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REVIEW

The microvasculature: a target for nutritional programming and later risk of cardio-metabolic disease

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Abstract

There is compelling evidence that microvascular deficits affecting multiple tissues and organs play an important role in the aetiopathogenesis of cardio-metabolic disease. Furthermore, both in humans and animal models, deficits in small vessel structure and function can be detected early, often before the onset of macrovascular disease and the development of end-organ damage that is common to hypertension and obesity-associated clinical disorders. This article considers the growing evidence for the negative impact of an adverse maternal diet on the long-term health of her child, and how this can result in a disadvantageous vascular phenotype that extends to the microvascular bed. We describe how structural and functional modifications in the offspring microcirculation during development may represent an important and additional risk determinant to increase susceptibility to the development of cardio-metabolic disease in adult life and consider the cell-signalling pathways associated with endothelial dysfunction that may be 'primed' by the maternal environment. Published studies were identified that reported outcomes related to the microcirculation, endothelium, maternal diet and vascular programming using NCBI PubMed.gov, MEDLINE and ISI Web of Science databases from 1980 until April 2013 using pre-specified search terms. Information extracted from over 230 original reports and review articles was critically evaluated by the authors for inclusion in this review.

Keywords developmental programming, endothelium, microvasculature, nutrition.

The metabolic syndrome is traditionally thought of as a non-communicable disease that occurs in adult life. It is characterized by at least three clinical risk factors which may include central obesity, hyperglycaemia, hyperinsulinaemia, raised serum triglyceride levels), low levels of high density lipoproteins and hypertension (Grundy *et al.* 2005). These risk factors predispose an increasing number of individuals to future type-2 diabetes mellitus and coronary heart disease, constituting one of the biggest health challenges in both developed and third-world countries today (Kassi *et al.* 2011, Defina *et al.* 2012). Epidemiological data from the National Health and Nutrition Examination Survey in the United States showed that the prevalence of metabolic syndrome (as defined by the National Cholesterol Education Program panel criteria) in adult males and females aged 20 years and over were 20.3 and 15.6%, respectively between 2003 and 2006 (Ervin 2009).

Various studies indicate that the aetiology of cardio-metabolic disease depends in part on the individual's genetic background as well as on lifestyle factors (smoking, high-calorie diets and inactivity). However, investigations into large-scale genome-wide

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associations have yet to provide strong evidence of a major genomic component such as single nucleotide repeats in the predisposition to the metabolic syndrome in the general population (Monda *et al.* 2010). Further, treatment strategies in the form of lifestyle interventions (diet and exercise) while often advised alongside pharmacological treatment have varied in their efficacy to reduce disease burden (Horton 2009). Mounting evidence now indicates that the rising incidence of cardio-metabolic disease may in fact have its origins in the individual's pre- and peri-natal environment (Gluckman *et al.* 2008). In the early 1990s, Hales and Barker reported that a strong risk factor for the development of cardio-metabolic disease was low birth weight (Hales & Barker 1992). Similarly, more recent evidence also demonstrates an inverse relationship between birth weight and cardiovascular disease and type-2 diabetes risk (Huxley *et al.* 2007, Whincup *et al.* 2008). Later insights led to the proposition that an altered maternal body composition and/or nutrition could give rise to permanent physiological and metabolic adaptations in the foetus and predispose it to the development of type-2 diabetes and metabolic syndrome in later life (Hales & Barker 2001, Armitage *et al.* 2008). Furthermore, it has been suggested that long-term effects of adaptations to an adverse intrauterine environment might be exacerbated if there is a nutritional mismatch between an individual's adaptations to the 'predicted' environment and the environment encountered in post-natal life (Gluckman *et al.* 2005).

For decades, investigations that targeted causal mechanisms of cardio-metabolic disorders neglected the likely involvement of a microvascular basis in their pathogenesis. Recent evidence suggests a link between microvascular dysfunction and cardio-metabolic disease and that structural and functional alteration in the microvasculature in key metabolic tissues and organs, resulting from exposure to an adverse maternal environment in early life, may constitute a key determinant in an individual's susceptibility to cardio-metabolic disease in adult life. This review focuses on our current understanding of the resultant magnitude and tissue-specific nature of these microvascular adaptations and current views of the functional outcomes of 'developmental microvascular priming' in early life.

