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Obesity and Hypertension in Children and Adolescents: Developing New Tools for the Diagnosis of Two Global Pediatric Challenges

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Globally, the prevalence of overweight and obesity is rising and is thought to be driving the increasing prevalence of pre-hypertension and hypertension in children and adolescents. In developing countries, this is additionally worrisome due to the persisting presence of communicable diseases and the double burden of disease it creates. Both obesity and hypertension arise from gene-environment interactions, making management by modulating the environmental factors possible especially when the disorder is detected early. Diagnosing obesity and hypertension early would help in the timely initiation of management strategies. This would in turn not only reduce both morbidity and mortality from the diseases, but also the economic burden the diseases place on individuals, families and the health system in general. The current "gold standard" diagnostic tools for obesity and hypertension in pediatrics are however unwieldy and difficult to use by non-professionals and professionals working in regions where the patient/doctor ratio is very high. The development of easy-to-use tools for the diagnosis of these diseases is clearly one very important means of improving early diagnosis and the benefits derivable from it. This paper reviews the literature on obesity and hypertension and highlights the recently developed diagnostic tools and the advantages they bring to the diagnostic table.

Key words: Adolescents, children, diagnosis, hypertension, obesity

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INTRODUCTION

Obesity and hypertension are two of the major chronic disease challenges facing children and adolescents globally. It is believed that the change in lifestyles, especially in developing countries is responsible for the increasing prevalence of obesity in those regions; while the access to abundant processed ready-to-eat energy dense foods and reduced physical exertion in developed countries drives the obesity epidemic there. Apparently, the balance between energy intake and expenditure is tilting towards a positive energy balance and this is at the center of the global obesity epidemic in both adults and children (Wright, 2013). With the rising prevalence of obesity and the link between obesity and hypertension (Fig. 1), it is not entirely surprising that the prevalence of pediatric hypertension is also rising globally. Hypertension is the principal risk factor for cardiovascular diseases and can lead to organ damage and even death.

Though, there are known management interventions for obesity and hypertension in pediatrics, early diagnosis often ensures the initiation of early intervention and better treatment outcomes (Nader *et al*., 2006). It is therefore important to develop easy to use diagnostic tools for these prevalent and inter-twined disorders, such that even non-clinicians may be able to identify children and adolescents that may need urgent attention and (pediatric) clinicians in resource-poor areas of the world could have easier-to-use tools for their work. Such early diagnosis may also reduce the high cost of managing these diseases (Hollinghurst *et al*., 2013).

