	At 20 years of age	Preterm young adult with VLBW	Bjuland et al.[29]
Liver	Reduced liver weight; differentially expressed proteins and activities of key metabolic enzymes	At 110 d of gestation and birth	IUGR pig	Liu et al.[30]; Wang et al.[31]
Intestine	Smaller tissue weight, thinner intestinal wall and reduced ratio of intestinal villus height:crypt; differentially expressed proteins and metabolic status	At birth and 1–21 d of age	IUGR pig	Wang et al.[31] Wang et al.[32] Xu et al.[33] He et al.[34]
Kidney	Lower kidney weight, ratio of kidney weight: body weight and fewer glomeruli	At birth	IUGR rat	Shen et al.[35]
Kidney	Lower glomerular filtration rate; higher urine Ca:creatinine ratio, fraction excretion of Mg and renal threshold for phosphate	At 4–5 years of age	Preterm children with VLBW	Gheissari et al.[36]
Skeletal muscle	Reduced myofiber numbers; differentially expressed proteins; increased proportion of type I fibres and capillary density	At 60, 90 and 110 d of gestation; at birth and at 1 d of age	IUGR pig	Wang et al.[37], Wang et al.[31], Bauer et al.[38]
Skeletal muscle	Decreased muscle mitochondrial content and impaired respiration in isolated mitochondria and permeabilised fibres	At 14 weeks of age	IUGR mice	Beauchamp et al.[39]
Skeletal muscle	Increased proportion of type IIx fibres, decreased type IIa fibres and elevated mean areas of muscle fibres	At 19 years of age	LBW young men with SGA	Jensen et al.[40]
Bone	Lower bone strength, quality and bone transmission time	At 11·28 years of age	Preterm and SGA children	Longhi et al. [41]
Thymus	A decrease in fetal thymic size	During pregnancy	IUGR human fetus	Cromi et al.[42]
Thymus	A smaller proportion of T-cell subsets	At 60, 90 and 110 d of gestation	IUGR pig fetus	Lin et al.[43]
Thymus	Decreased thymus and lymphocyte counts as well as alterations in CD4+ and CD8+ populations	At birth and at 21 d of age	IUGR rat	Contreras et al.[44]

VLBW, very low birth weight, <1500 g; IUGR, intra-uterine growth restriction; SGA, small for gestational age.

The reasonable levels of Na, K, Cl, Ca, P and Mg are assumed to be 3–5, 1–2, 2–3, 75–90, 60–67 and 7·5–10·5 mg/kg per d, respectively[61].

In total PN of infants, glucose is the most widely used intravenous carbohydrate for neonates because it is a main energy source and is readily available to the brain. Many other non-glucose carbohydrates such as fructose, galactose, sorbitol, glycerol and ethanol have been used as sources of carbohydrates. However, their effects are considered inferior to glucose[59]. Commercial lipid emulsions generally include soyabean oil, mixtures of olive and soyabean oils and mixtures of olive and fish oils[59]; the fish oil-based lipid emulsion may be a more effective source[62,63].

Enteral nutrition. Enteral feeding is the preferred pattern of nutrition provision for LBW infants. Human milk is not only the paramount EN source but also a supplier of various bioactive compounds to infants, which play vital roles in regulating GIT development and protection from infections[64]. However, it can be accompanied by side effects including feeding intolerance and other aforementioned complications. A combination of PN and EN is commonly practiced after birth until full EN can be accomplished[57]. Once full feedings have been established and PN has been terminated, EN is fully responsible for providing all nutrients to support normal growth[65]. Considering that the maternal milk from preterm mothers provides inadequate

quantities of nutrients[66], especially protein[61,66], targeted human-milk fortifiers are added to either the maternal or the donor milk to meet the nutritional needs of rapidly growing LBW infants[67]. It can be advised to supply a fortifier content of up to 1·3 g of protein/100 ml for these small infants, beginning from the time they can tolerate 50–70 ml/kg per d of milk[61]. Tolerance formulas including soya-protein, protein-hydrolysate and amino-acid-based formulas can be utilised to promote feeding tolerance in LBW neonates[57].