Microvascular function

The microvascular bed is generally taken to comprise small resistance arteries, arterioles, capillaries and venules with diameter <150 μm that lie within the tissue parenchyma (Pries & Secomb 2008). The fundamental structural variations between microvascular beds in different organs relate primarily to microvascular densities, branching patterns, and capillary ultrastructure, and the mechanisms by which vascular tone, and hence, tissue perfusion is regulated. The primary role of the microcirculation is to provide optimal exchange of gases, nutrients and metabolites between the blood and surrounding tissues. The physiological regulation of solute transfer is generally achieved through variations in the number of exchange vessels perfused and local blood flow. A reduction in either gives rise to suboptimal tissue perfusion and a failure to meet metabolic demand. Between 70 and 90% of the systemic arterial pressure may be delivered to the microcirculation. Thus, a second important role of the microvascular bed is to limit large fluctuations in hydrostatic pressure within the thin-walled capillaries. This is achieved at the level of arterioles through regulation of vascular tone, making the microvasculature an important site for the regulation of local and overall peripheral resistance and hence blood pressure (Delano *et al.* 1991).

Key to the regulation of vascular resistance and blood flow within the microvascular bed are local, neural and humoral and myogenic vasoregulatory mechanisms. Endothelial cells regulate vascular tone by releasing vasoconstrictors (e.g. thromboxane A_2, endothelin-1, prostaglandin H_2) and vasodilators that include nitric oxide (NO), prostacyclin (PGI_2) and endothelium-derived hyperpolarization factors (EDHF; Feletou *et al.* 2010). The relative contribution of these mediators to maintain vascular tone and adequate tissue perfusion varies across the vascular tree, in many disease states and across the life course. For example, the contribution of EDHFs to vasodilator tone increases as vessel size decreases, with predominant EDHF activity in small resistance arteries and within the microvasculature (Potocnik *et al.* 2009, Edwards *et al.* 2010). In cardiovascular pathologies characterized by a reduced NO bioavailability, a compensatory up-regulation of EDHFs serves to sustain dilatation and maintain tissue perfusion (Feletou & Vanhoutte 2009, Giachini *et al.* 2009, Goto *et al.* 2012). Finally, in early post-natal life, the rapid enlargement of many organs is accompanied by extensive growth of their microvascular networks and tissue-specific alterations in metabolic requirements that necessitates changes in local blood flow regulation (Boegehold 2010). This maturational shift is associated with a change in the relative influence of vasoactive molecules that are organ-specific and includes NO, EDHFs and metabolites of cyclooxygenase (COX) (Boegehold 2010, Kang *et al.* 2012). Taken together, these observations provide evidence for considerable plasticity in microvascular control in early life.

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Microvascular function in cardio-metabolic disease

Evidence that disturbances in microvascular structure and function play a key role in the patho-physiological manifestations of cardio-metabolic disease comes from longitudinal and cross-sectional studies in human cohorts and from rodent models such as the obese Zucker rat (OZR), db/db and ob/ob mouse models of cardio-metabolic disease, for example (Jonk *et al.* 2007, De Boer *et al.* 2012). Microvascular dysfunction has been shown to be present in individuals with hypertension and type-2 diabetes as well as in overweight and obese individuals in the absence of insulin resistance and hypertension (Wiernsperger *et al.* 2007, De Boer *et al.* 2012). Blood flow in skeletal muscle and coronary microvascular beds has also been found to negatively correlate with insulin resistance, obesity and type 2 diabetes, both at rest and during increased metabolic demand (Bauer *et al.* 2007, Copp *et al.* 2010, Wu *et al.* 2011, Quercioli *et al.* 2012), and changes in capillary perfusion have been shown to influence skeletal muscle oxygen uptake and insulin-mediated glucose disposal (Clark 2008). Similarly, microvascular exchange surface area and perfusion have been shown to be negatively associated with central obesity, insulin resistance and features of the metabolic syndrome (Caton *et al.* 2009, Krentz *et al.* 2009, Clough *et al.* 2011).

Although it is widely accepted that changes in the microcirculation may occur before clinical manifestations of end-organ microvascular disease, the extent to which early changes in microvascular health and function impact on overall cardio-metabolic disease severity is still not fully understood. Furthermore, the magnitude and timing of the physical and functional remodelling of the peripheral vascular tree that occurs in cardio-metabolic diseases remain uncertain. As yet, few data are available on microvascular dysfunction in deep tissues, and the majority of studies that suggest a contributory role of the microcirculation to the development and progression of cardio-metabolic disease are largely confined to measurements in accessible vascular beds in humans such as the skin and retina and to those in animal models of cardio-metabolic disease.

