Stunting and future risk of obesity: principal physiological mechanisms

Baixa estatura nutricional e risco de obesidade futura: principais mecanismos fisiológicos

Ana Lydia Sawaya [1]
Susan Roberts [2]

[1] Disciplina de Neurofisiologia e Fisiologia Endócrina, Departamento de Fisiologia, Universidade Federal de São Paulo. Rua Botucatu 862, São Paulo, SP 04023-060, Brasil. anafisi@ecb.epm.br
[2] Human Nutrition Research Center on Aging at Tufts University. 711 Washington Street, Boston, MA 02111-1524, U.S.A. susan.roberts@tufts.edu

Abstract   There is a fair amount of epidemiological evidence showing that nutritional stunting causes increased risks of obesity. Obesity is increasing dramatically not only in developed countries but also in developing countries, such as Brazil, especially among the poorer. The mere co-existence of undernutrition and obesity among poor people has a great impact, as the burden in the social, economic, and health care systems is remarkable. In addition, an increasing number of studies have shown that nutritional stunting causes a series of important long-lasting changes such as lower energy expenditure, higher susceptibility to the effects of high-fat diets, lower fat oxidation, and impaired regulation of food intake. These findings suggest that a broader and more detailed understanding of the long-lasting effects of early undernutrition, direct cause of nutritional stunting, is needed. Within this context, we present data of some physiological mechanisms that substantiate the association between previous undernutrition and future obesity.
Key words   Nutritional Status; Obesity; Nutrition Disorders; Food Intake

Resumo   Existe uma quantidade significativa de evidências epidemiológicas mostrando que a baixa estatura nutricional aumenta o risco de obesidade futura. A obesidade vem aumentando dramaticamente, não apenas nos países desenvolvidos, mas também nos países em desenvolvimento, como o Brasil, especialmente entre indivíduos mais pobres. A mera coexistência de desnutrição e obesidade na população pobre tem um grande impacto, gerando enorme sobrecarga para o sistema de saúde e a estrutura sócio-econômica. Além disso, um número cada vez maior de estudos tem mostrado que a baixa estatura nutricional causa uma série de mudanças a longo prazo, como menor gasto energético, maior susceptibilidade aos efeitos de dietas com alto teor de gorduras, menor oxidação de gorduras e prejuízo na regulação da ingestão alimentar. Esses achados sugerem a necessidade de um entendimento mais amplo e detalhado dos efeitos tardios da desnutrição no início da vida, causa direta da baixa estatura para a idade. Dentro desse contexto, apresentamos alguns dados relacionados aos mecanismos fisiológicos subjacentes à associação entre desnutrição e obesidade futura.
Palavras-chave   Estado Nutricional; Obesidade; Desnutrição; Ingestão de Alimentos

Background

In developing countries both high mortality among children under-5 due to undernutrition and high adult mortality from non-communicable diseases are significantly greater among the least socially favored. The health situation is even more devastating if we consider that people in lower socioeconomic groups have the largest burden of disease and the fewest resources for adequate treatment. An example of this situation is Brazil where mortality has been shown to be approximately three times greater when comparing the least to the most socially favored occupational category (Duncan et al., 1995).

It is difficult to draw clear relationships for the epidemiological association between non-communicable diseases in adults and undernutrition in children. In particular, it is difficult to explain the higher increase in obesity in low-income people of developing countries, as this population still have a high prevalence of undernutrition. These higher rates of undernutrition are associated with much lower energy intakes than in countries like the United States. Overall, the national daily per capita calorie supply in Brazil, in 1996, was 1,711.2kcal, whereas in the United States, in 1994, it was 2,700 kcal (Monteiro et al., 2000; Putnam, 1999). A recent study in a very poor community (income less than US$1/day) in Northeast Brazil found overweight adults (17%, BMI ≥ 25) eating less than 80% of requirements (adjusted to stature) (Florêncio et al., unpublished results). For these reasons, it is still an open question whether the poor obese are indeed eating an "excess of energy" according to requirement. In spite of this, obesity is increasing in poor populations even more than among higher income people. Brazilian national surveys, for example, have described a marked increase in the frequency of obesity among adults. The highest increase was seen in lowest income women from the richest region of the country, i.e., the Southeast (227%, from 6.6% in 1975 to 15% in 1997). Patterns between genders are very different, as the prevalence of obesity increases with income in men whereas in women obesity increases with poverty, being higher in the poorest region of the country (Northeast) than in the highest income quartile of the richest region (Monteiro et al., 1999).

