Pediatric Obesity Comorbidity/Pathophysiology

Pathophysiology of hypertension in obese children: a systematic review

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Summary

Hypertension is increasingly common in overweight and obese children. The mechanisms behind the development of hypertension in obesity are complex, and evidence is limited. In order to effectively treat obese children for hypertension, it is important to have a deeper understanding of the pathophysiology of hypertension in obese children. The present review summarizes the main factors associated with hypertension in obese children and discusses their potential role in its pathophysiology. Systematic searches were conducted in PubMed and EMBASE for articles published up to October 2014. In total, 60 relevant studies were included. The methodological quality of the included studies ranged from weak to strong. Several factors important in the development of hypertension in obese children have been suggested, including endocrine determinants, such as corticosteroids and adipokines, sympathetic nervous system activity, disturbed sodium homeostasis, as well as oxidative stress, inflammation and endothelial dysfunction. Understanding the pathophysiology of hypertension in overweight and obese children is important and could have implications for its screening and treatment. Based on solely cross-sectional observational studies, it is impossible to infer causality. Longitudinal studies of high methodological quality are needed to gain more insight into the complex mechanisms behind the development of hypertension in obese children.

Keywords: Children, hypertension, obesity, pathophysiology.

Introduction

In the recent decades, the global prevalence of overweight and obesity in children and adolescents has increased persistently, resulting in a major public health concern. The International Obesity Task Force defined overweight as a body mass index (BMI) corresponding with an adult BMI ≥ 25 kg m^{-2} and obesity with an adult BMI ≥ 30 kg m^{-2} (1). In 2010, worldwide, an estimated 40 million children under the age of 5 were overweight. The global prevalence of childhood overweight increased from 4.2% in 1990 to 6.7% in 2010 (2). In the United States, in 2009–2010, 16.9% of children aged 2–19 years were obese

(3). European countries are not far behind, with a prevalence of overweight between 13% and 28%, and obesity between 2% and 13% (4–9). Not only is the incidence increasing, but the severity of obesity has tripled in the past 25 years (10).

This obesity epidemic in children and adolescents is not without consequences. Obesity in children is associated with a variety of non-communicable diseases. Insulin resistance leads to fasting hyperinsulinaemia, which can be followed by impaired fasting blood glucose, impaired glucose intolerance and type 2 diabetes mellitus. Associated cardiovascular risk factors may include high blood pressure, high small-dense low-density lipoprotein cholesterol levels and

low high-density lipoprotein cholesterol levels and serum triglyceride levels (11). Hypertension, defined as blood pressure ≥ 95th percentile for age (12), is becoming increasingly common in obese children and adolescents. Several studies confirm a direct association between overweight and obesity and hypertension in children, with a prevalence of hypertension in overweight children of 4–14% and in obese children of 11–23% (13–16). This development is worrisome since both obesity and hypertension tend to track from childhood into adulthood, increasing the burden of hypertension in adults as well (17,18).

If not timely identified and treated, hypertension in childhood can lead to the development of atherosclerosis in young adulthood (19–21). Atherosclerosis, in turn, can result in ischaemia, myocardial and cerebral infarction, and renal failure (22).

The mechanisms behind the development of hypertension in obese children seem to be complex and interdependent, and evidence is limited. Suggested mechanisms for the pathophysiology of hypertension include sympathetic activation via hyperleptinaemia and hyperinsulinaemia, vascular damage as a consequence of inflammation, endothelial dysfunction and oxidative stress, and vasoconstriction and sodium and fluid retention through activation of the renin–angiotensin system (23–25). In order to treat obese children for hypertension effectively, it is important to have a deeper understanding of the complex pathophysiology of hypertension in obese children. The present review summarizes the evidence of the main factors associated with hypertension in obese children and discusses their potential role in the pathophysiology of obesity-induced hypertension in children.

Methods literature review

Search strategy and eligibility criteria

We conducted systematic search in the bibliographic databases PubMed and EMBASE from inception to 30 October 2014. The search terms included controlled terms, e.g. MeSH in PubMed and EMtree in EMBASE, as well as free text terms. The search term 'obesity' was used in combination with search terms comprising 'children and adolescents (2–18 years of age)', 'hypertension', 'pathophysiology' and 'cross-sectional, cohort, case-control studies'. The PubMed search strategy can be found in Table S1. The search strategy used in EMBASE was based upon the PubMed strategy. In addition, the reference lists of the identified articles were searched for relevant publications.

Single studies were included if they met all of the following criteria: (i) outcome: obesity and hypertension; (ii) age group: children and adolescents (2–18 years of age); (iii) pathophysiology: articles about the mechanisms related to

the development of hypertension in obesity; (iv) study design: observational studies, case–control studies and cohort studies and (v) published in English, French, German or Dutch. We applied no restrictions regarding publication date.