In preterm formulas, as a reference for LBW infants, the carbohydrate source is a combination of lactose and sucrose[68], considering the inadequate lactase activity of the GIT[69]. A part of the sucrose or lactose in formula could be replaced by easily digestible glucose polymers to ensure low osmolality of formulas[61,68]. The protein sources are whey and casein derived from cows' milk, and sometimes soya protein. In addition, the fat source is a mixture of vegetable oils containing 30–40 % medium-chain TAG in lipids to improve fat absorption[61,68].

Continuous and intermittent bolus feeding. Compared with continuous feeding, intermittent bolus feeding is considered to be more effective in shortening the time to establish full enteral feeding, improving feed tolerance and accelerating weight gain in premature LBW infants[70,71]. Using the newborn NBW pig as a model, it has been demonstrated that intermittent bolus

feeding increases protein synthesis to a greater extent than continuous feeding by improving activation of amino acids and insulin-induced translation initiation[72,73]. On the other hand, contradictory results have also been reported[74,75]. This observation in pigs would also be useful to provide some implications for clinical practice in LBW infants. Dsilna et al.[76] demonstrated that continuous feeding could contribute to reduced behavioural stress response compared with intermittent bolus feeding among premature VLBW infants. In spite of these data, it is still difficult to recommend either method of gavage feeding, and more trials in LBW infants or animals are needed to evaluate the benefits and side effects of both methods.

Macronutrients

LBW infants are generally fed high-protein/energy formulas to improve their growth rates and N retention[77–81]. For instance, Fenton et al.[82] demonstrated that a higher protein intake (≥3.0 but <4.0 g/kg BW per d) could accelerate weight gain and N accretion in formula-fed hospitalised infants, which indicated by an enhancement of postnatal growth. Providing a nutrient-rich formula to preterm infants (20 % energy-enriched and 40–60 % more protein and minerals than term formula) increased body weight, length and head circumference growth during the first 18 months[83]. Similar results were shown in a piglet study in which the LBW piglets had a comparable growth rate with the normal piglets when fed a high-protein content diet between 7 and 28 d of life[84]. Han[85] also reported that when LBW piglets received a high-nutrition-level diet with all nutrients at about 1·5-fold those of the control, they had markedly increased weight gain of the *psoas major* muscle. This was probably due to the enhanced gene expressions of *IGF-I, IGF-I receptor* and *mammalian target of rapamycin (mTOR)*.

Another widely used strategy to promote the growth of LBW infants is increasing energy intake. However, it has been stated that the major effect of higher energy intake (594 v. 502 kJ/d (142 v. 120 kcal/d)) in LBW infants is an increase in fat accretion[77]. Studies in experimental animals show that protein/energy malnutrition can affect the utilisation and deposition of protein and fat[86]. High nutrient intake in IUGR piglets led to abnormal immune function during the suckling period by lowering serum concentrations of cytokines such as TNF and IL-1β. Moreover, intense nutrient intake induces excessive oxidative stress[87–89], which can impose a further burden on the immature antioxidant system in LBW offspring[90–92].

Considering the potential risk for inducing metabolic problems, the intensive nutrition strategy might not be a proper nutritional intervention for LBW infants. Research on rats showed that postnatal energy restriction can be considered as an effective strategy to alleviate the metabolic syndromes in LBW offspring, like obesity and diabetes[93–95]. Che et al.[96] reported that restricting the intake of 7-d-old IUGR piglets (approximately 70 % of the control's intake) can improve the antioxidant system at the expense of maintaining a low growth rate in the neonatal phase[97].

It is worth noting that protein:energy ratio (PER) of diets will be important for the relative composition of net protein and fat stored in tissues while considering the different nutritional requirements of growth and maintenance[98]. In this case, therefore, an appropriate PER in infant formulas is necessary to maintain a positive N balance, ensure protein utilisation and prevent excessive fat storage[57,99]. The PER of mature human milk ranges from 1·3–1·8 g/418 kJ (100 kcal), whereas the ratio ranges from 2·2–2·5 g/418 kJ (100 kcal) in standard formulas for normal infants[100]. However, a higher PER, approximately 3 g/418 kJ (100 kcal), is recommended for preterm LBW infants[57,101], which would lead to increased lean mass with relatively decreased fat deposition[99]. Once protein intake is adequate to meet the needs of lean body accretion, excessive energy will primarily lead to relatively more fat deposition[98], and then increase the risk for adult obesity[102]. Taken together, the optimal constitution and appropriate PER levels in formulas designed specifically for these LBW infants can be useful in achieving the desired growth rate while avoiding extra stress on their defective metabolic system.

