The prodromal phase of obesity-related chronic kidney disease: early alterations in cardiovascular and renal function in obese children and adolescents

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ABSTRACT

Childhood overweight and obesity is a relevant health condition with multi-organ involvement. Obesity shows significant tracking into adult life and is associated with an increased risk of serious adverse health outcomes both during childhood and later adulthood. The classical sequelae of obesity such as hypertension, metabolic syndrome and inflammation do develop at a paediatric age. Cardiovascular consequences, such as increased carotid intima-media thickness, and left ventricular hypertrophy, as well as functional alterations of the heart and arteries, are commonly traceable at an early age. Renal involvement can occur at a young age and is associated with a high probability of progressive chronic kidney disease. There is solid evidence suggesting that consequent treatment including both lifestyle changes and pharmacological therapy can reduce cardiovascular, metabolic and renal risks in obese children and adolescents.

INTRODUCTION

Around the globe, the prevalence of childhood obesity has been steadily on the rise over the past decades [1]. The secular trend of increasing weight at early age was first highlighted in the Bogalusa Heart Study >25 years ago, and subsequent studies confirmed a continued increase in obesity prevalence [2, 3]. In the first decade of this century, up to 12% of preschool and 28% of school children in developed countries were estimated to be overweight or obese [1, 4]. In view of these figures, the WHO referred to overweight and obesity as a ‘global epidemic’ in children and in adults [5], and the International Obesity Task Force (IOTF) addressed childhood obesity as a ‘public health crisis’ [6].

DEFINITION OF OVERWEIGHT AND OBESITY

The evaluation of weight for age, weight for height and BMI for age in children and adolescents has traditionally been based on percentile charts. Anthropometric surveys are updated from time to time to account for the secular trend in height. In this context, the parallel secular trend toward an ever-increasing weight for age and height raises a serious problem: in updated reference charts the upper weight/BMI percentiles will necessarily be shifted upward, thereby raising the thresholds defining overweight and obesity and compromising the sensitivity of anthropometric indices to identify patients at risk of obesity-related morbidity.

Several approaches have been used to address this issue. Most studies concerning obesity in children in the USA are based on the 2000 Centers for Disease Control and Prevention (CDC) growth charts [2, 3, 7]. Children under the age of 2 years are considered overweight if their weight for recumbent length is above the 95th percentile, and at risk for overweight between the 85th and 95th percentile. Between 2 and 19 years, BMI between the 85th and 95th percentile defines overweight and above the 95th percentile obesity. The CDC charts include data of healthy North American children and adolescents observed between 1963 and 1994. However, BMI data from children who were older than 6 years between 1988 and 1994 were excluded for chart construction to avoid an upward shift of the 85th and 95th percentiles.

The IOTF, using a large international population sample, defined paediatric overweight and obesity by extrapolating those population percentiles to which BMI values of 25 and 30 kg/m² correspond at young adult age into adolescence and childhood [8]. The rationale for this approach was that these cutoff values are linked to adverse health outcomes in adults [9]. Whether the children identified as overweight or obese by
this approach are indeed at a higher risk for obesity-related morbidity remains to be determined.

The most recent recommendations have been made in 2010 by the WHO [10]. The latest WHO growth charts combine the WHO Child Growth Standards from birth to 5 years and the WHO reference data for 5–19-year-old children and adolescents [11, 12]. Overweight and obesity are defined as 2 SD and 3 SD above the mean, respectively, for children below the age of 5 years, and as 1 and 2 SD above the mean for subjects aged 5–19 years.

GLOBAL EPIDEMIOLOGY OF OBESITY

Much attention has been paid recently to the prevalence of childhood obesity and related health consequences. A meta-analysis of anthropometric surveys in preschool children from 144 countries around the world noted an increase of overall overweight and obesity (defined as BMI SDS >2 SDS) from 4.2 to 6.7% between 1990 and 2010. Childhood obesity rates showed a high degree of regional variability. Whereas obesity continued to be more prevalent in the developed world, the developing countries tended to catch up with higher increase rates during the last 20 years [4].