Selection process and data analysis

Two reviewers (A.W. and J.K.) independently screened the titles and abstract obtained from the search for relevance. Any disagreement between the reviewers was resolved based upon the full-text assessment. Thereafter, the reference lists of all studies selected for inclusion were scanned for other relevant references. All studies that did not meet the inclusion criteria or that met the exclusion criteria were removed. Eligible studies were further reviewed. Two reviewers (A.W. and J.K.) independently evaluated the methodological quality of the papers using a Dutch Cochrane Centre checklist (Table S2) adapted from *The Dutch Cochrane Centre Amsterdam, Amsterdam Medical Centre, 2013* (http://www.cochrane.nl). Details about the following elements were extracted and tabulated from the publications (Table S3): (i) study type; (ii) study population; (iii) sample size; (iv) selection bias; (v) exposure; (vi) outcome and (vii) confounders. Each element was scored either positive (+), negative (−) or with a question mark (?) if the paper provided insufficient information on the specific item. Finally, the study was scored either strong ('S'; no weak ratings, e.g. no '−' or '?'), moderate ('M'; one weak rating) or weak ('W'; two or more weak ratings). Disagreement between the reviewers on individual items were identified and resolved during a consensus meeting.

Results

Figure 1 summarizes the selection process of studies. In total, 1,976 references were obtained using PubMed ($n = 1813$) and EMBASE ($n = 163$). Subsequently, 78 duplicate references were removed. About 1,898 articles were screened for relevance, after which 1,828 references were excluded, resulting in 70 articles for full-text assessment of eligibility. An additional 25 full-text articles were included after scanning the reference lists of the studies selected for inclusion. Subsequently, 35 studies that did not meet the inclusion criteria or that met the exclusion criteria were removed. In total, 60 studies were considered eligible and further reviewed, and were included in the present review. The quality of the included articles is summarized in Table S3.

Findings

The pathophysiology of hypertension in obese children is found to be multifactorial and complex. The results are summarized in Fig. 2.
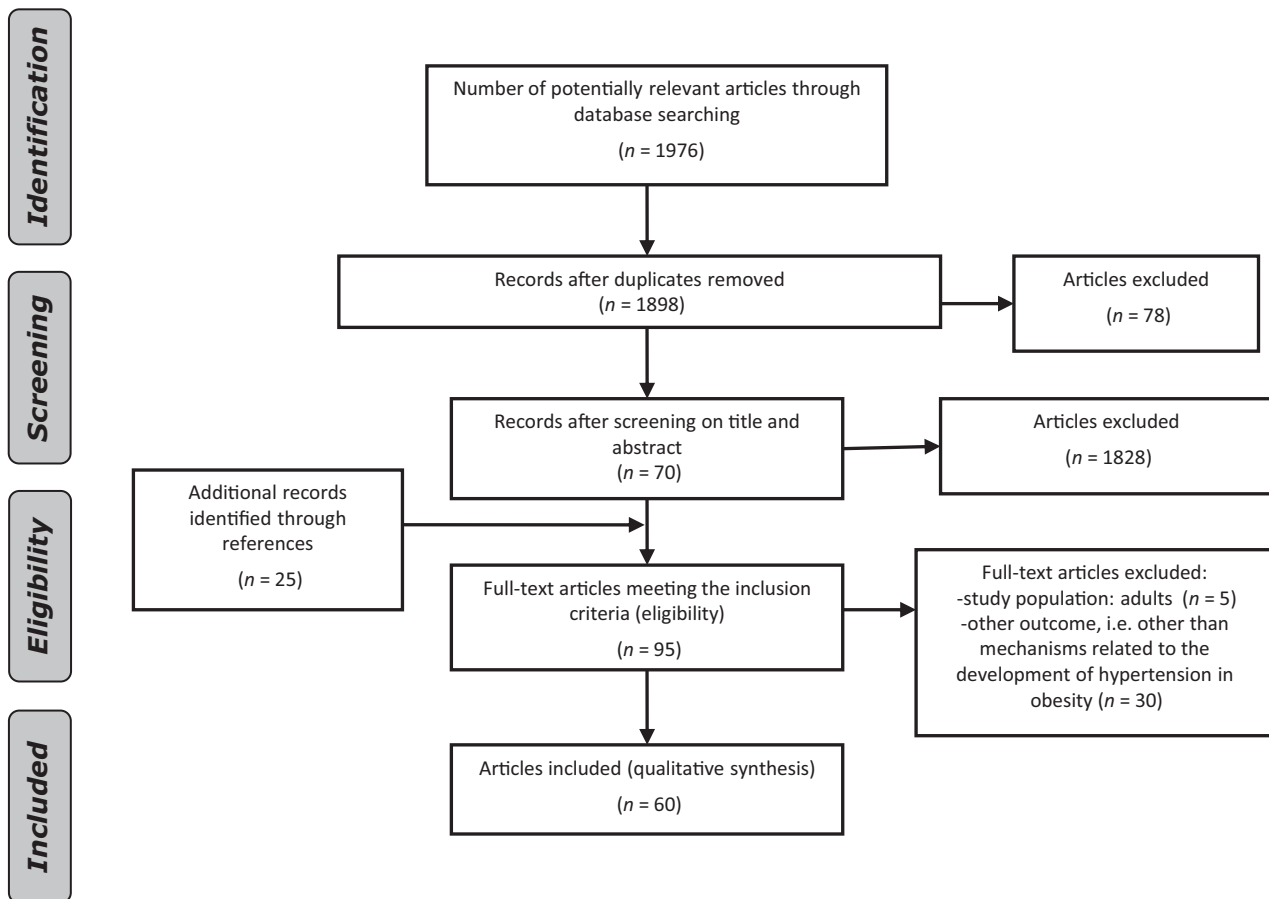
Figure 1 Flowchart of the search and selection procedure of studies.