These results raise the question whether the increase in the prevalence of obesity is greater among poor people of transitional societies, because these populations, especially women, have higher susceptibility to the deleterious effects of Western lifestyle (high intake of animal and processed food, low physical activity, etc.). This hypothesis is still under debate, and one strong candidate for this higher susceptibility seems to be early undernutrition, as it could permanently "program" the individual to increase and/or preserve fat stores.

To our knowledge, the first epidemiological evidence for this hypothesis came from the study of the Second World War Dutch Famine. As one of the most important epidemiological sets, this population has been extensively studied. Ravelli et al. (1976) showed an increase in the incidence of obesity in 19 year-old men whose mothers suffered food deprivation during the first half of gestation. Subsequently, it was shown that undernutrition during early gestation was associated with higher BMI and higher waist circumference in 50 year-old women but no longer in men (Ravelli et al., 1999).

Our group at the Federal University of São Paulo has been studying the association between undernutrition and obesity in the low-income population since the 1990s. In 1995 we described a coexistence of undernutrition and obesity in a shantytown population in the city of São Paulo (Sawaya et al., 1995). In particular, this study showed a high prevalence of undernutrition (low weigh-for-age and/or low height-for-age) in children (30%) with a shift towards overweight and obesity (high weight-for-height and BMI) among adolescents (21% in girls and 8.8% in boys) and adults (14.6%). Moreover, a high prevalence of obesity associated with stunting (indicative of chronic growth faltering during childhood and the main consequence of poor nutrition in developing countries) has been found in a number of protocols over the years, indicating that obesity could occur in an individual subsequent to growth faltering (Kosin et al., 1987; Sawaya et al., 1989, 1995). Later, other studies have replicated these findings showing an association between stunting and overweight in other countries such as Russia, China, and South Africa, all of which are undergoing nutritional transition (Popkin et al., 1996).

In Brazil stunting has been related to poverty level and not to genetic background. The national survey PNSN (1989) showed that stunting increased negatively according to income; with higher income Brazilian children's growth pattern being similar to National Center for Health Statistics (NCHS) standards (INAN, 1990). Among adults from different communities (landless workers – MST, homeless) mean height was significantly associated with poverty and living conditions; the shorter having worse living conditions (Florêncio et al., 2001).

A more recent study in Alagoas, one of the poorest states in Brazil, found a clear co-existence of high levels of stunting and obesity (Florêncio et al., 2001). Three hundred and fifteen families (1,247 people) living in the outskirts of Maceió in a "homeless" people's encampment were surveyed. Monthly family income was US$ 40.3 and per capita income was US$ 9.6. Among children (10 years or less) the prevalence of underweight (less than -2 Z score of w/a), stunting (less than -2 Z score of h/a), and underweight plus stunting (less than -2 Z score of w/a and h/a) was 3.8%, 8.3%, and 8.7% respectively. A high prevalence of low BMI-for-age (13%, below 5th percentile) and stunting (11%, below -2 Z score of height-for-age) was found among adolescents. Overweight/obesity (6.2%, above 85th percentile of BMI-for-age) was seen specifically in girls, trends found in other studies. The adults exhibited a high prevalence of overweight/obesity (25%, BMI ≥ 25), but stunting were also significantly present (22%, less than -2 Z score of oldest age of NCHS standards). Of the stunted individuals, 30% suffered from overweight/obesity and 16.3% were underweight. Overweight/obesity and underweight coexisted in 30% of households. These results suggest that at least in transitional populations, obesity may possibly be occurring as a sequelae of undernutrition earlier in life. We have speculated in the past that early malnutrition results in a decrease in energy requirements, and that this may promote a tendency towards a positive energy balance when food availability improves, for example when an increase in age permits the access to food aid programs in school or the ability to search for food autonomously, as in the case of street-children in Brazil, or when poor adults move from rural to urban areas.

This review describes some of the physiological mechanisms found to be related to positive energy balance and fat accumulation in previously undernourished individuals.

Physiological basis for long-lasting changes in positive energy balance in previously undernourished subjects

Effects on body fatness and growth velocity

There are a large number of studies demonstrating metabolic alterations in children suffering from undernutrition, in all tissues and body systems. The majority of these alterations work towards energy conservation and maintaining a low metabolism (Waterlow, 1994).