A survey in six European countries found overweight and obesity (BMI SDS >2) in 8–30% of preschool children [13]. Another European study showed similar findings with overweight rates between 12 and 32% [14]. The latest WHO report on overweight and obesity, based on the 2007 WHO growth reference, also found high rates of overweight for younger school children (6–9 years) with 18.4–49% of the children being overweight and 4.6–26.6% obese [15].

Based on the IOTF cutoff criteria, Lobstein and Frelut [16] reported prevalence of both overweight and obesity ranging from 10 to 36% in European children and adolescents aged 7–17 years. All European surveys noted a north–south gradient with higher rates of obesity and overweight in the Mediterranean region.

The estimated prevalence of overweight and obesity in US preschool children aged 2–5 years (BMI for age >85th and >95th CDC percentiles) was 27 and 12%, respectively [3]. The weight distribution in school children is even more alarming: The prevalence of overweight and obesity in otherwise healthy US children was 33 and 18%, respectively, in the 6–19 year age group [3].

RISK FACTORS FOR CHILDHOOD OVERWEIGHT AND OBESITY

Environmental and genetic factors are believed to play synergistic roles in the development of obesity starting in childhood. In addition to the nearly unlimited access to food in the developed world, sophisticated food processing often supplies a maximum of calories with highly engineered nutrition and soft drinks to the unmindful consumer [17]. Furthermore, genetic susceptibility to disproportionate weight gain to a given caloric load adds significantly to an individual child’s obesity risk. Up to 70% of BMI variability has been attributed to genetic factors [18]. Genome-wide association studies have identified several genes associated with obesity, which however explain only a small percentage of BMI variability [19]. Finally, prenatally acquired epigenetic alterations may contribute to the risk of developing obesity in adult life. The seminal analysis of children born during the Dutch Hunger Winter in 1944 disclosed that nutrient deprivation during early pregnancy leads to an increased obesity risk in adult life [20]. Also, in offspring exposed to famine periconceptually a specifically and persistently decreased methylation of the IGF2 gene was evident, suggesting epigenetic reprogramming. This effect has been demonstrated to endure for up to six decades [21]. There is even evidence of intergenerational transmission of epigenetic marks [22]. Insufficient fetal nutrient supply has not only been linked to obesity but also to an ample array of adult conditions including impaired glucose tolerance, higher rates of microalbuminuria, atherogenic plasma lipid profiles and coronary heart disease, the latter even occurring at an earlier age [23].

‘TRACKING’ OF CHILDHOOD OVERWEIGHT AND OBESITY INTO ADULTHOOD

Childhood overweight and obesity are likely to persist and even aggravate during adult life. The BMI attained during childhood years is highly correlated with the BMI in adulthood [24]. Whereas children who are obese at any age carry at a 2-fold risk of becoming obese adults, obesity during adolescence confers a 16-fold risk increase for obesity at adult age [25, 26].

LONG-TERM CONSEQUENCES OF CHILDHOOD OBESITY

Why is all this important? Does it not just show that we have altogether plenty of food and that there is a certain predisposition for body stature which manifests from childhood through adolescence into adulthood? It maybe does, but it also emphasizes that weight does matter already in childhood even if overt adverse consequences will only manifest at later age.

Early vascular lesions such as fatty streaks and fibrous plaques can already be detected during adolescence and early adult life. In the Bogalusa Heart Study the probability to find such lesions upon autopsy was associated with traditional risk factors such as higher BP and lipid levels but also, and independently, with increased BMI [27]. In the same study, the carotid intima-media thickness, a sensitive marker of early atherosclerotic lesions, at the age of 36 years was not only associated with the time-integrated BMI throughout the study period but also independently with childhood BMI [28]. Participants of the Harvard Growth Study who were overweight in adolescence (BMI >75th percentile) were at increased risk of cardiovascular morbidity after 55 years of follow-up, and men had a higher risk of overall and cardiovascular mortality [29].
CHILDHOOD OBESITY AND INTERMEDIATE CARDIOVASCULAR ENDPOINTS

Even though mortality rates related to childhood obesity can be evaluated with sufficient validity only in adulthood [30], intermediate endpoints for cardiovascular morbidity can be monitored non-invasively during childhood and adolescence and are considered to indicate an increased cardiovascular risk in adulthood. The IOTF described obesity-associated risk factors and early consequences in detail [6], ranging from sleep apnoea, lipid abnormalities, fatty liver disease, glucose intolerance and diabetes to hypertension and cardiovascular alterations. In a review of studies performed between 1997 and 2005 in obese children, virtually all studies identified a metabolic risk constellation, hypertension or both [31].