Sympathetic nervous system activation

Although the exact mechanisms are unclear, it has been recognized that obesity can lead to increased sympathetic nervous system (SNS) activity. The cardiovascular autonomic nervous system is seen as one of the principal initiators for the development of hypertension in obese individuals, of which heart rate variability can serve as a marker. Low-frequency (LF) components of heart rate variability indicate sympathovagal activity, whereas high-frequency (HF) components reflect vagal activity. The ratio of these parameters indicates sympathovagal balance. In a group of obese children and adolescents (aged 8–16 years), HF parameter levels were lower than in a lean control group, whereas the ratio LF/HF was significantly higher in obese children (26). These findings suggest that the SNS is activated in obesity while vagal activity is decreased. This could play a role in the development of obesity-related hypertension. Another study also found that obese adolescents had a higher LF/HF ratio than their normal-weight peers. Additionally, in multiple regression analysis, the LF/HF ratio, reflecting heart sympathetic overactivity, was associated with higher systolic blood pressure (27).

Increased blood pressure variability could be a manifestation of increased sympathetic activity as well. Obese children with isolated systolic hypertension had a higher resting heart rate and higher blood pressure variability, suggesting a role for SNS hyperactivity in the development of hypertension in obesity (28). A study performed in a group of obese children and adolescents aged 7–18 years confirmed the association of SNS activity with blood pressure. Elevated systolic blood pressure was associated with higher urinary noradrenaline levels, suggesting hyperactivity of the SNS (29).

Baroreflex is a known regulatory mechanism engaged in blood pressure control, providing a quick feedback loop to decrease or increase blood pressure through heart rate regulation, mediated by both sympathetic and parasympathetic nerves. In a group of normal and overweight adolescents, a decreased baroreflex sensitivity was associated with hypertension. No significant association was found between baroreflex sensitivity and BMI. Although a role for BRS in the development of hypertension has been suggested, the specific mechanisms remain unclear (30).
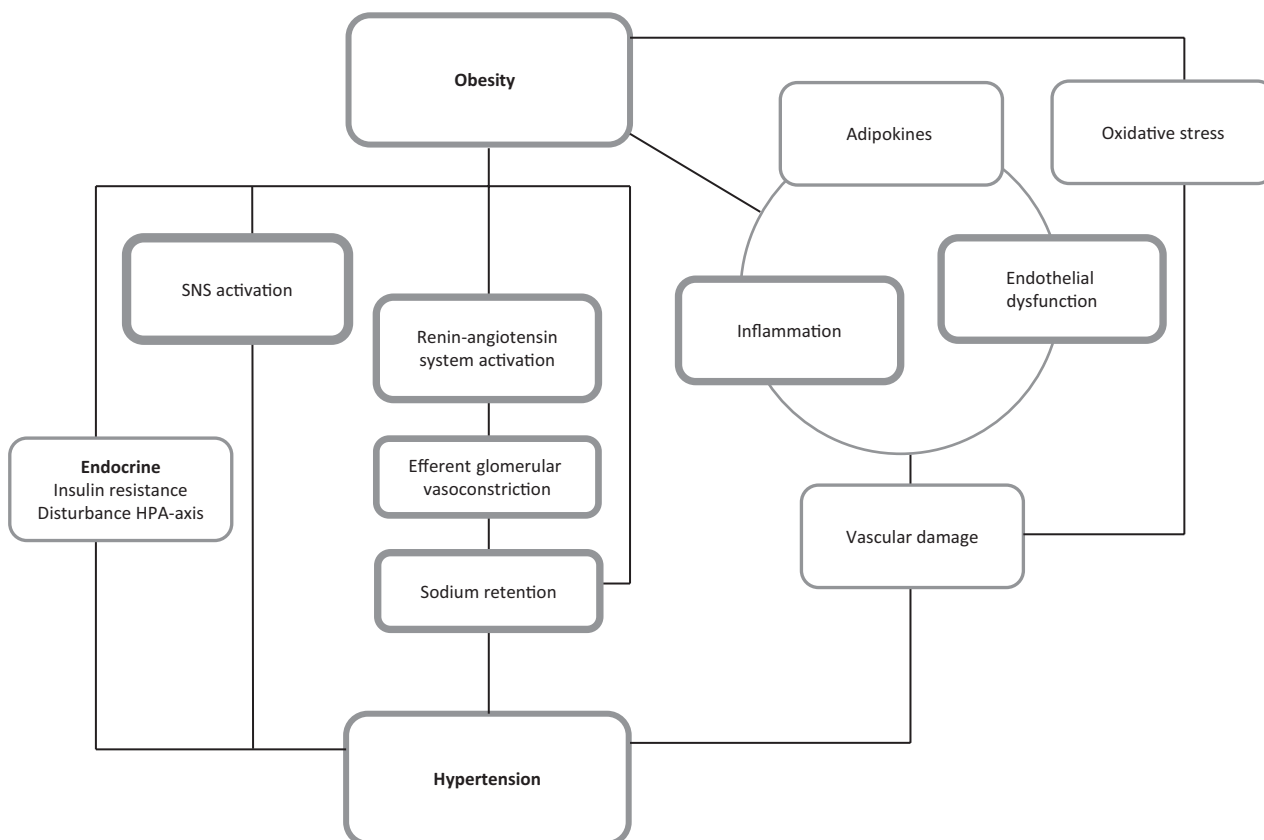
Figure 2 Possible pathophysiology of hypertension in obese children. A thicker frame of the categories indicates evidence of one or more strong quality studies.