Structural alterations of the microcirculation

Microvascular rarefaction, that is, altered microvessel numbers, branching patterns and microvessel morphology has been a consistent observation in obesity, hypertension and insulin-resistant states. These alterations result in constrained tissue/organ perfusion due to the longer capillary diffusion distances required for metabolic exchange (de Jongh *et al.* 2006, Levy *et al.* 2008). Studies using non-invasive vascular-imaging technologies suggest strong links between subtle changes in microcirculatory anatomy and both clinical and subclinical cardio-metabolic outcomes. In both the skin and retinal microcirculation, a reduction in capillary numbers and diameters has found in early stages of cardio-metabolic disease and worsen with the severity of disease (Sasongko *et al.* 2010, Benitez-Aguirre *et al.* 2011, Cheung *et al.* 2011, Gopinath *et al.* 2011, Ding *et al.* 2012, Sasongko *et al.* 2012). A direct relationship between insulin sensitivity and microvascular function has also been demonstrated, with endothelium-dependent vasodilatation and capillary recruitment in response to reactive hyperaemia inversely associated with insulin sensitivity in non-diabetic obese patients (Serne *et al.* 2002, de Jongh *et al.* 2004, Clough *et al.* 2009).

In db/db mice that represent a model of obesity, diabetes and dyslipidaemia, a reduction in network length and arteriolar lumen diameter is seen in the skeletal muscle microcirculation (Georgi *et al.* 2011). In the same report, the skeletal muscle of ob/ob mice, with hyperphagia, type-2 diabetes and obesity, displayed a significant alteration in microvascular network pattern and longer vessels with non-uniform lumen diameters (Georgi *et al.* 2011). Functional rarefaction in both db/db and ob/ob mice also gave rise to perfusion heterogeneity as a result of the reduction in the number of flow paths (Georgi *et al.* 2011). In non-obese diabetic rats, a significant reduction in capillary volume (Kondo *et al.* 2011), diameter and total microvascular surface area (Sexton *et al.* 1994) also appears indicative of structural rarefaction associated with vascular remodelling in the skeletal muscle microcirculation. Haemodynamic computational modelling studies using the spinotrapezius muscle from Zucker diabetic fatty rats showed a 37% decrease in microvascular branching and a 19% decrease in microvessel length density in early stages of the disease. Upon established diabetes in these rats, a 44% reduction in capillary network flow led to alterations in flow patterns as well as an insulin-mediated glucose exchange in skeletal muscles (Benedict *et al.* 2011). Similar findings have been reported from other animal studies and together suggest that microvascular rarefaction is associated with a decreased sensitivity and/or responsiveness to the metabolic actions of insulin and hence a reduced glucose disposal. In support of this, structural rarefaction in the microcirculation has been shown to lead to a marked insulin resistance in the skeletal muscle of the (lean) muscle-specific vascular endothelial growth factor (VEGF) knockout mouse (Bonner *et al.* 2012).

Interestingly, Frisbee (2005) has suggested that the reduction in skeletal muscle microvascular density in

young OZRs, which exhibit a metabolic syndrome phenotype, was not associated with hypertension. This led them to suggest that in these rats, other factors associated with a metabolic syndrome phenotype, such as insulin resistance, may underlie the progression of microvascular rarefaction and the exacerbation of cardio-metabolic disease. Microvascular rarefaction has been implicated in the elevation of vascular resistance in other studies, including in a computer simulation model, where a reduction in functional capillary density beyond 30% led to an exponential increase in vascular resistance (Hudetz 1993).

A decreased microvascular density is also associated with increased flow heterogeneity in the microvascular bed, resulting in a non-uniform distribution of blood flow among exchange vessels. Accordingly, a mathematical model of the hamster cheek pouch microcirculation demonstrated that a 40% reduction in microvascular density was associated with a 20% increase vascular resistance and a profound heterogeneity of blood flow within the microcirculation (Greene *et al.* 1989). Altered flow distribution at the level of the microvascular network has also been shown to contribute to the failure of the microvessels to match skeletal muscle metabolic demand with perfusion (Turzyniecka *et al.* 2009, Frisbee *et al.* 2011, Wu *et al.* 2011). Hence, early microvascular rarefaction in cardio-metabolic disease may affect both pressure and flow patterns and have consequences not only for vascular resistance, but also for muscle perfusion and metabolism.