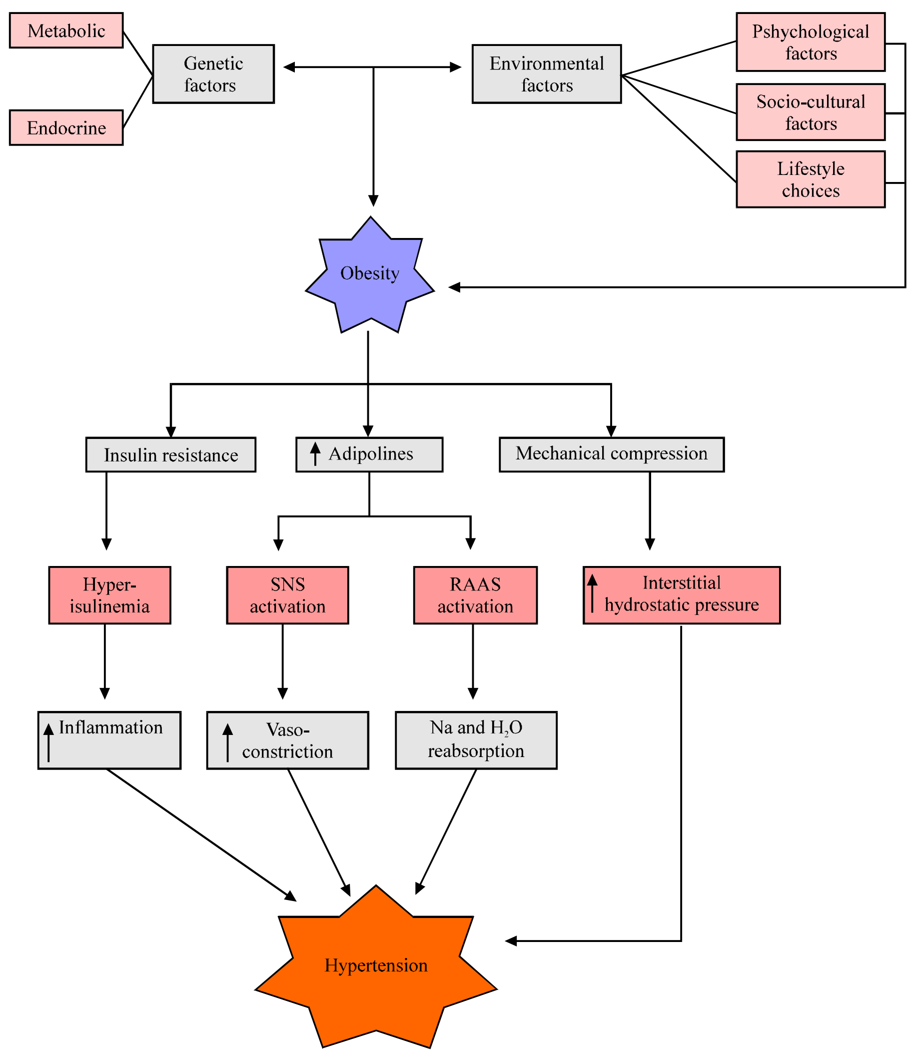

Fig 1: Etiology of obesity and hypertension, showing the link between the two diseases

The literature on pediatric obesity and hypertension is reviewed hereunder. Furthermore, attention is drawn to newly developed tools that simplify the diagnosis of both disorders. The advantages of the new diagnostic tools over existing options, especially the "gold standards" are discussed. Perspectives for the future research are also presented.

PEDIATRIC OBESITY

Etiology and pathogenesis: Multifarious interactions between genes and the environment are thought to be responsible for childhood obesity. Genetic conditions such as Prader-Willi syndrome, Bardet-Biedl syndrome and Cohen syndrome are known to be associated with predisposition to obesity. Obesity runs in families as parental obesity has been demonstrated to be positively associated with and also to be a predictor of, pediatric obesity (Reilly *et al*., 2005). Non-genetic risk factors for overweight and obesity include sub-optimal cognitive stimulation at home, poor socio-economic status (Strauss and Knight, 1999), poor food choices (Smiciklas-Wright *et al*., 2003), sedentary behaviours like excessive television viewing (Gortmaker *et al*., 1996) and disadvantageous socio-cultural factors like preference for large portion sizes (Young and Nestle, 2002).

Prevalence and consequence: Pediatric obesity is prevalent in both developed and developing countries and affects subjects irrespective of socio-economic groups, age, sex or race/ethnicity. The prevalence of obesity in pediatrics has tripled since the 1970s (Nader *et al*., 2006). Globally, it is estimated that 110 million children are overweight or obese (Haslam and James, 2005). In Africa and Asia the prevalence of pediatric obesity is believed to be below 10 per cent while it is thought to be above 20% in the Americas and Europe (Lobstein *et al*., 2004). By the advent of the 21st century, the prevalence of pediatric obesity (overweight) (%) in Africa, Americas, Eastern Mediterranean, Europe, South East Asia and West Pacific had reached 0.2 (1.6), 9.6 (27.7), 5.9 (23.5), 5.4 (25.5), 1.5 (10.6) and 2.3 (12.0), respectively (Kosti and Panagiotakos, 2006).

Currently, the prevalence of obesity in children and adolescents has reached 16.9% in the US (Ogden *et al*., 2012), 4.1-27.6% in seven European countries (Belgium, Greece, Hungary, Netherlands, Norway, Slovenia and Spain) (Brug *et al*., 2012), 15.7% in China (Andegiorgish *et al*., 2012) and 5.1 to 19.9% in developing countries of Asia (Yang *et al*., 2012), but 5.0% in Bostwana (Wrotniak *et al*., 2012). In developed countries, low socio-economic status is associated with obesity (Strauss and Pollack, 2001) whereas in developing countries, the reverse is the case (Chhatwal *et al*., 2004). It is thought that the nutrition transition and sedentary lifestyles, driven by urbanization and westernization which is taking place in developing countries, is driving the rise in the prevalence of obesity in such countries (Ejike *et al*., 2010a).