Several studies examined the association between polymorphisms of the β₃-adrenergic receptor gene, particularly the Trp64Arg polymorphism, obesity and cardiovascular risk factors. The goal of the adrenergic system is to regulate the energy expenditure. The β₃-adrenergic receptor is mainly present in visceral fat and is responsible for thermogenesis in brown adipose tissue. Obese children had significantly higher blood pressure and levels of insulin if they carried the Arg64 polymorphism when compared to obese children without the Arg64 polymorphism (31). Although another study did not find a significant difference between carriers of variations in the β₃-adrenergic receptor gene, systolic and diastolic blood pressure were highest in Trp64Arg homozygote children (32). These studies suggest that variations in the β₃-adrenergic receptor gene, particularly the Arg64 allele, are associated with elevated blood pressure in obesity.

In summary, seven studies – three strong quality studies, one moderate and three weak quality studies – addressed the association between SNS and hypertension. Since all studies found an association, SNS activation seems to play a role in the pathophysiology of hypertension in obese children.

Endocrine

Insulin resistance. In obese adults, hypertension has frequently been linked to hyperinsulinaemia and insulin resistance. One study compared hypertensive obese children with normotensive obese children and found a significant positive correlation between fasting serum insulin levels and systolic blood pressure ($P < 0.001$). This association was independent of obesity and age, suggesting a direct relationship between hyperinsulinaemia and blood pressure (33). In children, it has also been suggested that insulin sensitivity is associated with hypertension. The association between hypertension and *in vivo* insulin sensitivity in a group of 65 overweight and obese adolescents was studied, and a significant association between impaired *in vivo* insulin sensitivity and systolic blood pressure was found, although after adjustment for obesity, this association disappeared (34).

In conclusion, the results of the above-mentioned studies – both of moderate quality – were inconsistent so no clear conclusion can be drawn about the role of insulin in the development of hypertension in obese children.

Adipokines (adiponectin, leptin and others). Several studies have investigated the association between blood pressure, obesity and adiponectin in overweight and obese children and adolescents. Adiponectin is a protein with anti-inflammatory properties secreted by fat cells of white adipose tissue and is believed to be a marker for the 'metabolic syndrome'. Several studies found a significant and inverse association between adiponectin and blood pressure in obese children (34–39). After adjustment for BMI or fat mass, the correlation between adiponectin and blood pressure often persisted, suggesting an influence of adiponectin on blood pressure regulation (34,36,39).

Retinol-binding protein 4 (RBP4) is an adipokine responsible for the transport of retinol and it has been suggested that it contributes to insulin resistance in obesity. A study in which the link between RBP4 and obesity-related conditions in adolescents was examined found that RBP4 levels were significantly higher in obese adolescents in comparison with lean adolescents. RBP4 correlated significantly with the 24-h mean systolic blood pressure, independent of obesity measures. The correlation between RBP4 and random systolic and diastolic blood pressure lost significance after correction for BMI. Hence, there is an association between blood pressure and RBP4 in obese adolescents, although the severity of obesity appears to have an influence on this association (40).

Visfatin is an adipokine with pro-inflammatory effects and is often found to be elevated in obese children. Visfatin levels were found to be significantly and positively associated with blood pressure (≥90th percentile) in an all-obese group of children aged 3–17 years (41). Concentrations of apelin, another adipokine, did not differ between obese and healthy weight children. No association with cardiovascular risk factors in obese children was found. In addition, there was no difference in apelin levels before and after a 1-year lifestyle intervention programme (42). Hence, there could be a role for visfatin, although not for apelin, in the development of hypertension in obese children.

Leptin is an adipokine released from the adipose tissue and regulates the energy balance by acting directly on the hypothalamus. A disturbed production or release of leptin could be associated with a decrease in energy expenditure and could lead to the development of obesity. Leptin also exerts influence on the SNS as well as on local vascular tone by affecting nitric oxide levels in endothelium. Therefore, it could be plausible that leptin influences the development of high blood pressure in obesity. In a large cross-sectional study in Norway and Denmark, the association between leptin and blood pressure was studied in obese and lean children. Both BMI and leptin were significantly and positively associated with blood pressure ($P < 0.001$). While the relationship between leptin and blood pressure was almost entirely facilitated by BMI, the relationship between BMI and blood pressure was only to a small degree facilitated by

leptin (43). Similarly, several other studies did not find a BMI-independent association between leptin and blood pressure in obese children, which leads us to believe that there is no significant role for leptin in the development of obesity-induced hypertension (44,45).