Blood pressure

Obesity is the most common risk factor for ‘essential’ hypertension in the adult population [32].

The pathophysiological mechanisms underlying the association of obesity and hypertension are well established and include activation of the sympathetic nervous system, increased activity of the renin–angiotensin–aldosterone system as a result of angiotensinogen production by adipose tissue, and increased salt reabsorption [33].

For adolescents, the effect of weight changes on blood pressure was first described more than two decades ago in the Muscatine Study. Among almost 3000 school children who had their blood pressure measured twice several years apart, those with relatively greater weight gain had higher blood pressure [34]. Likewise, in 949 healthy school children studied by 24-h ambulatory blood pressure monitoring a higher BMI SDS was clearly associated with higher 24-h systolic BP [35]. A recent study of >4000 German preschool children extended the validity of the association between overweight/obesity and higher blood pressure to the early childhood years [36].

To cope with the impact of overweight on blood pressure in the healthy population, a reference study for casual blood pressure specifically excluded all children with BMI exceeding the 85th percentile [37] since exclusion of children with overweight significantly lowered the calculated blood pressure distribution percentiles. However, this maneuver appears rather arbitrary since the association of relative body weight and blood pressure in the upper BMI percentiles seems to represent a linear relationship rather than a threshold effect, as demonstrated by a survey of blood pressure and BMI in a survey of 18 000 children in the USA [38].

Finally, overweight and obesity is a key finding of children and adolescents diagnosed with ‘primary’ or ‘essential’ hypertension [39]. All these studies provide clear evidence that increased blood pressure is among the most immediate and relevant cardiovascular sequelae of overweight and obesity.

Carotid intima-media thickness

Carotid intima-media thickness (cIMT) is regarded as an intermediate endpoint of cardiovascular damage as it reflects early morphological changes of the large arteries. cIMT is increased in hypertensive children, and in addition associated with BMI and dyslipidaemia [40]. Intima-media thickness at an adult age can be tracked back to childhood conditions: in the Muscatine Study cIMT at age 33–42 years was significantly associated with total cholesterol levels in childhood; at least in women an additional positive association to childhood obesity was apparent by multivariate analysis [41]. In the Young Finns Study LDL cholesterol, systolic BP and BMI during adolescence (12–18 years) added up in predicting IMT between 33–39 years of age [42].

Vascular function

Functional vascular assessments predict overall and cardiovascular risk in adults [43, 44]. In this regard, much attention has been paid to pulse wave velocity (PWV) as a measure of regional arterial stiffness. In adults, PWV is a valid intermediate endpoint of cardiovascular morbidity; PWV predicts cardiovascular events independently of blood pressure and other risk factors [43]. Studies in children and adolescents have yielded conflicting results regarding the determinants of arterial stiffness in this age group. Lurbe et al. [45] found blood pressure to be positively associated with PWV, whereas obesity appeared to be independently associated with lower PWV. Other studies found a positive relationship between PWV and body fat [46] or, when using brachial-ankle PWV, no association with obesity [47]. Charakida et al. confirmed the established association between obesity and higher BP, but they also found a decrease of PWV in obese children compared with their normal weight peers. In addition, further functional measurements such as resting and hyperaemic blood flow and flow-mediated dilatation were increased in obese children, indicating endothelial activation [48]. But again, opposite results with decreased flow-mediated dilation [49] have also been reported in obese children. Yet another study found decreased compliance and distensibility and higher wall stress of the common carotid artery in obese children [50], associated with evidence for decreased endothelial function as indicated by reduced flow-mediated dilation. The latter was associated with markers of insulin resistance and low apolipoprotein A-1.

The conflicting results for vascular function in adolescent obesity are not fully explained; arterial stiffness might possibly be decreased during early weight gain as part of a physiological vascular adaptation to the requirements of increased body mass, whereas later on the adaptive capacity might be exceeded and reversed in the presence of coexisting high BP.