Functional alterations of microcirculation

Several lines of evidence indicate that mechanisms regulating vascular tone are altered in cardio-metabolic disease and that changes in endothelium-mediated vasoconstrictor and dilator responses mediated by locally produced autacoids contribute to microvascular dysfunction in such disease states (Tziomalos *et al.* 2010, Kabutoya *et al.* 2012, Rossi *et al.* 2013). The reduced availability of endogenous vasodilators required to maintain vascular tone and tissue perfusion has been attributed to the enhanced production of reactive oxygen species (ROS) in response to the elevated levels of pro-inflammatory cytokines, adipokines, glucose oxidation (in hyperglycaemic states) and free fatty acids (from peri-vascular adipose tissue; Goodwill & Frisbee 2012). Evidence for impaired endothelium-dependent NO-mediated dilation has been reported in numerous human studies in cardio-metabolic disease both in larger arteries using flow-mediated dilatation (FMD) and within the microvasculature using non-invasive imaging of the skin and deeper tissues (Steinberg *et al.* 1996, de Jongh *et al.* 2008, Kabutoya *et al.* 2012). Studies in rodent models have similarly shown alterations in NO-mediated dilation in skeletal muscle microcirculation (Frisbee 2003, 2005, Costa *et al.* 2011). The contribution of oxidative stress to these altered NO-mediated responses and microvascular dysfunction has been confirmed in cardio-metabolic disease (Pannirselvam *et al.* 2002, 2003, Cheang *et al.* 2011) and in the ageing microcirculation (Muller-Delp *et al.* 2012). Alterations in endothelium-dependent relaxation pathways due to oxidative stress have also been suggested to arise from reduced PGI_2 levels as a result of altered arachidonic acid metabolism in the microcirculatory beds of skeletal muscle (Frisbee *et al.* 2009, Hodnett *et al.* 2009) and reproductive organs (Sanchez *et al.* 2010). Changes in non-NO-mediated vasodilation associated with the hyperpolarization of both endothelial and vascular smooth muscle cells have also been reported in diabetic, obese and insulin-resistant states with up-regulation of EDHF-mediated dilation in cardio-metabolic disease (Giachini *et al.* 2009, Vanhoutte *et al.* 2009).

In summary, studies in a variety of animal models and in human microvascular beds show there are many factors that may influence optimal tissue function and increase risk of cardio-metabolic disease. The finding of changes in capillary number and regulation of network perfusion and the evidence of plasticity within the microvascular bed across the life course collectively support the concept that the microvasculature may be a target for developmental 'priming' and that mal-adaptations in the structure and function of the microvasculature in key organs and tissues in early life may increase susceptibility to cardio-metabolic disease risk factors in adult life.

Vascular programming and later risk of cardiometabolic disease

Deficits in vascular function, including at the level of the microvasculature, are strongly associated with birth weight (low and high) and later cardiovascular risk in infants, children and young adults born small or prematurely (Clough & Norman 2011, Torrens *et al.* 2011), and maternal calorific intake and calorific composition have been shown to influence microvascular angiogenesis, vasculogenesis and barrier integrity and maturation of the foetal vascular system (Leach 2011). In addition, a number of studies describe the effects of maternal diet and other maternal stressors on uterine and umbilical blood flows and the size of the placental vascular bed and their potential to affect foetal vascularization, independent of offspring birth weight so confirming the critical role of the placenta in developmental programming (Redmer *et al.* 2009,

Meyer *et al.* 2010, Reynolds & Caton 2012). While there have been few investigations of associations between overnutrition/obesity in pregnant women and cardiovascular risk in their children, a positive association between gestational weight gain and offspring obesity and systolic blood pressure has been reported in young children (Lawlor *et al.* 2004, Oken 2009) and young adults, where a greater gestational weight gain was associated with greater BMI and systolic blood pressure (Mamun *et al.* 2009). There are also an increasing number of animal studies examining the association between maternal overnourishment/obesity, foetal growth rate and placental vascularity (Ma *et al.* 2010), foetal organ development (George *et al.* 2010) and offspring organ and vascular function and a cardio-metabolic disease phenotype (Taylor *et al.* 2004, Samuelsson *et al.* 2008, Bruce *et al.* 2009, Torrens *et al.* 2012, Dong *et al.* 2013) as reviewed by Ainge *et al.* (2011).