Altogether, 12 studies – 5 of strong quality, 3 moderate and 4 of weak quality – discussed the association between hypertension and adipokines in obese children. Five studies – three of moderate and two of weak quality – found a significant association, independent of BMI, between an adipokine and hypertension. It seems that adiponectin, RBP4 and visfatin could play a role in the development of hypertension in obese children. However, although their role may be amplified by the degree of obesity, it does seem limited.

Hypothalamic–pituitary–adrenal axis. Adrenocorticotropic hormone (ACTH) is an important component of the hypothalamic–pituitary–adrenal (HPA) axis, stimulating the production and release of glucocorticoid steroid hormones, including cortisol. In adults, it has been suggested that disturbances in the components of the HPA axis are involved in the development of obesity-associated cardiovascular risk factors. To evaluate the association between morning ACTH and cortisol and obesity-induced cardiovascular risk factors, a group of 406 obese and overweight children and adolescents was studied. The results show that cortisol and ACTH levels were positively and significantly associated with systolic and diastolic blood pressure. Higher cortisol and ACTH levels, even though both within the normal range, increased the odds of having hypertension, independently of BMI (46). 11β-hydroxysteroid dehydrogenases (11β-HSD) are enzymes that catalyse the conversion from inert cortisone into active cortisol (11β-HSD1) or the inactivation of cortisol into inactive cortisone (11β-HSD2). 11β-HSD activity is reflected by the ratio of urinary cortisol metabolites tetrahydrocortisol (THF) + its isomer allotetrahydrocortisol (5α-THF)/tetrahydrocortisone (THE). In a group of hypertensive obese adolescents ($n = 15$), normotensive obese adolescents ($n = 11$) and normotensive non-obese adolescents ($n = 15$), hypertensive obese children had increased urinary excretion of cortisol metabolites in comparison with the other two groups. In addition, the THF + 5α-THF/THE ratio was significantly associated with systolic blood pressure, independent of BMI (47).

In a study into the association between *HSD11B1* gene polymorphisms and obesity and its complications in a group of 534 Spanish children, aged 6–15 years, one *HSD11B1* gene single nucleotide polymorphism (SNP), rs3753519 *HSD11B1* SNP, was found to be significantly associated with obesity ($P = 0.004$). However, no association was found with blood pressure and several inflammation markers (48).

The *CYP17A1* gene encodes the enzyme CYP17A1, part of cytochrome P450, which is indirectly involved in the biosynthesis of cortisol. An SNP near *CYP17A1*, rs11191548, is known to be associated with elevated blood pressure in adults. In children and adolescents aged 6–18 years, the SNP rs11191548 was found to be associated with systolic blood pressure in girls, but not in boys. This association was stronger in obese girls than in normal-weight girls, suggesting a sex-specific role for SNP rs11191548 in blood pressure regulation in obesity (49).

The results of these four studies, all of moderate quality, support the assumption that disturbances within the HPA axis play a role in the development of obesity-induced hypertension in children.

Renin–angiotensin–aldosterone system. It is well known that the renin–angiotensin–aldosterone system (RAAS) plays an important role in blood pressure regulation by influencing the regulation of vascular tone and sodium homeostasis. Gene polymorphisms encoding for any of the components of RAAS may therefore influence blood pressure. Different gene polymorphisms of RAAS, the l/D polymorphism of *ACE* gene, the M235T polymorphism of the angiotensinogen gene, and the angiotensin II type I receptor (AGT$_1$R) A1166C gene polymorphism, and their role in the pathogenesis of essential hypertension in children and adolescents were studied. One study found an interactive effect between obesity and the angiotensinogen TT genotype on essential hypertension risk in children (odds ratio [OR] = 19.3, 95% confidence interval [CI] 1.1–77.3). However, no relation was found between the l/D polymorphism of *ACE* gene and the AGT$_1$R A1166C AGT$_1$R gene polymorphism, and essential hypertension (50). Another study found that the D-allele of the *ACE1/D* variant was significantly associated with elevated blood pressure in obese children, independently of BMI (51). One study found that obese children with the *II* genotype of ACE polymorphisms had higher blood pressure than obese children with other genotypes. Children with the *II* genotype had also experienced more rapid growth (in weight) in the first three years of life, suggesting that the association between the ACE polymorphism and elevated blood pressure is facilitated by post-natal growth (52).

Patterns of the expression of the renin–angiotensin system in peripheral blood leukocytes were assessed in overweight children with hypertension, and a normotensive control group matched for age, sex and BMI, before and after 6 months of lifestyle intervention treatment. Prior to the treatment, leukocytes of the hypertensive children showed an increased expression of angiotensin-converting enzyme, decreased expression of angiotensinogen and angiotensin type 1 receptor mRNA, and an unaffected expression of renin, leptin and adiponectin receptors mRNA in comparison with the control group. Lifestyle treatment during 6 months resulted in a normalization of blood pressure and a down-regulation of genes of the renin–angiotensin system (53).