Functional components applied to optimise nutritional support for low birth weights infants

Functional amino acids and derivatives. Epidemiological and metabolic studies have provided novel insights into alterations in the amino acid profiles in LBW fetuses and neonates. Reduction in the concentrations of the arginine (Arg) family of amino acids (Arg, proline, citrulline, glutamine (Gln)) have been reported in the umbilical vein plasma of fetuses or in the plasma of LBW newborns in humans[103–105], pigs[11,34,106,107] and rats[108]. Branched-chain amino acids (BCAA) (leucine, isoleucine, valine) also show lower levels in the plasma of fetuses and neonates born with LBW[34,103,105,106]. All of the above implicate that these functional amino acids could be used as potential biomarkers for designing effective strategies to improve the outcomes in LBW neonates.

L-Arginine. L-Arginine (Arg) is an essential amino acid for the maximal growth of young mammals[109–111]. It is an essential precursor for the biological synthesis of important molecules such as glutamate, ornithine, proline, polyamines, creatinine, nitric oxide and agmatine[109,112–114].

A systematic review derived from eighty-three human studies reported that the concentration of Arg was about 0·94 g/l in preterm transitional milk[115], and the mean milk yield of preterm mothers at 6 weeks postpartum was approximately 541 (SD 460·9) ml/d[116]. Therefore, provision of Arg from milk is far from adequate to meet the high requirements of growth and metabolic function in preterm newborns[117]. Dietary supplementation of 0·6 % Arg to LBW piglets from 7 to 14 d of age resulted in increased average daily gain and daily DM[11]. The incidence of diarrhoea dropped by 61·5 %, accompanied by increased small intestine weight and mucosal villus height[11]. Notably, Arg supplementation was found to effectively reduce the incidence of necrotising enterocolitis (NEC) in premature infants with LBW[118–120]. In addition, a recent study observed daily dosing of Arg (145·0 mg/kg body weight per administration) to LBW piglets, from 1 to 17 d after birth, had an ability to revert

some of the abnormalities involving amino acids, energy, lipid and nucleotide (NT) metabolism caused by LBW[121]. However, these effects appear to be independent of the growth-regulation system because reduced growth rate is still present in these piglets[121]. Therefore, optimisation of Arg dosage and timing should be investigated to achieve desirable effects in LBW neonates.

Glutamine. Gln plays vital roles in maintaining several important functions such as energy metabolism, immune response and cell signalling as well as the synthesis of Arg, NT, hexosamines and glycoproteins[114,122–125]. The amount of Gln obtained from milk is far from sufficient in newborns to support the Gln requirements for growth[126]. Different studies have all shown that Gln supplementation (0·3 g/kg per d) in formulas can increase the growth rate in LBW infants[127], improve the tolerance to enteral feeding and decrease morbidity during the 1st month[128–130]. A previous study in IUGR piglets found that oral administration of Gln at 0·5 g/kg of body weight twice per d from days 0 to 21 of age could reduce amino acid oxidation, increase growth and reduce preweaning mortality[107]. Moreover, oral Gln (1 g/kg body weight every 12 h) during days 0 to 14 post weaning in LBW pigs induces an enhanced intestinal immunity by increasing heat shock protein 70 expression as well as the suppression of NF-κB[131]. Collectively, Gln is likely an effective amino acid to enhance the survival, immune response and postnatal growth of LBW infants.