However, few studies have investigated the permanence of such alterations after nutritional recovery. There is some evidence for a disproportionately greater replenishment of body fat stores than body protein stores during the catch-up growth in infants and children recovering from undernutrition. In a study of the growth rates of undernourished children, Ashworth (1969) used anthropometric variables to observe a specific increase in body fat at the time when the expected weight-for-height had been reached so that, after recovery, previously undernourished children were found to be fatter than well-nourished children of the same age and weight. More recent studies by Fjeld et al. (1989) have confirmed this finding using metabolic balance studies combined with measurements of total energy expenditure, determined using the doubly labeled water technique, to determine fat and protein accretions during weight gain. The mean fat content in those studies was approximately 42% of weight gain (Fjeld et al., 1989), which is nearly double the expected mean body fat content of 24% in young children (Fomom et al., 1982). In the same study, it was also shown that there was no difference in the fat content of new tissue between infants gaining weight at a moderate rate (6g/kg/day) or a rapid rate (12g/kg/day). Studies such as these have noted that high-energy feeding of undernourished children is relatively easy, implying that the children are hungry, perhaps because their low body fat stores have triggered signals encouraging hyperphagia (Zhang et al., 1994).

The cause of the very high ratio of fat to protein accretion in children recovering from undernutrition is not known. One possible explanation for this preferential fat deposition in detriment of protein is the lower cost for fat deposition relative to protein. In addition, it is likely to be relevant that the rates of weight gain encouraged in infants and children recovering from undernutrition are very high: typically 5-15 times greater than the usual mean rate of gain in normal children. These high rates of weight gain are necessitated by the fact that slow rates of gain delay recovery with the possible consequence of cognitive impairment, prolong expensive treatment, and encourage the continuation of opportunistic infections that can cause further problems. However, while essential in many respects, these high rates of gain are probably not entirely dictated by the underlying metabolic mechanisms of normal growth and may have long-term repercussions with respect to the risk of excessive increase in body fatness. In healthy children of

normal weight, the balance of evidence suggests that at least some and perhaps the majority of bone growth takes place in intermittent spurts rather than gradually over time (Lampl et al., 1992) and is regulated by a choreographed cast of circulating hormones and local growth factors (Nilson et al., 1994). It is thought that muscle growth is a natural consequence of bone growth, with muscle stretching acting as one of the primary muscle growth stimulants (Tirapegui et al., 1994). Thus, in the normally nourished child, growth can be viewed as an event that occurs in response to a delicate balance of growth hormone and other growth factors. Under these particular metabolic conditions, a relatively high proportion of bone and muscle growth occurs in relation to fat deposition. In contrast, when weight gain or growth occurs in the absence of the correct balance of growth factors, the result is a higher proportion of fat and a lower proportion of lean tissue that more closely resembles the composition of new tissue that occurs in non-growing adults when they gain weight (Saltzman & Roberts, 1995).

The combination of these studies and observations strongly suggests that rapid weight gain following undernutrition causes children to be fatter and to have proportionately less muscle tissue than a child with similar age and weight-for-height who was never undernourished. These suggestions are consistent with the limited information available at the current time. There is no reason to suppose that this reduction of muscle mass (relative to the accretion during normal growth) and the increase in fat mass ceases to persist in the long-term following undernutrition.

In line with the above considerations, it is interesting to note that in some cohort studies of stunted children, a marked increase in weight-for-height or BMI is not followed by increases in height-for-age (Benefice et al., 2001; Sawaya et al., 1998). In addition, in one longitudinal study, a group of stunted and non-stunted school girls was followed for two years (Sawaya et al., 1998). A series of metabolic differences were found between these two groups. Stunted school girls in comparison to non-stunted ones, showed a higher susceptibility to gain weight-for-height when higher fat diets were consumed and had also higher central fat accumulation as seen by higher waist-to-hip ratio. Figure 1 shows the growth curve of the two groups during the follow-up. A higher increase in weight-for-height was observed among stunted girls in comparison to non-stunted.

Effects on energy balance and fat oxidation

Until recently, our understanding of the cause of differences in body fat mass between individuals was primarily influenced by the guiding principle of energy balance: *Energy Stored = Energy Intake - Energy Expenditure*.