One study found that obese adolescents have significantly higher plasma aldosterone concentrations in comparison with non-obese adolescents. Additionally, a weak correlation was found between plasma aldosterone and blood pressure, indicating that aldosterone might be of some influence on blood pressure control, but not independent of BMI (54).

In summary, five studies – one of strong quality and four of weak quality – found an association between blood pressure and RAAS. Hence, components of RAAS could play a role in the pathophysiology of obesity-induced hypertension in children, although evidence is weak.

Sodium homeostasis

Although the relationship between sodium intake and blood pressure is well established, the role of obesity in this relation is less well known. In a cross-sectional study among 6,235 children and adolescents aged 8–18 years, sodium intake was associated with systolic blood pressure. This association was stronger in overweight and obese children as compared to children with normal weight. For every 1,000 mg per day increase in sodium intake, the risk for elevated blood pressure increased by 74% among overweight and obese children, while in children with normal weight, the risk for elevated blood pressure increased by as little as 6% (55). A case–control study analysed the role of sodium intake in blood pressure regulation in obese adolescents by a salt intake intervention in obese and non-obese adolescents. When the adolescents changed from a high-salt intake to a low-salt diet, the obese group had a significantly greater change in mean blood pressure than the non-obese group ($P \leq 0.001$). The study suggests that elevated blood pressure in obese adolescents might be caused by enhanced sodium sensitivity (56).

The results of these two studies – one of strong quality and one of weak quality – suggest that disturbed sodium homeostasis, whether enhanced sodium sensitivity or relative sodium retention, exerts influence on blood pressure regulation in obese children.

Oxidative stress

It has been reported that obesity is associated with an increase of various free radicals, produced via mitochondrial respiration, which, in turn, could be accountable for the development of several cardiovascular diseases. A cross-sectional study examined oxidative stress levels in childhood obesity by investigating plasma levels of reactive oxygen metabolites (ROMs) through the diacron reactive oxygen metabolite (D-ROM) test, which provides a measure of the generation of peroxy radicals. D-ROM levels were increased in obese children when compared to

controls and were independently correlated with systolic blood pressure in a multivariate model. This suggests a role for oxidative stress in the development of hypertension (57).

By contrast, another study found no association between oxidative stress and blood pressure in overweight and obese children. In a randomized trial, the effect of exercise training on oxidative stress was studied in overweight and obese children aged 7–12 years. Isoprostane, used in this study as a marker for oxidative stress, was associated with measures of obesity, but no relation was found with blood pressure (58). Another study did find a correlation between isoprostane and elevated blood pressure in a multi-ethnic population of obese children. In the same study, a correlation with hydrogen peroxide, another marker of oxidative stress, and blood pressure was not found (59).

Altogether, of these three studies – one of moderate and two of weak quality – two studies found a significant association between oxidative stress and hypertension, and one did not. These ambiguous results show that the influence of oxidative stress on the development of hypertension in obese children is questionable. However, only a limited amount of research was conducted on the role of oxidative stress in the pathophysiology of hypertension in obese children.

Inflammation

Several studies found evidence that obesity is associated with markers of inflammation and increased cardio-metabolic risk profile. Tumour necrosis factor-α (TNF-α) is a pro-inflammatory cytokine, often increased in obesity. One study analysed TNF-α serum levels and its receptors in obese adolescents and a lean control group. In the obese group, TNF-α and sTNF-R1 also correlated positively with systolic and diastolic blood pressure. These results suggest a role for TNF-α in blood pressure control of both obese and non-obese children (60). Adolescents carrying the G-308A TNF-α variant had a significantly higher systolic blood pressure than adolescents not carrying that specific allele. However, there was no significant difference in blood pressure between normal-weight and overweight carriers of the allele. The G-308A TNF-α variant might facilitate the development of hypertension, independently of obesity (61).

C-reactive protein (CRP) is an inflammatory marker and is considered a marker for atherosclerosis. Although two studies found a significant association between CRP and blood pressure in obese children, independently of BMI (62,63), one study did not (64).

In a group of hypertensive obese, normotensive obese, lean hypertensive and healthy children, the association between the endothelial inflammatory marker's soluble intercellular adhesion molecule 1 (sICAM-1) and sE-selectin with dysfunction of vasodilatation activity

measured with flow-mediated dilatation (FMD), and with atherosclerotic changes measured with intima-media thickness (IMT) was studied. In hypertensive obese children, a significant and positive relation was found between sICAM-1 and IMT, and a significant negative relation with FMD. sE-selectin was significantly and positively associated with IMT. These results suggest complex inter-relationships between several risk factors for atherosclerosis in obese children with hypertension (65).

Similarly, a study found significantly higher serum levels of inflammatory and endothelial activation markers (CRP, fibrinogen, interleukin [IL]-6, ICAM-1 and vascular cell adhesion molecule 1 [VCAM-1]) in hypertensive obese children in comparison with normotensive obese children. This suggests that low-grade inflammation and endothelial activation are associated with hypertension in obesity (66). A study in a group of obese children confirmed the link between inflammatory markers and hypertension in obese children. All inflammatory markers analysed in this study, IL-6, IL-1β, CRP and fibrinogen, correlated significantly with hypertension (67).