Maternal undernutrition

The first report linking 'intrauterine under-nutrition' with later obesity and cardiovascular disease was described in an epidemiological study on adult offspring of female survivors of the Dutch famine of 1944. Ravelli *et al.* (1976) suggested that maternal undernutrition during early gestation was associated with the development of hypertension in the offspring in adult life (Roseboom *et al.* 1999, 2001). In later stages of gestation, however, under-nutrition gave rise to offspring with an increased adiposity and glucose intolerance when subjects were compared to well-nourished offspring (Law *et al.* 1992, Ravelli *et al.* 1999). Studies in other human cohorts have shown similar findings. Yajnik *et al.* (1995, 2003) pioneered the first study of 'foetal origins' in India where they tested the hypothesis that low birth weight was an independent predictor of glucose tolerance and insulin resistance variables in 4- and 8-year-old urban children born in the city of Pune, India. Children with a low birth weight were found to have a significantly high systolic blood pressure, plasma cholesterol and insulin, and were significantly heavier than non-low-birth weight children. A more recent study showed that offspring born after the Chinese famine (1959–1961) had a higher risk of developing hyperglycaemia and type-2 diabetes in adulthood. This risk was found to be higher in subjects who went on to adopt a Western dietary pattern (Li *et al.* 2010). Together these studies also suggest that an important driver for future cardio-metabolic risk was the 'nutritional mismatch' experienced by the offspring during their intrauterine and early post-natal life. This paradigm formed the basis of the predictive adaptive response hypothesis described by Gluckman and colleagues (Gluckman & Hanson 2004, Gluckman *et al.* 2008, Vickers & Sloboda 2012).

Oxidative stress resulting from compromised endogenous antioxidant defences is a common feature of cardio-metabolic disease and has emerged as a key link between birth weight and increased morbidity later in life as a consequence of sustained oxidative stress. Reduced levels of superoxide dismutase, catalase, glutathione and serum malondialdehyde have been observed when cord blood from small for gestational age (SGA) babies was compared to that of healthy children that were born appropriate for gestational age (AGA) (Gupta *et al.* 2004). Furthermore, there is evidence that the raised levels of biomarkers of oxidative stress in addition to insulin resistance persist in pre-pubescent life (Franco *et al.* 2007, Chiavaroli *et al.* 2009).

Several human studies have also provided evidence for impaired endothelium-dependent and endothelium-independent vasodilation in low birth weight individuals at birth, at 3 months of age, in later childhood and in early adult life (Goh *et al.* 2001, Norman & Martin 2003). In infants, vascular dysfunction was evidenced by a significant reduction in acetylcholine-induced vasodilation in the microvasculature and a reduced ability of the brachial artery to dilate in response to increased blood flow following occlusion (Martin *et al.* 2000). In a recent study in children aged 7–15 year, it was observed that non-obese SGA children similarly displayed a lower FMD compared with obese AGA children (Jouret *et al.* 2011).

In many countries, preterm birth is a more common cause of low birth weight than foetal growth restriction. Prematurely born infants display an increased risk for developing metabolic (insulin resistance) and cardiovascular disorders (elevated blood pressure and abnormal retinal vasculature) as adults (Kistner *et al.* 2005, Kerkhof *et al.* 2012). Interestingly, these individuals have been shown to have otherwise healthy endothelial function in childhood and early adulthood at both microvascular and macrovascular levels (Bonamy *et al.* 2005, 2007, Mikkola *et al.* 2007). Adolescents and young adults born premature have higher blood pressure, abnormal retinal vascularization and lower peripheral skin blood flow than control subjects (Kistner *et al.* 2002, Bonamy *et al.* 2005). In another study, adult women born preterm appear to have a 2.5-fold increased risk of developing hypertension compared with women born at term (Pouta *et al.* 2004). Interestingly, in those studies, SGA subjects were not different from AGA subjects, both within the premature and the term groups, suggesting an important role of preterm birth itself in the programming of cardiovascular function in later life. Although the

mechanisms linking prematurity and later cardiovascular disorders remain unclear, it is evident that it is associated with impaired nephrogenesis and vasculogenesis (Gilbert *et al.* 2005, 2007) as well as oxidative stress (Yeung 2006), all of which may contribute to later end-organ microvascular dysfunction and the risk of developing cardio-metabolic disease. The extent to which the microvasculature is altered in other tissues in premature and low birth weight individuals has important implications for cardio-metabolic health, and remains to be clarified. For instance, muscle capillary density determines diffusion and tissue concentration of insulin, as described above. Functional and/or structural loss of muscle capillaries could therefore be a mechanism linking low birth weight and/or preterm birth to later insulin resistance.