Branched-chain amino acids. There are three amino acids recognised as BCAA: valine, isoleucine and leucine. They play vital parts in protein synthesis in skeletal muscle. The mechanisms that BCAA are involved in include the mTOR signalling pathway, decreasing rates of protein degradation[132] and regulating cell differentiation and apoptosis[133]. Importantly, BCAA are substrates for the synthesis of glutamate and Arg in the metabolic pathway of amino acids[134,135]. A recent study using weaned LBW pigs as a model showed that dietary supplementation with 0·35 % L-leucine improved the growth rate of LBW piglets by increasing the levels of phosphorylated mTOR and ribosomal S6 kinase 1, and also by reducing muscle atrophy F-box protein[136]. Similar results have also been observed in fetal[137] and postnatal LBW rats[138]. Obviously, BCAA, particularly leucine, may have a potential effect on accelerating the early growth rate and protein synthesis in LBW offspring. Given the fact that BCAA play a major role in stimulating protein synthesis in skeletal muscle, the optimal BCAA supplement dosage should depend on whether it provides enough for maximum protein deposition in the skeletal muscle of LBW neonates.

L-Carnitine. L-Carnitine (3-hydroxy-4-N,N,N-trimethylamino-butyric acid) is a water-soluble quaternary amine essential for a series of indispensable functions in the intermediary metabolism of mammals. L-Carnitine serves as a shuttling molecule for the transportation of activated long-chain fatty acids from the cytosol into the mitochondrial matrix to produce energy[139]. Preterm infants with LBW problems are at a high risk for carnitine deficiency because of an immature biosynthetic ability, insufficient transplacental transportation and exogenous supplementation[140]. A previous investigation implied that routine parenteral supplementation with L-carnitine had no demonstrable effect on growth, apnoea or length in LBW infants[140]. Nevertheless, evidence suggests that in piglets, adding L-carnitine to diets could accelerate the rates of protein and fat accretion[139,141,142] by stimulating IGF-I signalling, while inhibiting the expression of pro-apoptotic and atrophy-related genes or genes of the ubiquitin–proteasome system[139,143]. In particular, Losel *et al.*[144] reported that an oral administration of L-carnitine (400 mg/d) from 7 to 27 d of age resulted in an intensified myogenic proliferation in LBW suckling pigs, which demonstrated that increasing enteral L-carnitine could be considered as an effective method to improve growth outcomes of LBW neonates. Therefore, supplemental L-carnitine is recommended in LBW infants, but further clinical trials are needed to focus on the safe dosage and outcomes of L-carnitine usage.

PUFA. The major long-chain PUFA (LC-PUFA) such as arachidonic acid (ARA, 20 : 4n-6), EPA (20 : 5n-3) and DHA (22 : 6n-3) are essential nutrients for maintaining health, cognition and development during fetal as well as early postnatal life in humans[22,145]. Previous evidence illustrated that neonates, including the LBW ones, can synthesise DHA and ARA from essential fatty acids such as linolenic acid (n-3 LC-PUFA) and linoleic acid (n-6 LC-PUFA)[146–148]. However, the LC-PUFA synthesis rate in these LBW infants was not enough to meet the requirement for optimal growth and development[146,149,150]. The decreased proportion of ARA to linoleic acid as well as DHA to α-linolenic acid was seen in the fetal plasma of IUGR pregnancies[151], indicating a deficit in LC-PUFA profiles in the IUGR fetus. Therefore, dietary LC-PUFA supplementation can be considered as an efficient strategy to counteract the defective fatty acid composition of IUGR neonates. In a clinical trial, preterm infants fed with a formula containing DHA (0·16 %) + ARA (0·42 %) for the 1st year had higher lean body mass and reduced fat mass at 1 year of age[152]. A systematic review reported that ω-3 LC-PUFA supplementation was found to reduce the incidence of NEC in extremely preterm infants ($\leq$32 weeks)[153]. Notably, supplementing fish oil (rich in EPA and DHA) has been considered as a potential nutritional intervention to facilitate catch-up growth with normal body composition in preterm infants[154], because of its effect on suppressing the differentiation of fat cells and fat accumulation[155,156]. In addition, EPA and DHA play a key part in mediating inflammatory response, which can in turn improve insulin sensitivity[157,158].

Nucleotides. NT are a group of bioactive agents regulating nearly all biochemical processes including transferring chemical energy, biosynthetic pathways and coenzyme components[159]. NT account for approximately 20 % of the natural non-protein fractions in milk[160] and play important roles in optimising intestinal and immunological function[161]. *De novo* synthesis, salvage pathways and daily food are sources of NT in mammals[162]. Cells of the intestinal mucosa have a limited capability for *de novo*

synthesis[163]. In a rapid growth stage, exogenous NT would become essential nutrients for optimal function especially when the mucosa has already been damaged, which is typically seen in LBW neonates. Recently, research using LBW pigs as a model showed that when LBW piglets received NT-supplemented formula from 7 to 28 d of age, intestinal villus height and lactase and maltase activity were improved, which led to a better growth rate[162].