The health consequences of obesity in children are becoming more evident and appreciated within and outside the scientific community (Daniels, 2006; Cali and Caprio, 2008). Many of the complications are silent and therefore often go unreported and undiagnosed. Pediatric obesity could nonetheless result in severe consequences, including orthopaedic complications, type 2 diabetes, dislocated sleep patterns, compromised immune function, skin diseases, compromised movement and hypertension (Wabitsch, 2000). It can result in additional psycho-social consequences (such as a low self-esteem and lack of self-confidence, leading to social alienation) due to its effect on the individual's physical appearance (Must and Strauss, 1999; Wabitsch, 2000). Other social consequences of obesity in children and adolescents include discrimination (Dietz, 1998) and depression (mainly in girls) (Erickson *et al*., 2000). Due to the tracking of obesity into adulthood, it has some long-term consequences. These include increased risk of cardiovascular disease, renal disease, diseases of the metabolic syndrome, gall bladder disease, osteoarthritis and some cancers (Must and Strauss, 1999). Pediatric obesity is therefore a very important risk factor for obesity and its sequelae in adult life (Freedman *et al*., 2005; Harris *et al*., 2006).

Definition, diagnosis and management: Age and gender-specific reference charts for body mass index (BMI) are widely utilized in the definition of obesity and overweight pediatrics. A child is classified as obese or overweight if their "BMI is equal to or greater than the 95th percentile" or if their "BMI is greater than the 85th percentile, but lower than the 95th percentile", respectively, of the age-gender-specific charts (WHO, 2006; Neovius and Rasmussen, 2008). The diagnosis of overweight and obesity in children and adolescents therefore requires measuring their weight and height, calculating the BMI and matching the data on the growth charts in order to identify the percentile to which it falls into. The WHO Multicenter Growth Reference Study tables are available free online (http://www.who.int/childgrowth/mgrs/en/).

The management of obesity revolves around reducing energy intake and increasing physical exertion. Recommendations such as avoiding excess sugar, energy dense snacks, soft drinks, saturated fat and processed foods; while increasing the intake of dietary fiber (in the form of fruits, vegetables and whole grains), are very useful (Lo *et al*., 2013). Family based intervention that combine education with the modifications above have been shown to be very successful (Austin *et al*., 2005). Medical therapy and surgery may be required in cases of morbid obesity, especially where it is apparent that only conventional dietary and lifestyle modifications have failed to yield the desired results (Shield *et al*., 2008).

Challenges in the diagnosis of obesity and new paradigms: Though BMI is widely used as a measure of obesity in children and adults, it is known to be a proxy for body size (Neovius *et al*., 2005) and therefore to have some limitations. BMI does not always correlate with central obesity (Neovius and Rasmussen, 2008) and it does not differentiate between muscle mass, bone density and fat mass (Hall and Cole, 2006). That is, BMI is correlated with total adiposity, but does not address the distribution of body fat the critical factor in the comorbid pathologies that form the obesity sequelae (Goh *et al*., 2004; Jassen *et al*., 2004, Okorodudu *et al*., 2010).Waist-to-Height Ratio (WHtR) has therefore been recently proposed as an easily measurable anthropometric index that detects central obesity and is associated with cardiometabolic risk factors (Srinivasan *et al*., 2009; Nambiar *et al*., 2010). The WHtR is calculated by dividing the waist circumference (WC) (measured at the level of the umbilicus, in cm) by height (in cm). It is thought to be superior to BMI and WC because it combines the WC (which is a measure of abdominal adiposity) and adjustments for the size of the individual. A cut-off of 0.5 is used to define obesity in children and adolescents, independent of age and sex (Nambiar *et al*., 2009; Browning *et al*., 2010).

WhtR has been shown to be better than WC and BMI at predicting adiposity in pediatrics (Brambilla *et al*., 2013). It distinguishes between normal weight children with cardiometabolic risks and obese children without such risks (Mokha *et al*., 2010; Nambiar *et al*., 2010). Furthermore, since WHtR is not age dependent, it is possible to use a single cut-off value for all children (Aeberli *et al*., 2011). Beyond these, using the WHtR abrogates the need for the often confusing growth charts and makes it feasible for non-clinicians (parents and teachers for example) to easily check their children's/ward's weight status and therefore adjust their nutrition or exercise routine as the case may be. This is even more advantageous in developing countries where even professionals often have so many patients and would appreciate less cumbersome diagnostic tools. In a classic systematic review of seventy eight published papers on WHtR, Browning *et al*. (2010) succinctly reported that the WHtR was superior to BMI or WC and concluded that the "weighted mean boundary value of 0•5" supports "the simple public health message keep your waist circumference to less than half your height".