Intrauterine undernutrition is associated with endothelial vasodilator dysfunction in the adult offspring (Lamireau *et al.* 2002, Taylor *et al.* 2004, Torrens *et al.* 2009). Animal models of maternal undernutrition support a role for programming of hypertension through altered endothelium-dependent dilations in resistance arteries in the offspring (Torrens *et al.* 2003) via altered NO signalling (Rodford *et al.* 2008, Torrens *et al.* 2009). Consistent with this, Lamireau *et al.* (2002) showed that maternal protein deprivation resulted in a 50% reduction of NO-dependent relaxation in resistance cerebral microvessels which was associated with reduced cGMP and soluble guanylate cyclase expression. Reduced NO levels in undernourished offspring have also been attributed to oxidative stress following an increased superoxide generation (Ceravolo *et al.* 2007) and reduced tetrahydrobiopterin (BH_4), an important cofactor in nitric oxide synthase (NOS) activity and therefore in the conversion of L-Arg to NO, in resistance arteries (Franco *et al.* 2002, 2003, 2004). The administration of antioxidants (Franco *et al.* 2003) and exogenous BH_4 (Franco *et al.* 2004) was found to reduce oxidative stress and blood pressure thus improving vascular function. In support of this, endothelial dysfunction and reduced antioxidant protection in resistance arteries in male offspring of protein-restricted rats were linked to the reduced expression of the antioxidant enzyme, haem oxygenase-1 (HO-1) (Rodford *et al.* 2008).

Strong correlations between endothelial function in adult offspring and micronutrient intake during pregnancy have also been found. In a protein-restricted model, low folate levels were linked to a reduced NO bioavailability and endothelial NOS mRNA expression (Torrens *et al.* 2006). Similarly, vitamin D deficiency during development and early life in rats was associated with a reduced EDHF-induced dilation and an increased myogenic tone in resistance arteries in adult offspring (Tare *et al.* 2011).

Structural alterations in small resistance arteries have also been implicated in mediating vascular dysfunction and hypertension in offspring exposed to intrauterine calorie restriction (Khorram *et al.* 2007a, b,c). For example, reduced microvessel numbers and branches found in the mesenteric and renal microcirculation as a result of decreased angiogenesis in offspring of calorie restricted dams are thought to contribute to an increased peripheral vascular resistance and hypertension in later life (Khorram *et al.* 2007a). Further, capillary rarefaction in skeletal muscle in young rats (7 and 28 days old) but not in foetal rats with programmed raised blood pressure associated with a maternal low-protein diet, suggesting an early post-natal disruption in normal microvascular development (Pladys *et al.* 2005). In the sheep, capillary rarefaction in skeletal muscle and a reduced capillary to myofibre ratio have also been linked to a reduction in myofibre density but not in size, in a muscle-specific manner, following maternal undernutrition (Costello *et al.* 2008).

Microvascular rarefaction associated with impaired angiogenesis or active disappearance of blood vessels has been reported in some but not in all maternal dietary restriction models in skeletal muscle and cerebral cortex (Pladys *et al.* 2005, Khorram *et al.* 2007a, Costello *et al.* 2008) and reviewed by Clough and Norman (2011). A reduced NO bioactivity or increased oxidative stress in early life that is associated with many dietary models could be postulated to impact on microvessel formation and survival through perturbation of angiogenic and/or apoptosis signalling pathways (Pladys *et al.* 2005, Cambonie *et al.* 2007, Neville *et al.* 2010). However, a reduction in VEGF and VEGFR protein expression seen in neonates appears reversed and/or normalized by adulthood (Khorram *et al.* 2007a). Placental IGF-I synthesis is also down-regulated in placental insufficiency and foetal growth restriction, and low serum concentrations of IGF-I in preterm infants have been associated with growth arrest of the microvasculature in the eye (Hellstrom *et al.* 2003) which is modifiable by nutritional intervention (Engstrom *et al.* 2005).

An imbalance between angiogenic and anti-angiogenic factors involved in regulation of number and function of foetal endothelial progenitor cells has also been suggested to be involved in developmental programming of hypertension and cardiovascular disease (Ligi *et al.* 2010). Altered angiogenic properties of cord blood endothelial colony-forming cells (ECFCs) have been in preterm neonates compared with those studied at term (Ligi *et al.* 2011). Similarly, subsets of circulating progenitor cells (CPCs) with robust angiogenesis-facilitating functions have been shown to be reduced in women with gestational diabetes (Acosta

et al. 2011). However, the impact of these increases in CPCs does not appear to be translated into altered vascular function in the neonates, as endothelial function appears normal (Acosta *et al.* 2011). Thus, to what extent impaired angiogenic properties of CPCs and ECFCs and other factors may influence early vascular remodelling and/or angiogenesis has yet to be explored.