Vitamins and minerals. The augmented intakes of Ca, P, trace elements and vitamins in LBW infants are significantly beneficial in improving postnatal growth outcomes. For instance, bone mineralisation is obviously higher in preterm infants when fed Ca- and P-enriched formulas[164] compared with conventional preterm formulas. LBW formulas could be designed with much higher contents of Na and K in order to compensate for reduced kidney function[68,165]. Because of a high incidence of vitamin A, D and E deficiency in VLBW infants[166,167], addition of these vitamins is essential in parenteral or enteral feedings. Vitamin A supplementation in LBW neonates has the potential to improve lung and visual development[168] as well as to reduce death and retinopathy[169]. Similarly, a systematic review showed that, as an antioxidant agent, vitamin E supplementation in preterm infants was able to reduce the risk for retinopathy and intracranial haemorrhage[170]. The addition of vitamin D contributed to higher levels of serum vitamin D[171], higher Ca retention[172], and therefore lower incidence of bone hypomineralisation[173]. More clinical trials are still required to determine the optimal regimens for these nutrients.

Probiotics and prebiotics. Compared with adults, the enteric microbiota of infants is extremely unstable in terms of composition because of the fast development of the GIT[174]. *Lactobacillus* supplementation remarkably depresses feeding intolerance[175,176] and increases growth velocity[177] in VLBW infants. Supplementing single-strain *Bifidobacterium* in early life is able to improve body weight gain of LBW infants[177,178] and promote *Bifidobacterium* colonisation[179]. Furthermore, a meta-analysis of twenty randomised and controlled trials showed reduced risks for NEC and mortality were achieved by *Bifidobacterium* or *Lactobacillus* supplementation in preterm VLBW infants[180]. Accordingly, the use of nutritional intervention to foster a beneficial intestinal microbiota composition can be a good strategy to prevent potential health problems[181]. Multi-strain probiotic combinations have shown greater efficacy than single-strain probiotic supplementation for GIT and immune outcomes in animals and humans[182]. A combination of *Bifidobacterium* and *Lactobacillus* supplementation is proven to reduce the occurrence of NEC[183,184], mortality[185] and to increase the growth rate[186] in LBW infants.

Supplementation with prebiotics in formulas could promote the growth of beneficial microbes in LBW infants. Generally, prebiotics consist of one or more carbohydrates such as inulin, lactulose, fructo-oligosaccharides (FOS) or galacto-oligosaccharides (GOS). For example, supplementing the preterm formula with a mixture of FOS and GOS may stimulate the growth of *Bifidobacteria*[187,188], whereas lactulose addition increases the growth of *Lactobacillus*[189]. Moreover, Dilli *et al.*[190] reported that adding a synbiotic (*Bifidobacterium lactis* plus inulin) to breastmilk or formula could decrease the risk for NEC in VLBW infants. Similar results were observed by supplementing another kind of synbiotic containing *Lactobacillus*, *Bifidobacterium* and FOS[191]. Overall, we can speculate that supplementing probiotics and prebiotics alone, or as a combination, might be useful for optimising the intestinal micro-ecology, GIT health and further stimulating the growth outcomes of LBW offspring.

Hormone regulation

Leptin. Leptin is a 16-kDa cytokine mainly produced by the adipose tissue and is responsible for the central regulation of food intake and energy balance as well as for enhancing the postnatal maturation of numerous peripheral organs. Its deficiency will lead to morbid obesity and diabetes as well as various neuroendocrine anomalies[192–194]. Evidence illustrates that human newborns with LBW show significantly lower serum leptin levels than do normal newborns[195]. Studies using pigs as a model confirmed that this reduction may be a result of abnormal hypothalamic distribution of leptin receptors[194] and lower expressions of the leptin gene in perineal adipose tissue[196]. In piglets, leptin injection (0·5 mg/kg) from days 2 to 10 of age can improve body weight and lean mass of LBW piglets by increasing organ weights, like that of the pancreas, liver and lung[194]. Interestingly, leptin treatment can normalise the composition of the adipose tissue by decreasing white-adipocyte density while increasing the individual adipocyte size[194]. These findings suggest that leptin treatment in early postnatal life has the potential to correct abnormal fat deposition in LBW offspring through regulation of body weight gain, organ development and body composition.

