Original article

Postnatal growth and prevalence of obesity in infants born large-for-gestational age during the first 3 years of life: Personal experience and exploration of current literature

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Abstract. *Aims of study:* We evaluated the growth patterns in a cohort of infants (n = 120) born large-for-gestational-age (LGA) [birth weight (Bwt) > 4 kg] from birth to age 3 years of age in comparison with normal age and sex-matched children (WHO). *Results:* LGA infants had high weight for age Z score (WAZ) at birth that decreased significantly during the first 6 months of life (by a mean of − 0.67 SD) that was followed by significant gain during the following 6 months of life (around + 0.4 SD). These children grew on a higher centile of WAZ with no significant change during the second and third years of life. The prevalence of obesity (WAZ > 2) increased markedly from 24% at the end of their first year to 34% and 36% at the end of the second and third years of life, respectively. The mean length for age Z score (LAZ) decreased significantly during the first 6 months (by a mean of -0.9 SD) but was maintained at high centile (> 1 SD) during the second and 3rd years. The weight for length SDS (WLZ) increased significantly during the first 18 months of life and decreases gradually during the second half of the 2nd year and the 3rd year. Their head circumference SDS decreased significantly in the first 6 months and then sustained around the 70th centiles (+1 SD) in the following 18 months. *Conclusion:* Our study showed that in LGA babies obesity increased progressively after the first year of life to reach 36% at the end of the third year. Therefore, it is important to apply early nutritional intervention to decrease the occurrence of obesity and reduce later cardiometabolic risks. (www.actabiomedica.it)

Key words: Large for age (LGA), postnatal growth, obesity.

Introduction

The prevalence of childhood obesity has been trending upwards over the last few decades and has led to the classification of childhood obesity as an epidemic. In 2020, about 40 million children below 5 years were overweight or obese (1).

Overweight or obesity during childhood has important short-term and long-term consequences. In the short term, children who are overweight or obese are more likely to suffer from: low self-esteem, emotional and behavioural disorders, liver complications, musculoskeletal problems, especially in the lower extremities, metabolic and cardiovascular risk factors. In the long term, because childhood onset obesity frequently persists into adulthood, it is also associated with increased long-term morbidity and mortality (2).

Therefore, prevention of pediatric obesity by promoting healthful diet, activity, and environment should be a primary goal, as achieving effective, long-lasting results with lifestyle modification once obesity occurs is difficult (3,4).

The predictable normal infant growth starts with a fast deceleration of growth velocity starting from birth that reaches a near plateau at the end of the first year of life and then continues to slow slowly through the second year. Postnatal growth of full-term infants can be classified as delayed, normal, or rapid depending on their infantile growth velocity that displays a sharp descending, a steady, or a sharp ascending change on the growth reference charts (5).

One definition of fast infantile growth is the change in weight or length-for-age standard deviation score of more than + 0.67 from birth to the age of 24 months. On the other hand, delayed growth can be defined as the change in weight or length-for-age standard deviation score of more than – 0.67 from birth to 2 years of age (6).

Neonatal macrosomia has been reported to increase over the past 50 years (7). Macrosomia is a term used to describe a baby who is significantly larger than average. Whereas large-for gestational-age (LGA) relates to a baby's size before and at birth, macrosomia is usually used to describe babies following birth who are larger than the 90^{th} or 95^{th} percentile for sex and gestational age on an infant growth chart or who weigh 4 kg or more at birth (8) These LGA babies are more susceptible to neonatal complications. Later in life, they are reported to suffer from hypertension, obesity/overweight, insulin resistance, metabolic syndrome, and type 2 diabetes later in life. It was suggested that fast weight gain and rapid linear growth during the infancy period can predispose to obesity and adverse cardiometabolic outcomes during adulthood (9-13).

Substantial variation in prevalence of macrosomia occurs in different countries, ranging from 0.5% (India) to 13.9% (China) while the prevalence of LGA ranges from 4.3% (Korea) to 22.1% (China) (14,15).

The most frequently seen causes of LGA are gestational diabetes, maternal obesity and excessive gestation weight gain (GWG) during pregnancy, which can in part be caused by overconsumption of high-fat, calorie-dense foods (16). Gestational diabetes mellitus and maternal obesity are associated with increased rates of LGA in humans as well as in animal models.