Nutrient restriction has also been shown to induce remodelling of the vascular extracellular matrix with increased collagen deposition and matrix metalloproteinase expression in the walls of both mesenteric arterioles and the aorta, perhaps driven by the overexpression of VEGF, in adult offspring (Khorram *et al.* 2007a). Other studies report a 30% reduction in venular basement membrane type IV collagen in 8-week-old male offspring of undernourished rat dams (Landgraf *et al.* 2007) which may also modify angiogenesis and/or apoptosis of microvessels. More recently, maternal undernutrition has been shown to alter offspring vascular expression of micro-RNAs (miRNAs) including those targeting genes involved with the regulation of collagen, elastin, enzymes involved in ECM remodelling and angiogenic factors (Khorram *et al.* 2007b, 2010). These in turn could regulate the expression of genes involved with angiogenesis and extracellular matrix remodelling. While these findings help us to understand the links between the early life environment and structural remodelling of the microvasculature, the cell-signalling mechanisms that underlie functional deficits have yet to be fully elucidated.

Animal studies also give insight into the effects of the timing of dietary intervention in pregnancy on the extent of vascular programming. Intrauterine growth restriction in late gestation led to region-specific programming of vascular dysfunction, but not to hypertension and obesity in 18-month-old female offspring. In these females, vascular dysfunction, as manifested by a reduction in EDHF-mediated relaxation and structural rarefaction, was seen in the uterine artery but not in the mesenteric, renal and femoral arteries (Mazzuca *et al.* 2010). In contrast, intrauterine growth restriction induced by restricting blood flow to the gravid uterus (day 14 of gestation) in rats resulted in growth-restricted female offspring that were hypertensive as adults and had an increased smooth muscle contractility and altered endothelium-dependent and -independent relaxation in the mesenteric microcirculation (Anderson *et al.* 2006). Further, the effects on the offspring were transgenerational. More recently, Torrens and others showed the vascular effects of foetal programming may have long-term consequences for the development of the next generation of offspring. In this study, offspring of rats that experienced intrauterine protein restriction exhibited a high blood pressure and endothelial dysfunction even in the absence of an additional dietary challenge (Torrens *et al.* 2008).

Maternal overnutrition

Consistent with the developmental origins of cardiovascular disease hypothesis, altered vascular biology is not confined to those who are small at birth. Epidemiological data from human cohorts have shown a positive correlation between increased birth weight (used as a surrogate for maternal overnutrition) and a high BMI and/or obesity in adulthood (Sen *et al.* 2012). In addition to weight gain, other studies have provided a strong link between maternal obesity and subsequent development of the metabolic syndrome in adulthood, independent of maternal diabetes (Boney *et al.* 2005). However, while an association between maternal overnutrition and foetal growth, adiposity and cardiovascular risk factors in well-nourished populations (Drake & Reynolds 2010, Freeman 2010) has been shown, there is little evidence as yet for the consequences of maternal overnutrition on offspring microvascular function. However, the maternal insulin resistance, which is induced by an increased maternal fat mass, is likely to affect not only foetal growth, but also microvascular structure and function. Increased maternal body fat, serum leptin and triglycerides are associated with altered placental vascular development and a 30% decrease in the number of mature blood vessels that stained positive for smooth muscle actin (Hayes *et al.* 2012) which these authors hypothesize may result in a reduced oxygenation of foetal tissue contributing to poorer outcomes. A number of recent studies have further shown that greater pre-pregnancy BMI and pregnancy BMI are associated with adverse retinal microvessel number and structure (Li *et al.* 2012) and that retinal arterioles and venules may be differentially associated with offspring growth in early life, and early adiposity may adversely affect the microcirculation (Tapp *et al.* 2013).

In a recent systematic review by Ainge *et al.* (2011) of studies on developmentally primed offspring of overnourished rodent dams, including *ad libitum* feeding of high-fat diets supplemented with sweetened condensed milk or high-fat and/or high sugar junk food/cafeteria diet who are then weaned onto a laboratory chow diet, offspring consistently exhibited hyperphagia, increased adiposity, hypertension, abnormal glucose homoeostasis and reduced insulin sensitivity, and endothelial dysfunction in resistance and conduit arteries that persists into adulthood (Samuelsson *et al.* 2008, Elahi *et al.* 2009). Furthermore, there is increasing evidence that these cardio-metabolic disease risk