Insulin and insulin-like growth factor-I. In neonatal miniature pigs, oral insulin administration can stimulate ileal growth and enhance the specific activities of lactase and maltase[197]. Several studies demonstrated that an extra addition of IGF-I in infant formula might improve GIT growth and function in newborn colostrum-deprived pigs[198–200]. Infusion of IGF-1 (4 µg/h) to IUGR piglets aged 3–10 d evidently increased the circulating concentration of IGF-I and the rate of weight gain by approximately 10 %, because of the increase in protein and fat accretion levels[201]. The potential mechanisms of this enhancement contain a stimulated cell proliferation in the GIT[198], increased brush-border disaccharidase activity[199] and increased intestinal weight and ileal villus height[200]. In VLBW infants, continuous insulin infusion (0·05 units/kg per h) from 24 h after birth to 7 d of age led to an increase in IGF-I concentrations in the serum at 28 d and therefore, an increase in both body weight and head circumference[21]. Similar insulin therapy (0·025 units/kg per h) reduced the incidence of hyperglycaemia in VLBW infants[202]. On the basis of this information, IGF-I and insulin could be two potential growth promoters in LBW offspring during the early postnatal period.

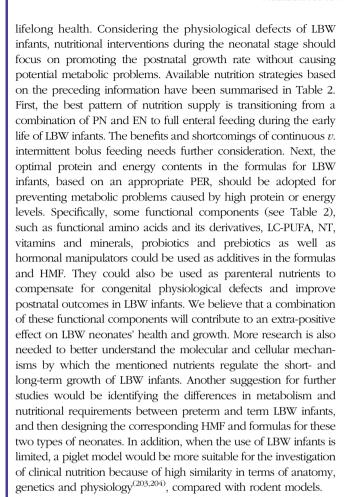### Conclusions and perspectives

In addition to the reduced growth rate after birth, LBW infants are also born with abnormalities in hormone regulation and nutrient utilisation, all of which might have adverse effects on

Table 2. Examples of nutrition strategies for improving growth, development and health of low birth weight (LBW) infants