Left ventricular hypertrophy

Hypertrophy of the left ventricle is a key adaptive process in arterial hypertension [51]. Left ventricular hypertrophy (LVH) is both an intermediate endpoint and a risk factor for cardiovascular events in hypertensive patients. LVH is present in ~40% of hypertensive children when defined as the age-specific 95th percentile for left ventricular mass; 13–16% have severe LVH meeting the adult definition (>51 g/m²) [52, 53]. BMI values exceeding the 95th percentile are associated with LVH and most studies in children with primary hypertension and LVH found higher mean BMI compared with healthy controls.
Moreover, obese children not only show morphological alterations but also subclinical functional impairment of the left ventricle with reduced systolic and diastolic deformation patterns and alterations of ventricular–arterial coupling [54, 55].

**Obesity, dyslipidaemia and inflammation**

The metabolic consequences of childhood obesity generally resemble those observed in adulthood. In the Avon Longitudinal Study of Parents and Children, overweight children were at a 2–3-fold, and obese children at a 4–10-fold higher risk for dyslipidaemia with high-triglyceride and low-density lipoprotein levels. At the same time, inflammatory markers such as C-reactive protein and interleukin-6 (IL6) steadily increased from normal weight through overweight to obesity [56]. Likewise, cardiovascular risk factors (i.e. high blood pressure and dyslipidaemia) accumulated with the degree of overweight in a study in children from Germany, Austria and Switzerland [57].

The prevalence and severity of metabolic abnormalities depends on the BMI thresholds applied. An analysis of the Bogalusa Heart Study by Katzmarzyk et al. [58] suggested that BMI thresholds well below the internationally recommended cutoffs for overweight and obesity predicted the presence of metabolic abnormalities with superior sensitivity and specificity. Litwin et al. demonstrated that the BMI thresholds established by Katzmarzyk et al. also predicted LVH with higher sensitivity than the 95th BMI percentile [59].

Fat is an active endocrine tissue producing specific hormones (adipokines) and inflammatory cytokines such as IL6 and tumor necrosis factor-alpha. There are direct associations between BMI, adipokine and cytokine levels and the inflammatory status [60]. Obesity-related dyslipidaemia and fat-derived cytokines promote glucose intolerance, associated with hyperinsulinaemia and insulin resistance, ultimately leading to diabetes mellitus (DM). Type II DM is increasingly diagnosed in children and adolescents [61, 62]. Nonimmune-mediated forms currently account for 8–45% of newly diagnosed paediatric DM cases in the USA [65]. This trend is largely attributable to the obesity epidemic as DM type 2 is predominantly diagnosed in patients with moderate-to-severe obesity [65].

**Therapeutic interventions in paediatric obesity**

Childhood obesity has been tackled by various interventional strategies, primarily aiming at dietary adjustment and increased physical activity [7]. The potential of weight loss to attenuate sequelae of obesity has been recognized both in adults and children [63, 78, 80], and current guidelines consider pharmacotherapy of obesity-related conditions as second line treatment after the exhaustion of conservative measures. However, lifestyle changes require a high degree of understanding and endurance, which might partially explain the low rates of substantial and sustained weight loss attained with these approaches alone [80]. Therefore, medication-based approaches are often considered for the management of hypertension, hyperlipidaemia and glucose intolerance [81].

In a study of mostly overweight children with primary hypertension, lifestyle changes (low salt intake, physical activity) combined with antihypertensive medication proved efficacious in reducing hypertension-induced target organ damage with reductions in both IMT and LV mass [82]. Ample clinical evidence supports the adverse impact of hypertension on the preservation of kidney function both in adults and children showed a pattern typical of obesity-related CKD, with proteinuria without oedema, normoalbuminaemia and glomerulomegaly in renal biopsy. The median renal survival was 15 years for pre-term obese and 23 years for term obese children.