factors persist in spite of a healthier post-natal diet (Taylor *et al.* 2004, Armitage *et al.* 2008) and may be increased further by an adverse post-weaning diet and by age (Ford & Long 2011, Masuyama & Hiramatsu 2012, Torrens *et al.* 2012, Yan *et al.* 2013). Similarly, we (Torrens *et al.* 2012) have shown there to be significant effects of maternal diet on offspring body weight, systolic blood pressure and endothelium-dependent relaxation to ACh measured in the femoral artery. Having controlled for differences in maternal diet, post-weaning offspring diet significantly influenced systolic blood pressure and endothelium-dependent relaxation. There was also a significant interaction between maternal diet and offspring diet to influence NO bioavailability associated with an increase in ROS in the artery wall and insulin resistance (Bruce *et al.* 2009). In humans, an increased expression of ROS in the placenta has been suggested to be one of the initiating factors in neonatal insulin resistance and obesity in response to maternal overnutrition (Radaelli *et al.* 2003).

While the NO pathway has been implicated in the endothelial dysfunction observed in the offspring of overnourished mothers, this does not apply to all models or all arteries. In their model of maternal high fat, Khan *et al.* (2005) showed impaired dilatation of the mesenteric arteries to ACh, which was still present after blockade of NOS and COX pathways, leading them to suggest this was an EDHF-related adaptation. Interestingly, this did not appear to be the case in the femoral arteries of the same animals. Evidence for an up-regulation of EDHF-mediated relaxation is seen in small resistance arteries and arterioles from other animal models of diet-induced obesity (Chadha *et al.* 2010, Feher *et al.* 2010, Haddock *et al.* 2011), hypercholesterolaemia (Ashraf *et al.* 2007), hypertension (Zhang *et al.* 2011), diabetes (Leo *et al.* 2011) and in apolipoprotein E and low density lipoprotein receptor-deficient mice fed a high-fat diet in adult life (Wolfle *et al.* 2009). Further, Kelsall *et al.* (2012) have demonstrated that in addition to an altered ACh-mediated vasorelaxation in mesenteric arteries from offspring of high-fat-fed rat dams, the type and amount of maternal dietary fat differentially influenced vasomotor tone and *de novo* biosynthesis of arachidonic acid in vascular smooth muscle. The extent to which the foetal environment impacts on EDHF or other signalling pathways in the human microcirculation remains to be established. Further, the impact of low-grade inflammation in the maternal environment through increased expression of pro-inflammatory cytokine genes and ROS in the placenta (Radaelli *et al.* 2003, Zhu *et al.* 2010), and increased foetal serum levels of TNF-α and IL-6 (Stewart *et al.* 2007) on the microvasculature has yet to be elucidated.

Mechanisms of microvascular programming

The aim of this review was to explore the evidence for the impact of the maternal environment on microvessel structure and function in the offspring and the influence that this might have on later risk of cardiometabolic disease. Through this it has become clear that programmed microvascular structural and functional rarefaction are associated with a complex range of causal and/or contributing factors but that the mechanisms underlying a 'primed' microvasculature remain obscure. Epigenetic dysregulation has been reported to mediate a number of the effects of early nutritional status on adult cardio-metabolic phenotype (Langley-Evans 2013). Thus, while many studies support that there are transgenerational effects of maternal under and overnutrition on the microvasculature, evidence for changes in DNA methylation or methylCpG-binding domain proteins at the level of the microvasculature or in microvascular microRNAs (Zhang *et al.* 2009) has yet to emerge. We can only speculate that changes in the microvascular epigenome may contribute to microvascular priming.

Perspectives

It is currently estimated that over 20% of women of childbearing age and almost 25% of pregnant women in the UK are overweight or obese with a BMI >30 kg m^{-2}. Higher maternal weight entering pregnancy is associated with higher weight and consequent risk for obesity, elevated blood pressure and diabetes among children. Obesity, hypertension and impaired insulin-mediated glucose disposal are all associated with abnormal microvascular structure and function. In the short term, elucidation of the impact of the developmental environment on the microvasculature, and of how structural or functional rarefaction during development limits the functional capacity of the microvasculature, will provide a much needed scientific basis for future mechanistic studies into programmed deficits in microvascular function in key tissues and organs.

Microvascular (dys)function is easily and non-invasively measured in a clinical setting. Subclinical changes in the microvasculature resulting from unfavourable lifestyle and environmental factors may therefore be detected early and possibly reversed through lifestyle interventions such as diet and exercise that are associated with reduced risk of microvascular disease. In the longer term, the identification of 'primed' proteins and genes associated with microvascular signalling pathways and the mechanisms by which this priming occurs may inform targeted intervention studies in at risk women and their children to

improve microvascular function before the onset of overt cardiovascular and metabolic disease.

Conflict of interest

None.

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