The currently available evidence highlights the association between infant growth rate and subsequent obesity risk, however, there is a limited comprehensive understanding of this relationship between the pattern of growth rate and the development of childhood obesity in infants born LGA. The aim of our study was to evaluate the growth patterns of a cohort of infants born LGA from birth to age 3 years in comparison with normal age and sex-matched children.

Subjects and methods

This was a retrospective observational study of 120 LGA infants who were born between January 2016 and December 2017 in Qatar.

Out of the 120 LGA (78 males and 42 females), 69% were infants of mothers with gestational diabetes (IDM), 93/120 were delivered vaginally and 27 infants were delivered by C-Section. 48/120 were born between 40 and 41 weeks, 47/120 were born <40 weeks and 25/120 were born after 41 weeks of gestation. 45/120 were Qataris, 43 were Arabs and 32 were Asians (Indians, Pakistanis, and Filipinos). Infants were evaluated at birth, 2, 4, 6, 12, 18, 24 and 36 months of age. Infant anthropometric measurements were taken at each visit and included weight, length, head circumference. Weight for age Z score (WAZ), length for age Z score (LAZ), and weight for length Z score (WLZ) were calculated using WHO standards for age and sex.

Statistical analysis

Data are reported as mean ± SD, or as frequencies and percentages. Student paired t-test was used to compare the different variables at the different periods in the same group of infants when the data were normally distributed and Wilcoxon rank sum test when the data were not normally distributed. Significance was accepted when P: < 0.05. Linear regression models were run to detect the independent effects of various infant anthropometric data on 3-year child body mass index Z score (BMI-Z) and WLZ.

Ethics

All procedures were in accordance with the 1964 Helsinki declaration and its later amendments in October 2013 (www.wma.net). The study was approved by the Ethical Committee of Hamad Medical Centre approved the study (MRC-01-21-277).

Results

LGA infants had high WAZ at birth that decreased significantly during the first 6 months of life (by around – 0.7 SD) that was followed by significant gain during the next 6 months of life (by around + 0.4 SD). At the end of the first year, 60% of these infants had catch down while 40% had no change or had catch up in WAZ. Most of these children grew on a higher centile of WAZ with no significant change during the second and third year of life (Figure 1 and Table 1).

The prevalence of obesity (WAZ > 2) increased markedly from 24% at the end of their first year to 34,2% and 36,6% at the end of the second and third years of life respectively (Figure 2).

The mean LAZ decreased significantly during the first 6 months (by around - 0.9 SD) but was maintained at high centile (> 1 SD) during the second and 3rd years (Figure 3).

The weight for length SDS (WLZ) increased significantly during the first 18 months of life and decreases gradually during the second half of the 2nd year and the 3rd year (Figure 4).

The head circumference SDS decreased significantly in the first 6 months and was maintained around the 70th centiles (+1 SD) for the next 18 months. (figure 5)

The degree of catch-up or down in WAZ during the first year in relation to obesity (WAZ > 2) at three years of age showed the following:

a. 60% of the infants born LGA had WAZ > 2 at 3 years.
b. 37 % of LGA had catch down > 0.67 during the first year. Only 2.2 % of them had obesity at 3 years of age.
c. 20 % of children had WAZ catch up > 0.67 during the first year of life, 75 % of them had WAZ > 2 at 3 years of age.
d. 41 % of children had WAZ change between -0.67 and + 0.67 during the first year of life, and 50 % of them had obesity at 3 years.

Correlations

a. WAZ 36 mo. was correlated significantly with WAZ 6 mo. (r = 0.6, P <0.001), WAZ 12 mo. (r = 0.75, P <0.001), WAZ 18 mo. (r = 0.83, P < 0.001), WAZ 24 mo. (r = 0.77, P <0.001) and LAZ 36 mo. (r = 0.64, P < 0.001);