Furthermore, obesity-associated dyslipidaemia contributes to progressive CKD by promoting inflammation and endothelial dysfunction [71]. Lower concentrations of apolipoprotein A1, the major component of HDL, are associated with a higher incidence of CKD in the general population [72]. Evidence for a link between dyslipidaemia and reduced renal function in children was recently noted in a population-based study from Turkey (CREDIT-C study), where both hypercholesterolaemia and a higher BMI were associated with a lower eGFR [73].

Studies assessing proteinuria in obese children without CKD yielded conflicting results. Some authors were unable to document any association between BMI and albuminuria [59], whereas others found that microalbuminuria was even less prevalent in overweight compared with normal weight adolescents [74]. Nonetheless, the latter study still showed that unlike in non-obese subjects, albuminuria, when present in obese adolescents, was associated with cardiovascular risk factors such as insulin resistance, hypertension and smoking.

Obviously, the association of obesity, metabolic derangements and renal damage is most intrinsic in patients with type II DM. The increasing prevalence of type II DM among obese adolescents is of particular concern as diabetic nephropathy is one of the major causes of end-stage renal disease in adulthood [75]. As many as 10% of young patients with type II DM may develop renal failure at an early adult age [7]. In a large cohort of young adults, glucosuria and a morbid obesity (BMI >35 kg/m²) are independently associated with an increased risk of albuminuria as an early sign for renal damage [76]. Among Pima Indians with type II DM, those with adolescent-onset DM had an 8-fold increased risk to develop ESRD compared with those with adult-onset DM [77].
with CKD [83–86], and the ESCAPE trial has provided evidence that strict blood pressure control is effective in slowing CKD progression in children [87]. The nephroprotective effect of stringent blood pressure control should hold true also for children with obesity-associated CKD. Furthermore, the superior nephroprotective effect of RAS antagonists has been widely demonstrated in adults with diabetic nephropathy [88–90] and it is reasonable to assume that this benefit will extend to obese adolescents with, or at risk of, diabetic nephropathy.

The other potential targets of pharmacotherapy in obese children and adolescents are more controversial. Lipid-lowering therapy appears to be effective in obese children and has been recommended (preferably using statins) in children from the age of 10 years who are refractory to diet and lifestyle change [91–93]. However, long-term safety data are still lacking.

The use of anti-obesity drugs in children is debated even more controversially, with very limited efficacy and safety information available to date. Early data suggest that the insulin sensitizer metformin, the centrally acting anorexigenic sibutramine and the fatty acid synthase inhibitor orlistat effectively induce weight loss at least in the short term, but are fraught with significant side effects [94–96]. Even bariatric surgery has been applied successfully in selected cases of super obesity [97].

**CONCLUSION**

Childhood overweight and obesity is a serious condition with multi-organ involvement. Apart from a possible direct effect of obesity on the kidneys, the vicious triad of hypertension, inflammation and metabolic alterations put children and adolescents at high risk for cardiovascular and renal damage at an early age.

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**CONFLICT OF INTEREST STATEMENT**

None declared.

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Using linked administrative data to study periprocedural mortality in obesity and chronic kidney disease (CKD)

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ABSTRACT

Both obesity and chronic kidney disease (CKD) are associated with adverse periprocedural outcomes, but it is unknown how these two common conditions interact to influence risk. We examined the feasibility of combining a new procedure-related, obesity-specific flag with administrative and laboratory data and assessed the joint association between obesity and CKD with mortality. Since 2007, Alberta physicians may claim a fee supplement for performing eligible surgical and non-surgical procedures on patients with documented BMI ≥ 35 kg/m².

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We linked this information to the Alberta Kidney Disease Network registry. Participants were classified into four mutually exclusive groups based on the presence/absence of both obesity (BMI ≥ 35 kg/m²) and CKD (eGFR < 60 mL/min/1.73 m²). Mortality was assessed at 30 days following the index procedure. Of 393,659 participants, 9% were obese. Overall, 8% had obesity only, 78% neither obesity nor CKD, 13% CKD only and 1% both obesity and CKD. Unadjusted risks of mortality at 30 days were 0.3, 0.4, 2.0 and 2.1%, respectively—but decreased to 0.1, 0.2, 0.3 and 0.3%, respectively, after adjustment for age, sex, socioeconomic status, procedure type and other comorbidities. Administrative data can be feasibly combined with disease registries.