Resistin is an adipose-derived hormone with pro-inflammatory properties. It has been put forward that resistin is associated with obesity and has a role in insulin tolerance. The role of resistin in the development of high blood pressure in obese children is yet unclear. One study did find a significant association between resistin and blood pressure (68), while another study did not (64).

Overall, nine studies addressed the association between inflammation and hypertension in obese children. One study was of strong quality, five of moderate quality and three studies were of weak quality. Eight studies found a significant association between inflammation parameters and hypertension, while one study did not. In conclusion, these studies suggest a role for inflammation in blood pressure control in obese children. However, its role seems complex, and it is difficult to determine the causal relationship between hypertension and inflammation, i.e. what is the cause and what is the effect?

Endothelial dysfunction

Obesity is believed to lead to endothelial dysfunction, which, in turn, can result in an increased risk of cardiovascular disease. One study showed that FMD and nitroglycerin-mediated dilatation (NTGMD), both markers of endothelial function, were significantly and inversely correlated with ambulatory systolic blood pressure in a group of obese children, suggesting that impaired FMD and NTGMD could be markers of hypertension in obese children. However, arterial IMT measured in this study as well did not show a correlation with blood pressure (69). This is in contrast with other studies that did find a significant association between IMT and blood pressure (65,70).

Consequently, based upon the ambiguous results of these three studies – one strong and two of moderate quality – endothelial dysfunction may play a role in the pathophysiology of hypertension in obese children. However, the specific role is as yet unclear and it is difficult to determine what is the cause and effect in this relationship.

Genetics: obesity-associated genes

The melanocortin-4 receptor (MC4R) is also involved in energy homeostasis. Mutation in this receptor results in extreme cases of obesity. Two common variants near MC4R, rs17782313 and rs12970134, and their relation with obesity and associated risk factors were studied. Both variants were associated with overweight and obesity in adolescents. The rs17782313 variant was significantly associated with increased diastolic blood pressure in boys and with decreased diastolic blood pressure in girls. The same variant was also associated with insulin levels, in both sexes (71). These results lead to the assumption that variants in genes involved in energy homeostasis could be of influence on the development of hypertension in obese children.

The role of different variants of the fat mass- and obesity-associated (*FTO*) gene in the development of hypertension was examined in a large group of Chinese children and adolescents. Variants of the *FTO* gene have previously been related to the development of obesity. One study found that the common SNP rs9939609 in the *FTO* gene modifies the influence of obesity on the development of high blood pressure in children. Obese children, with all different *FTO* gene subtypes, were more likely to have elevated blood pressure, in comparison with non-obese children. The largest effect was measured for the subgroup of children with AA genotype (OR = 10.37, 95% CI 1.59–67.43), suggesting that modification of the *FTO* gene could lead to an elevated blood pressure in obese children (72). By contrast, in another study, no associations between one of the studied *FTO* gene polymorphisms and blood pressure in obese children were found (73).

In conclusion, the results of the three studies – one of strong quality and two of moderate quality – are conflicting. Two studies found a significant association between variants of obesity-associated genes and hypertension, and one study did not.

Other

Low cardiorespiratory fitness has, in adults, been associated with adiposity and cardiovascular disease. A cross-sectional study, of strong quality, in Brazil found that cardiorespiratory fitness and BMI are independently associated with blood pressure in children. Children unfit and/or overweight have a greater risk of presenting hypertension (74).

Insulin-like growth factor type II (IGF-II) plays a role in glucose homeostasis, lipid metabolism and the regulation of cardiovascular functions. The association between two IGF-II polymorphisms, 6815 A/T and 820 G/A, and obesity and blood pressure in children was studied. The 6815 A/T variant showed a significant association with systolic blood pressure, measured through ambulatory blood pressure monitoring. However, the 820 G/A IGF-II polymorphism showed no association with blood pressure in obese children and adolescents (75). Hence, the results of this strong quality study suggest a role for IGF-II gene variants in blood pressure regulation in obese children.

In a randomized prospective study of weak quality, the effect of vitamin C, an antioxidant, on blood pressure regulation and vasodilatation response was analysed in obese children aged 8–12 years, who were supplemented with vitamin C or with placebo. After the intervention, in the group that received vitamin C, mean blood pressure was significantly decreased (81 ± 2 mmHg vs. 75 ± 1 mmHg, $P = 0.01$), whereas in the group that received a placebo, blood pressure remained unchanged. In addition, forearm vascular conductance was increased after supplementation with vitamin C, indicating that vitamin C has a positive effect on peripheral vasodilatory response (76). The results of this study – of weak quality – suggest a role for vitamin C in blood pressure regulation.

Disturbed sleep patterns could be of influence on obesity and consequently on blood pressure, presumably via metabolic and endocrine dysfunction (77). In a longitudinal cohort study among 334 children aged 6–11 years, sleep patterns were studied using in-home polysomnography. Over a 5-year follow-up period, increased obesity levels and a decreased total sleep time were significantly associated with increased systolic blood pressure, but not with diastolic blood pressure. No significant relationship was found between sleep-disordered breathing and the development of hypertension (78). Based upon the results of this moderate-quality study, it seems that a decreased total sleep time is associated with blood pressure in children.