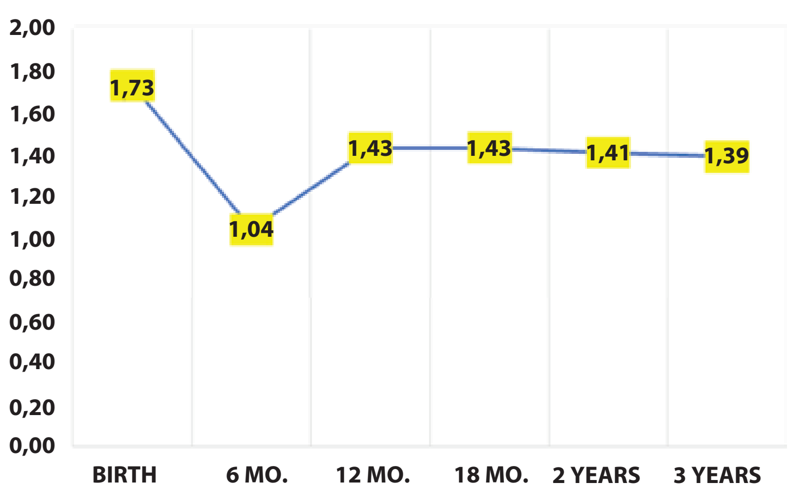

Figure 1. Postnatal changes in weight for age Z score (WAZ) in large-for-gestational-age infants (LGA) from birth to 3 years of age.

Table 1. Three years postnatal growth parameters in infants born > 4 kg.

	Birth	6 mo.	12 mo.	18 mo.	2 years	3 years
WAZ						
mean	**1.73**	**1.04**	**1.43**	**1.43**	**1.41**	**1.39**
SE	**0.04**	**0.09**	**0.10**	**0.11**	**0.11**	**0.12**
LAZ						
mean	**1.99**	**1.06**	**1.18**	**0.97**	**1.11**	**1.27**
SE	**0.09**	**0.10**	**0.10**	**0.12**	**0.11**	**0.15**
WLZ						
mean	**0.07**	**0.66**	**1.19**	**1.26**	**0.82**	**0.72**
SE	**0.10**	**0.10**	**0.10**	**0.12**	**0.12**	**0.11**
HCSDS						
mean	**1.34**	**0.80**	**0.84**	**0.98**	**0.96**	**0.99**
SE	**0.08**	**0.09**	**0.10**	**0.09**	**0.07**	**0.07**

Legend: Weight for age Z score (WAZ), length for age Z score (LAZ), weight for length Z score (WLZ), and head circumference SDS (HCSDS).

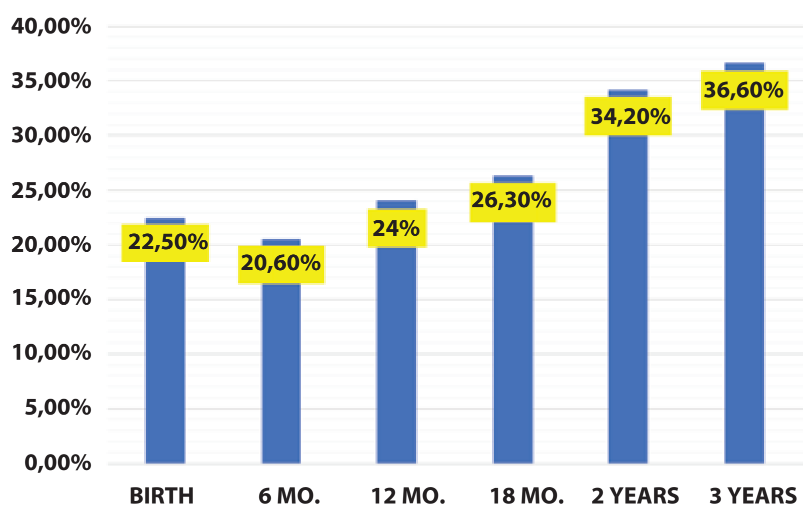

Figure 2. Weight for age Z score WAZ > 2 from birth to 3 years of age in infants (n=120) born at term (> 4 kg).

b. LAZ 36 mo. was correlated significantly with WAZ 6 mo. ($r = 0.63$, $P < 0.001$), WAZ 12 mo. ($r = 0.54$, $P < 0.001$), WAZ 18 mo. ($r = 0.67$, $P <0.001$), WAZ 24 mo. ($r = 0.56$, $P <0.001$), and WAZ 36 mo. ($r = 0.64$, $P <0.001$);

c. BMIZ 36 mo. was correlated significantly with WAZ 12 mo. ($r = 0.58$, $P <0.001$), WAZ 24 mo. ($r = 0.60$, $P <0.001$), and WAZ 36 mo. ($r = 0.68$, $P <0.001$).

d. WLZ was correlated significantly with BMIZ at the end of the first year and at the end of the 3rd year ($r = 0.75$, $P <0.001$).