Thus, it has been recognized that high levels of body fat (i.e., energy) cannot have been accumulated without energy intake being relatively high or energy expenditure being unusually low, or a combination of these two options. A number of investigations have suggested that both excessive energy intake to actual requirements and low energy expenditure can play important roles in facilitating excessive body energy storage in both children and adults (Jequier, 1993; Saltzman & Roberts, 1995). There remains controversy over the extent to which hyperphagia and low energy expenditure are direct causes of body energy gain as well as being responses to underlying signals that drive energy regulation (including the putative energy sign leptin). However, several lines of evidence suggest that energy intake and energy regulation have direct as well as indirect effects. For example, less than half of individual variability in body fat content is thought to be genetic (Bouchard & Peruse, 1988), suggesting that energy intake and energy expenditure are influenced by factors other than the underlying metabolic determinant of fatness. A similar direct effect is demonstrated by intervention studies reporting changes in body composition with imposed physical activity in the expected direction (i.e., increased energy expenditure for physical activity is associated with a decrease in body energy storage) (Ballor & Keesey, 1991).

More recently, as an extension of the energy balance principles detailed above, it has been suggested that body carbohydrate and lipid balances play a critical role in overall energy regulation (Flatt, 1988, 1995). The basic principle behind this model of energy regulation (which is in keeping with the much earlier glucostatic theory of energy regulation) is that balances of the primary energy substrates, fat and carbohydrates, have to be considered separately (Flatt, 1988, 1995). Thus, energy balance requires that the balance of each major substrate individually be maintained constant since: *Fat Stored = Fat Intake - Fat Oxidation*, and *Carbohydrate Stored = Carbohydrate Intake - Carbohydrate Oxidation*.

Because the energy in carbohydrate stores is very small in relation to that in fat stores, the carbohydrate stores have a high turnover rate and are liable to be depleted quickly and fre-

quently. The essential requirement of key tissues for glucose suggests that signals should exist to efficiently monitor and correct body carbohydrate balance. An extension of this model is that dietary macronutrient composition may play an important role in determining body fat content (Flatt, 1988, 1995). This is because the higher the dietary fat content, the more total food (and energy) needs to be consumed to maintain carbohydrate intake and therefore carbohydrate stores, and the fatter the individual will become because of increased energy intake.

Support for the importance of nutrient balance in the overall regulation of energy balance can be derived from several sources. Of critical importance, Flatt (1988, 1995) has demonstrated in mice that energy balance is adjusted on a day-to-day basis to maintain stable body carbohydrate balance, through adaptive fluctuations in food intake, and several studies in humans have indicated that carbohydrate balance is more closely regulated than fat balance (Abbott et al., 1988; Schutz et al., 1989). In addition, reduced fat oxidation as measured by indirect calorimetry has been linked prospectively to weight gain (Zurlo et al., 1990). Further support is gained from studies linking changes in body fat content to changes in fat oxidation (Schultz et al., 1992). Of relevance, it has been shown that respiratory quotients (RQs) of chronically undernourished adults have higher basal, 12h post-absorptive RQs than well-nourished adults, which indicates that these individuals have higher rates of carbohydrate oxidation and lower rates of fat oxidation (Shetty, 1992). This author attributes the high RQs to two main factors: the high carbohydrate intake of undernourished individuals, and a selective use of carbohydrate as fuel even in the post-absorptive, fasted state. The selective utilization of carbohydrate illustrates how closely carbohydrate oxidation is adjusted as demonstrated by Flatt (1988, 1995). In addition, the selective use of carbohydrate as fuel has obvious metabolical advantages to the undernourished individual since carbohydrate (glycogen) oxidation results in more ATP generation than iso-energetic amounts of fat or protein (Shetty, 1999). Hence, it is not unlikely that the high fasting RQs of the undernourished reflect to some degree the metabolic efficiency of the active tissues of these subjects by resorting to specific metabolic pathways that favor more efficient utilization of the available metabolic fuel.

Another important candidate for the control of energy balance in undernourished individuals is Resting Energy Expenditure (REE).