PEDIATRIC HYPERTENSION

Etiology and pathogenesis: Hypertension is the consequence of imbalances in the regulatory systems of blood pressure. It is thought to arise from gene-environment interactions that result in defective sodium excretion. Salt excretion by the kidneys is central to the mechanism of hypertension (Guyton, 1991). The pressure-natriuresis approach which the body adopts in order to maintain salt and water homeostasis, in cases of sodium surfeit, ultimately leads to hypertension (Lifton *et al*., 2001; O'Shaughnessy and Karet, 2004). In fact, the genes identified to be related to the development of hypertension are known to be involved in the regulation of salt homeostasis by the kidneys (Oparil *et al*., 2003).

The factors that are regarded as culprits in the causation and progression of essential hypertension include increases in sympathetic nervous system activity arising from an increased exposure, or reaction, to psychosocial stressors; activation of the renin-angiotensin-aldosterone system (RAAS) resulting in imbalance in sodium and potassium handling; inadequate concentrations of vasodilators, such as prostacyclin, Nitric Oxide (NO) and the natriuretic peptides; etc. (Carretero and Oparil, 2000; Vasan *et al*., 2004). It is currently speculated that both structural and functional vascular abnormalities as is typified by endothelial dysfunction, vascular remodelling and heightened oxidative stress may precede clinical hypertension (Oparil *et al*., 2003).

Primary hypertension is associated with many risk factors, including genetics, nutrition, BMI, race and sex. Secondary hypertension usually arises as a result of other underlying pathologies. Some pathological conditions known to result in secondary hypertension include glomerulonephritis, reflux nephropathy and the attendant renal scaring, polycystic kidney disease, chronic renal failure, etc. (Flynn, 2001; Viera and Neutze, 2010).

Prevalence and consequence: The prevalence of pediatric prehypertension and hypertension is rising steeply and developing countries now have an appreciable burden of the disease (Ejike *et al*., 2010b). This rising prevalence has been attributed to urbanization (Ejike *et al*., 2008) and the obesity that comes with it (Cali and Caprio, 2008). The prevalence of hypertension in the general pediatric population is 1-5% (Lurbe *et al*., 2010; Obarzanek *et al*., 2010), while in children with a BMI >95th percentile, the prevalence is about 11% (Sorof *et al*., 2004). Recent data suggest that the prevalence of hypertension in US children and adolescents is 3.0% (May *et al*., 2012) while it is 3.1% for their Chinese counterparts (Meng *et al*., 2013). Hypertension in younger children is more likely to be secondary hypertension, while in older children and adolescents, it is more likely to be primary hypertension (Flynn and Alderman, 2005; Viera and Neutze, 2010).

In adults, hypertension is a fairly well established risk factor for renal, cardiovascular and cerebrovascular diseases. In children it appears that the consequences of hypertension (hypertensive encephalopathy, renal impairment, cardiac failure and cerebrovascular accidents) if not fatal, result in scars that linger into adult life (McNiece *et al*., 2007; Brady *et al*., 2008; Litwin *et al*., 2010). High levels of blood pressure therefore require immediate diagnosis and intervention to rectify underlying anomalies, lower blood pressure and avoid end-organ damage (National Heart, Lung and Blood Institute, 2011). Based on the above, the fourth report of the US National High Blood Pressure Education Program (NHBPEP) Working Group on High Blood Pressure in Children and Adolescents recommends, the initiation of blood pressure monitoring early in life (NHBPEP, 2004).

Definition, diagnosis and management: Pediatric prehypertension is defined as Systolic Blood Pressure (SBP) or Diastolic Blood Pressure (DBP) values that are "equal to or greater than the 90th percentile but less than the 95th percentile for age, gender and height". Hypertension is defined as SBP or DBP readings measured on at least three different occasions/visits, that are "equal to or greater than the 95th percentile for age, gender and height, or that are persistently greater than 140/90 mmHg" (NHBPEP, 2004; Luma and Spiotta, 2006; Lurbe *et al*., 2009). It is important not to conclude on the presence of hypertension from measurements taken at one time point. Lo *et al*. (2013) reported that the prevalence of hypertension in children and adolescents may be lower than is reported in many studies especially those that report point hypertension in school based subjects. In adolescents hypertension is categorized as stage 1 (defined as SBP or DBP from the "95th to 99th percentile for age, gender and height, plus 5 mm Hg") or stage 2 ("SBP or DBP above the 99th percentile for age, gender and height, plus 5 mm Hg") (NHBPEP, 2004; Luma and Spiotta, 2006). The full table for the diagnosis of hypertension in pediatrics is available (and free) online (http://www.nhlbi.nih.gov/health/prof/heart/hbp/hbp_ped.htm).