Discussion

Adjustments and adaptations during the intrauterine environment can induce fetal developmental

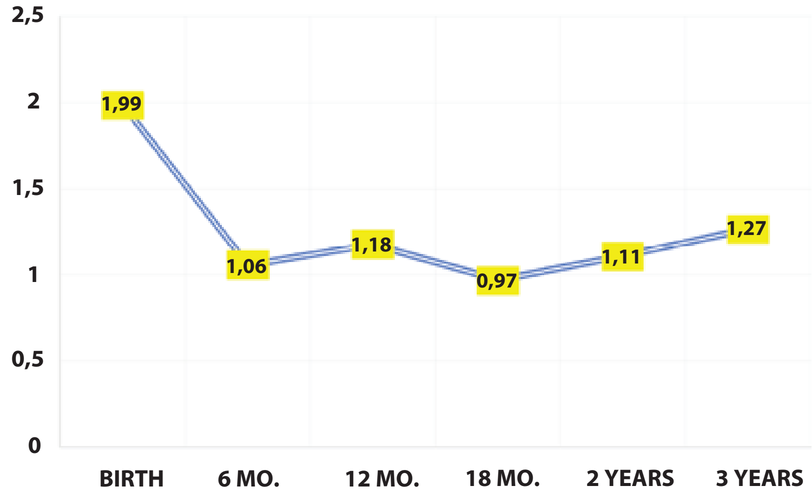

Figure 3. Length for age Z score (LAZ) in large-for-gestational-age infants (LGA) from birth to 3 years of age.

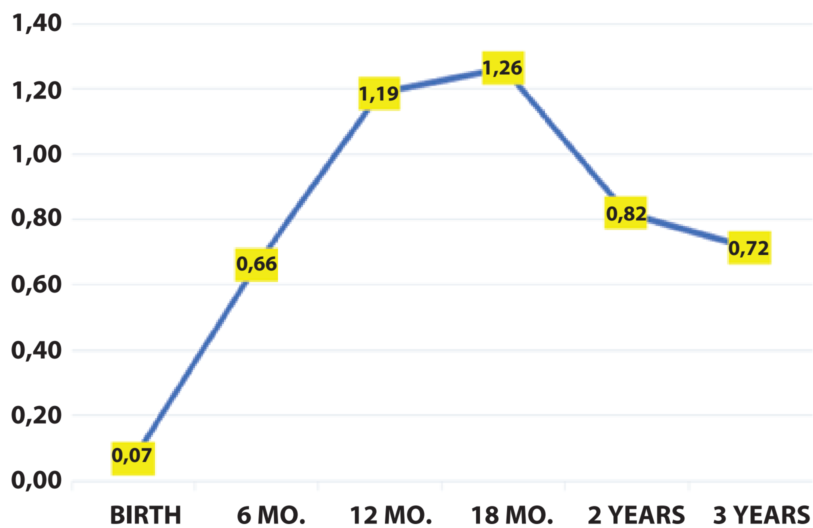

Figure 4. Weight for length Z score (WLZ) in large-for-gestational-age infants (LGA) from birth to 3 years of age.

variations that might have lengthy postnatal negative effects on the offspring (17). Maternal factors such as maternal obesity, rapid weight gain during pregnancy, and gestational diabetes are associated with a marked increase in the number of LGA infants (18).

Nonetheless, a considerable number of these LGA infants are born to healthy and normoglycemic women, and in such cases, the underlying mechanisms for oversize at birth are yet to be fully identified (19,20).