Figure 1

Association between baseline percentage of dietary energy from fat and change in weight-for-height (percentage of median) during the follow-up period, in stunted and non-stunted school girls living in shantytowns in the city of São Paulo, Brazil.
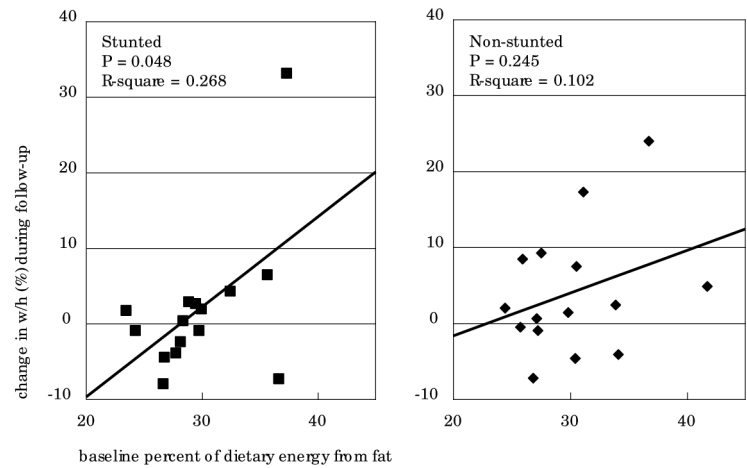
Experimental semi-starvation studies on well-nourished adult human volunteers carried out by Benedict et al. (1919), Keys et al. (1950), and subsequently by Grande et al. (1958), have invariably shown a reduction in REE. This consistent finding of a reduced REE during experimental semi-starvation was explained both on the basis of a decrease *per se* in the activity of the metabolically active tissues of the body and as a consequence of a loss of active tissue mass due to loss of body weight. In this condition, a decrease in insulin, thyroid hormones, sympathetic nervous system, and catecholamines has been described, associated with an increase in glucagon, growth hormone, protein catabolism, and free fatty acids (Shetty, 1999). Studies in chronically undernourished adults found lower REE expressed either in absolute terms, or expressed per unit body surface area, although these same studies have failed to demonstrate any significant decrease in metabolic rate per kg of active tissue mass. These observations in the chronically undernourished were in marked contrast to the demonstration of decrease in REE per kg of active tissue mass during semi-starvation in well-nourished adults (Shetty, 1999).

In chronically undernourished children, data are much scarcer. One investigation has studied 58 pre-pubertal boys and girls aged 8-11 years from the shantytowns of São Paulo.

Twenty-eight were mildly stunted (height-for-age ≤ -1.50 Z scores) and 30 had similar weight-for-height but normal height (height-for-age > -1.50 Z scores). Parents of the two groups were of equivalent height and body mass index. In one set of experiments, fasting and post-prandial energy expenditure, RQ, and substrate oxidation were measured by indirect calorimetry in a 3-day resident study. Compared to control children, stunted children had normal resting energy expenditure relative to body composition and normal post-prandial thermogenesis. However, stunted children showed significantly higher fasting RQ, and in consequence fasting fat oxidation was significantly lower. It was concluded that childhood nutritional stunting was associated with long-term impairment of fat oxidation, a factor that strongly predicts obesity (Hoffman et al., 2000a).

In another set of experiments, free-living total energy expenditure (TEE) was measured over 7 days using the doubly labeled water method. It was found that stunted girls had significantly lower TEE than boys, which may help to explain the particularly high risk of obesity in stunted adolescent girls and women as described in previous studies (Hoffman et al., 2000b).

In a third set of experiments, the hypotheses that these nutritionally stunted children had impaired regulation of energy intake was tested. A 753 kJ yogurt supplement was administered at breakfast and its effect on daily energy intake assessed. There were no differences in energy intake between stunted and non-stunted children, even though the stunted children weighed 10% less. Energy intake per kg body weight was significantly higher in the stunted children, and the ratio energy intake/resting energy expenditure was also significantly higher. In addition, the absolute difference in energy intake between supplement and control days was higher in stunted children compared to non-stunted ones (Hoffman et al., 2000c). These findings suggest important metabolic changes present in previously undernourished children (with low height/age but normal weight/height).

Conclusion

Evidence of a higher susceptibility of low-income populations to obesity is unquestionable both in developed and developing countries. At the same time, an increasing amount of evidence for coexistence of obesity and undernutrition (and/or nutritional stunting) in developing countries has been published. Undernutrition in developing countries lasts throughout gestation, childhood, and from one generation to another, and the individuals who survive are very likely the ones who have both the physiological adaptation mechanisms and environmental conditions to minimize the effects of undernutrition. This review presented evidence of a series of physiological alterations in stunted individuals which are in line with basic research on growth velocity, fuel utilization, and energy balance. Considering the importance of the present issue for worldwide Public Health, the need is clear for longitudinal and intervention studies to better investigate the causal relationships between nutritional stunting and obesity.

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