Low birth weight and a steep weight increase in childhood have been frequently associated with elevated blood pressure later in life. A cohort study found that a substantial BMI increase over a 6-year period was significantly associated with higher systolic and diastolic blood pressure at adolescence, independent of the BMI in early childhood (79). Several other studies found that low birth weight was a significant predictor for high blood pressure in later years of childhood (80,81). It seems that a moderate increase in weight, in comparison to a steep increase, protects against elevated blood pressure. In line with these results, a study found that an earlier adiposity rebound, the rise of BMI after infancy, before 4 years of age, leads to higher BMI and systolic and diastolic blood pressure in boys at 12 years of age, but not in girls (82). Hence, all four studies – two of

strong quality and two of moderate quality – found an association between birth weight and/or rapid weight gain in early childhood and hypertension.

Hyperuricaemia is a proposed risk factor for cardiovascular disease in adults and is part of, or often co-exists with, the metabolic syndrome. It has been suggested that uric acid can lead to a decrease in endothelial nitric oxide production and consequently to endothelial dysfunction (70). Serum uric acid was positively and significantly associated with systolic blood pressure (b 0.945, $P < 0.0017$) in a cross-sectional study among 269 obese children and adolescents (83). Another cross-sectional study among children confirmed these results; within the obese study group, serum uric acid was significantly associated with systolic blood pressure (r 0.345, $P < 0.0001$) (70). Hence, based on the results of these two studies – one of strong quality and one of weak quality – it seems that there could be a role for serum uric acid in the development of hypertension.

High levels of serum lipids and lipoproteins in childhood are related to cardiovascular diseases in adult life. Apolipoprotein E (ApoE) has been linked to lipid metabolism. One study of moderate quality found that ApoE polymorphism influences serum lipid levels, but no association between ApoE alleles and BMI, blood pressure or other risk factors related to obesity was found in children, leading to the assumption that there is no role for ApoE polymorphisms in the development of hypertension in obesity (84).

Atrial natriuretic factor (ANF) is a hormone that can influence blood pressure through vasodilatation, natriuresis and suppression of RAAS activity. In children and adolescents with and without essential hypertension, the ScaI gene polymorphism of ANF and its influence on essential hypertension was studied. The study – of weak quality – showed an interactive effect, although not significant, between ScaI ANF gene polymorphism and obesity. Children with the A1A1 genotype of ScaI ANF polymorphism seem to have a higher risk of developing increased blood pressure if they are obese (OR = 13.1, 95% CI 1.6 – 106) (56).

The association between telomere length and obesity and accompanying conditions in children was studied. A telomere is an area of repetitive DNA sequences at each end of a chromosome. Due to cell division, a telomere becomes shorter over time. It has been shown that telomere length could function as a marker of oxidative stress, and it has been associated with multiple chronic diseases including coronary artery disease and obesity. In obese boys, telomere length was shorter in comparison to their normal-weight peers. However, this was not the case for obese girls. In addition, systolic blood pressure in boys was significantly associated with a shorter telomere length (85). The results of this study of weak quality suggest that telomere length could function as a predictive marker for hypertension in obese boys, although evidence is limited.

Conclusion

To date, the multifactorial pathophysiology of obesity-induced hypertension is complex and interdependent and is not completely understood. However, understanding of the pathophysiology of hypertension in overweight and obese children is important and could have implications for its screening and treatment.

In the present review, potential factors in the development of hypertension in overweight and obese children are summarized and discussed. There seems to be a role for endocrine determinants, such as RAAS, corticosteroids and adiponectin. SNS (hyper)activity and sodium retention seem also of influence on the development of hypertension in obese children, as well as oxidative stress, inflammation and endothelial dysfunction, but their role is complex and it is often difficult to distinguish between cause and effect. Genetic factors play a role as well, several genetic variations have been associated with hypertension. Several other factors have been discussed such as birth weight, altered sleep patterns and hyperuricaemia. Most of these factors are not independently associated with hypertension, but interact with others at multiple levels, making the pathophysiology of hypertension in obesity complex and difficult to grasp. Due to the high frequency of obesity-related factors, associations and correlations found do not necessarily reflect causality. Suggested factors that may be of influence on hypertension are often based on a small amount of studies, of varying quality, and often with small numbers of children. Although most of the observations are in line with observations found in adults, more evidence is needed to support the suggested pathways of development of hypertension in children.

Longitudinal studies, including intervention studies aimed at reducing weight and blood pressure, are needed to gain more insight into the complex mechanisms behind the development of hypertension in obese children. In this way, a pathophysiological basis for the choice of treatment of hypertension can be provided.

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Conflict of interest statement

No conflict of interest was declared.

840 Hypertension in obese children *A. J. G. Wirix* et al.

obesity reviews

Supporting information

Additional Supporting Information may be found in the online version of this article, http://dx.doi.org/10.1111/obr.12305

Table S1. Search strategy in PubMed on the 30th of October 2014 (read bottom-up).
Table S2. Checklist of methodological quality, adapted from *The Dutch Cochrane Centre. Amsterdam: Amsterdam Medical Centre; 2013*. http://www.cochrane.nl
Table S3. Quality assessment selected articles.

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