There is a paucity of longitudinal data on the growth outcomes of LGA infants (21,22). We observed a decrease in WAZ, LAZ, and HCZ in the majority of LGA infants during the first 6 months postnatally. 60% of our LGA had catch down, of any degree, during the first year with 37% had catch down > 0.67 SD. During the second and third years of life their growth in weight and length was stable at a higher centile for age and sex (around +1 SD). 36.6 %

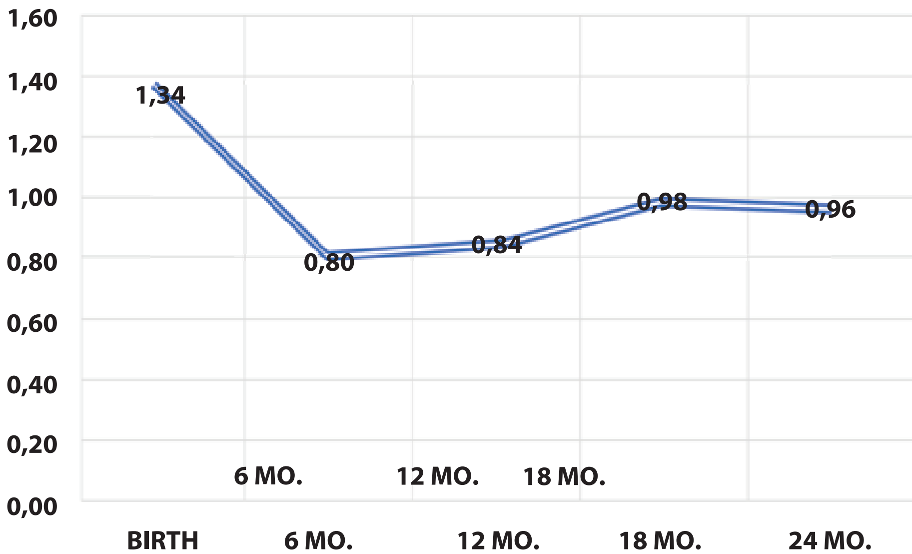

Figure 5. Head circumference SDS in large-for-gestational-age infants (LGA) from birth to 2 years of age.

of our LGA infants were overweight or obese at the end of their 3rd year of life.

Davies et al. (23) followed growth of 38 LGA infants in comparison to 100 with appropriate for gestational age (AGA) during the first 6 months of life. A substantial shift to the mean in weight, but great diversity in growth patterns was reported.

Ng et al. (24) studied the anthropometric data of 53 LGA babies > 4kg, born to non-diabetic mothers, for 6 months. Growth in all physical dimensions, especially weight, showed a downward shift towards a reference means.

Our LGA infants who had catch up in WAZ during the first year of life (20%) had high prevalence of overweigh/obesity at the end of the 3rd year (75%). Those with catch-down (>0.67 SD; 37%) had low prevalence of overweight/obesity at the end of the 3rd year (2.2%). In support with our findings, Lei et al. (12) divided LGA infants according to their postnatal growth trajectory into: (a) rapid catch-down growth (25.2%), (b) small catch-down growth (54.4%), and (c) no catch-down growth (20.6%). LGA infants without catch-down growth had increased risks of obesity at 7 years of age while term LGA infants with small catch-down growth had lower risks of obesity and growth restriction at age 7 years as compared with AGA children.

Taal et al. (25), reported that children born LGA showed infant catch-down growth, and their mean head circumference, length, and weight remained larger until the age of 4 years. LGA infants without catch-down growth had an increased risk of being overweight. 50 % of our LGA infants who did not have catch down at the end of first year were overweight or obese at the end of the 3rd year.

A recent systemic review of 31 studies indicated that LGA infants have increased fat mass at birth, but in the long term, those who developed catch down during infancy had a lower body fat ratio during childhood (26).

Moschonis et al. (27) studied the growth of 2,374 Greek pre-schoolers (1-5 years). Children born LGA were 4.59 and 2.19 times more likely for being overweight at 6 and 12 months of age, respectively, compared to children born appropriate for gestational age. Our LGA had WAZ around 1.43, 1.41, and 1.39 at the 18, 24, and 36 mo. postnatally. In addition, WAZ at 36 mo. was correlated significantly with WAZ at 6, 12, 18 and 24 mo. (P <0.001) denoting continuous tendency to be overweight during infancy and early childhood. In support to our data, Hediger et al. (28), compared the growth profiles of infants and young children born LGA with those of AGA. The weight status of LGA infants remained at about + 0.50 SD till 47 months of age.