In some countries, BP percentiles different from the US definitions described above are used in the definition of elevated blood pressure in pediatrics. In the UK for example, hypertension in children and adolescents is defined as BP above the 98th percentile for age, gender and height (Jackson *et al*., 2007). Reference values for BP that are slightly different from the US values have also been reported for Northern Europe (Munkhaugen *et al*., 2008) and Asia (Sung *et al*., 2008). The relationship between BP and gender, age, height and body weight throughout childhood has been nonetheless consistently significant (Falkner, 2010) and the European Society of Hypertension agrees with the diagnostic recommendations of the fourth report of the US NHBPEP Working Group (Lurbe *et al*., 2009).

The management of hypertension in pediatrics involves lifestyle modification and medical therapy, depending on the nature of the case. Lifestyle modifications targeted at weight loss, a reduction in sodium consumption (and an increase in potassium intake) and a reduction in psycho-social stress are often helpful. Diuretics, angiotensin 1 converting enzyme (ACE-1) inhibitors, Angiotensin Receptor Blockers (ARBs), Calcium Channel Blockers (CCBs) and Beta-blockers (BBs) are some of the pharmacological treatment options used in the management of primary hypertension (Stephens *et al*., 2012). The management of secondary hypertension requires identifying and addressing the primary cause of the disorder.

Challenges in the diagnosis of hypertension and new paradigms: Due to the unwieldy age-, gender- and height-specific reference standards for both SBP and DBP, the "gold standard" for the diagnosis of pediatric (pre)hypertension (described earlier) is difficult to understand and challenging to use, by parents and non-medical professionals (Lu *et al*., 2011). Even among clinicians, the method can be cumbersome and even though electronic normograms exist, they may not be available in resource poor settings and may be time consuming and difficult to integrate with a pediatrician's routine work flow (Hansen *et al*., 2007). It is thought, that these may be responsible for the under-diagnosis of hypertension in pediatrics. Furthermore, the observation of racial differences in pediatric blood pressure patterns implies that one single diagnostic chart may not be valid and appropriate for use in different racial populations (Marras *et al*., 2009; Brady *et al*., 2010).

Based on the above, the blood pressure-to-height ratios (BPHR) have been proposed as a simple diagnostic tool for the diagnosis of (pre)hypertension first in adolescents in China and Nigeria (Lu *et al*., 2011; Ejike, 2011) and thereafter in children in both countries

(Ejike and Yin, 2013; Lu *et al.*, 2013). These findings have been replicated in adolescents of other races by other researchers (Rabbia *et al.*, 2011; Galescu *et al.*, 2012; Guo and Sun, 2012). Child and adolescent blood pressure is unequivocally dependent on age, gender and height and varies accordingly. The BPHR is significantly correlated and associated with BP in children and adolescents, but not with age. Its major advantage is that one cut-off point each, only, is required for adolescent boys and girls. This is because BPHR is not associated with age and height is incorporated in its derivation. Applying this new diagnostic tool therefore makes it easier for lay people to identify elevated blood pressures early in adolescents and seek medical attention promptly.

CONCLUSION AND FUTURE PERSPECTIVE

Given the burden of pediatric obesity and hypertension globally and the projected increases in the prevalence in the future, early diagnosis of the diseases is critical to ameliorating or even abrogating the negative impact these diseases have on individuals and health systems, especially in countries under-going the nutrition transition and facing the double burden of infectious and chronic diseases. The WHtR and BPHR already developed for the diagnosis of obesity and hypertension should therefore make diagnosis easier for clinicians and the lay public. The high degree of sensitivity, specificity and overall diagnostic ability of the tools coupled with their ease of use and interpretation make them excellent replacements for the respective “gold standards” and would ultimately save some healthcare expenditure (which is critical in countries where per capita healthcare expenditure is already paltry) by ensuring early diagnosis and intervention. There is an urgent need for more wide-spread utilization of these techniques in order to appropriate fully, the advantages inherent in them. Further studies are however required especially for the BPHR, with a view to proving global cut-off points that will be both sensitive and specific within populations or across populations (as the case may be).

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