Interventions	Experimental model	Feeding methods	Primary benefits/side effects
Appropriate patterns of nutrient delivery			
PN	Preterm LBW infant	Started immediately after birth or within the first 2 h of life	Avoiding feed intolerance and achieving full enteral feeding earlier
EN	Preterm LBW infant	A combination of PN and EN after birth until achieving full enteral feeding; supplementing targeted HMF or LBW formulas	Providing adequate nutrients to support rapid growth and promoting feeding tolerance
Continuous feeding	Preterm LBW infant	Orogastric tube feeding by continuous infusion	Lower stress response
Intermittent bolus	Preterm LBW infant	Orogastric tube feeding by intermittent bolus infusion	Faster time to establish full enteral feeding; improving feed tolerance and accelerating weight gain; higher stress response
Macronutrients			
Overnutrition	Preterm LBW infant; LBW piglet	Increasing protein and energy intake	Accelerating weight gain, brain and muscle development and N accretion; increasing fat accretion, inducing more oxidative stress and abnormal immune function
Nutrition restriction	IUGR rat or piglet	Decreasing protein and energy intake	Alleviating obesity and diabetes; improving the antioxidant system; lower growth rate
Higher PER	Preterm infant	Approximately 3 g/418 kJ (100 kcal) in formulas	Increased lean mass with relatively decreased fat deposition
Amino acids and its derivatives			
Arg	LBW piglet	Oral administration/dietary supplementation	Promoting growth rate, GIT health and nutrition metabolism
Gln	LBW infant or piglet	Oral administration/dietary supplementation	Increasing growth, intestinal immunity; decreasing FI and mortality
Leu	LBW piglet or rat	Dietary supplementation	Improving growth rate and protein synthesis; decreasing muscle atrophy
L-Carnitine	LBW piglet	Oral administration/dietary supplementation	Accelerating the rates of protein and fat accretion, and myogenic proliferation
LC-PUFA			
DHA + ARA	Preterm infant	Dietary supplementation	Higher lean body mass and reduced fat mass
EPA + DHA	Preterm infant	Dietary supplementation	Suppressing fat accumulation; improving insulin sensitivity; regulating inflammatory response
NT	LBW piglet	Dietary supplementation	Higher growth rate, intestinal villus height as well as lactase and maltase activity
Minerals			
Ca and P	Preterm LBW infant	Dietary supplementation	Improving bone mineralisation
Na and K	LBW infant	Dietary supplementation	Normalising kidney function
Vitamins			
Vitamin A	Preterm LBW infant	Oral administration/dietary supplementation	Improving mortality, lung and visual development
Vitamin E	Preterm LBW infant	Oral administration/dietary supplementation	Reducing the risk for retinopathy and intracranial haemorrhage
Vitamin D	Preterm LBW infant	Oral administration/dietary supplementation	Higher Ca retention and lower incidence of bone hypomineralisation
Probiotics/prebiotics			
Lactobacillus/Bifidobacterium	LBW or VLBW infant	Oral administration/dietary supplementation	Increasing the growth velocity and colonisation of beneficial bacteria; reducing the risk for NEC and mortality
FOS + GOS	LBW or VLBW infant	Oral administration/dietary supplementation	Stimulating the growth of *Bifidobacteria*
Lactulose	LBW or VLBW infant	Oral administration/dietary supplementation	Stimulating the growth of *Lactobacillus*
Synbiotic	LBW or VLBW infant	Oral administration/dietary supplementation	Decreasing the risk for NEC
Hormones			
Leptin	LBW piglet	Intramuscular injection	Normalising the composition of the adipose tissue
IGF-I	LBW piglet	Oral administration/infusion	Improving body weight gain and intestinal development
Insulin	VLBW infant	Oral administration/infusion/dietary supplementation	Increasing IGF-I concentrations, body weight; reducing the incidence of hyperglycaemia

PN, parenteral nutrition; EN, enteral nutrition; HMF, human-milk fortifiers; IUGR: intra-uterine growth restriction; PER, protein:energy ratio; Arg, arginine; GIT, gastrointestinal tract; Gln, glutamine; LC-PUFA, long-chain PUFA; ARA, arachidonic acid; NT, nucleotides; VLBW, very low birth weight, <1500 g; NEC, necrotising enterocolitis; FOS, fructo-oligosaccharides; GOS, galacto-oligosaccharides; ; IGF-I, insulin-like growth factor.

lifelong health. Considering the physiological defects of LBW infants, nutritional interventions during the neonatal stage should focus on promoting the postnatal growth rate without causing potential metabolic problems. Available nutrition strategies based on the preceding information have been summarised in Table 2. First, the best pattern of nutrition supply is transitioning from a combination of PN and EN to full enteral feeding during the early life of LBW infants. The benefits and shortcomings of continuous v. intermittent bolus feeding needs further consideration. Next, the optimal protein and energy contents in the formulas for LBW infants, based on an appropriate PER, should be adopted for preventing metabolic problems caused by high protein or energy levels. Specifically, some functional components (see Table 2), such as functional amino acids and its derivatives, LC-PUFA, NT, vitamins and minerals, probiotics and prebiotics as well as hormonal manipulators could be used as additives in the formulas and HMF. They could also be used as parenteral nutrients to compensate for congenital physiological defects and improve postnatal outcomes in LBW infants. We believe that a combination of these functional components will contribute to an extra-positive effect on LBW neonates' health and growth. More research is also needed to better understand the molecular and cellular mechanisms by which the mentioned nutrients regulate the short- and long-term growth of LBW infants. Another suggestion for further studies would be identifying the differences in metabolism and nutritional requirements between preterm and term LBW infants, and then designing the corresponding HMF and formulas for these two types of neonates. In addition, when the use of LBW infants is limited, a piglet model would be more suitable for the investigation of clinical nutrition because of high similarity in terms of anatomy, genetics and physiology[203,204], compared with rodent models.

Acknowledgements

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