Our LGA had LAZ of 0.97, 1.1 and 1.27, respectively, at the 18, 24 and 36 months postnatally. LAZ at 36 months was correlated significantly with WAZ at 6, 12, 18. 24 and 36 months (P <0.001). In addition, they had HCZ of 0.8, 0.84. 0.98 and 0.96 at 6,12,18 and 24 months, respectively. These data denote that these infants remained relatively tall and had relatively large head with good correlation between their length and weight.

In 2010, the Canadian perinatal registry including 4,298 children showed that those who were born LGA had higher risk to be overweight (OR=1.23) at 10-11 years of age (29).

The increased risk to develop overweight/obesity was furtherly confirmed in a meta-analysis that included 20 of published studies. A birth weight (BW: > 4 kg) was associated with an increased risk of obesity versus those born with BW ≤ 4 kg (30).

Rogers et al. (31) measured the body composition using dual-energy X-ray absorptiometry in 9-10 years old children (n = 3,006 boys and 3,080 girls) in relation to their weight and length at birth. A positive association between birth weight, lean body mass (LBM) and total body fat was found in both sexes.

In a meta-analysis that included 30 prospective studies, authors identified significant and strong independent associations with childhood overweight related to maternal pre-pregnancy overweight, high infant birth weight and rapid weight gain during the first year of life (32).

Xie et al. (33) studied 600 LGA infants. They subdivided them according to their maternal overweight or obesity before pregnancy (OW/OB), diabetes mellitus (DM), and excessive gestational weight gain. The LGA subgroup who were offsprings to OW/OB and those with DM who experienced normal gestational weight gain had a "continuous high increasing" BMI Z-score trajectory from 9 months to 4 years. The LGA subgroup who were offsprings for mothers with normal weight and normal weight gain during pregnancy had a similar BMI Z-score trajectory ("stable low") from 9 months to 4 years.

In our study, WLZ at the end of the first year was correlated significantly with BMIZ at the end of the 3rd year (r = 0.77, P <0.001) suggesting a good correlation between weight relative to linear growth at 1 and 3 years of age.

A study done in children, aged 9 to 12 years, showed that severe obesity was associated with LGA and maternal severe obesity. No significant behavioral factors had an influence on severe obesity in any age group of their study (34). Researchers suggested that the development of abnormal epigenetic mechanisms, particularly related to DNA methylation, in the brains of LGA offspring, can lead to disruptions in the cell cycle in development and alter gene expression in adulthood (35). This hypothesis was not confirmed by a genome-wide analysis on umbilical tissue of LGA (n= 29) and AGA (n= 42) infants (36).

Encouraging breastfeeding, reduction of protein content of formulated milks, and diet in the first 12–24 months, involving family and schools in interventions that promote physical activity and healthy diet, are hopeful strategies for decreasing the risk of childhood obesity (37).

A recent intervention study in young children starting from age 2 years, showed that the optimal target population for the intensive intervention are children who have milder obesity, are younger, and do not have a mother with severe obesity (38).

In conclusion, our data show a significant prevalence of overweight/obesity in children born LGA at 3 years of age especially those who do not have catch down growth during the first year of life. Since later cardiometabolic risk is often mediated by early growth patterns, it is important to apply early nutritional intervention to decrease the occurrence of obesity and reduce later cardiometabolic risks in LGA children. Reporting and following the growth of infants born LGA, would early capture the tendency to obesity and allow for identification of contributing factors and early prevention/ management.

Conflicts of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Author's Contribution: Fawzia Alyafei: Idea of research, data collection and analysis, and approved the manuscript for publication.

Ashraf Soliman: Substantial contributions to the conception of the work; extensive searching of the literature and drafting the review; and approved the manuscript for publication. Vincenzo De Sanctis: Contributed to the conception of the work and critically revised the manuscript for accuracy and integrity and approved the manuscript for publication. Noor Hamed: Shared actively in searching the literature and writing up the review; and approved the manuscript for publication. Nada Alaaraj: Shared actively in searching the literature and writing up the review; constructing the tables. and approved the manuscript for publication. Shayma Ahmad: Shared actively in searching the literature and writing up the review; and approved the manuscript for publication. Fatima AlKhori: Data analysis, tables construction and approved the manuscript for publication. Saleha Abbasi: Data collection and approved the manuscript for publication.

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