

Obesity as the Sequel of Childhood Stunting: Ghrelin and GHSR Gene Polymorphism Explained

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ABSTRAK

Stunting pada anak merupakan masalah gizi yang cukup signifikan di negara-negara berkembang seperti Indonesia. Stunting dapat memengaruhi perkembangan otak dan fungsi kognitif. Beberapa studi menyebutkan bahwa stunting juga meningkatkan risiko kejadian obesitas saat dewasa dan hal ini berkaitan dengan pengaruhnya pada efisiensi metabolik. Anak-anak yang mengalami stunting memiliki resting energy expenditure yang lebih rendah dibandingkan dengan anak-anak yang tidak mengalami stunting. Anak dengan stunting juga memiliki respiratory quotient yang lebih tinggi dimana hal ini menandakan tingginya penggunaan karbohidrat sebagai sumber energi dibandingkan dengan penggunaan lemak. Mekanisme inilah yang diperkirakan memperantarai hubungan antara stunting dengan obesitas yaitu rendahnya oksidasi lemak serta kecenderungan yang lebih tinggi untuk menyimpan lemak.

Review ini membahas status penelitian terbaru di bidang nutrigenetik mengenai hubungan antara stunting pada anak dan kejadian obesitas di saat dewasa. Diperkirakan bahwa anak dengan stunting lebih mudah mengalami obesitas karena memiliki metabolic rate yang rendah. Beberapa gen telah diteliti dan gen yang berkaitan dengan mekanisme kerja ghrelin diketahui terlibat pada fenomena ini.

Kata kunci: stunting, obesitas, ghrelin, growth hormone secretagogue receptor (GHSR), gen polimorfisme.

ABSTRACT

Stunting or short stature in children is a significant nutritional problem in developing and underdeveloped countries. Stunting during childhood might affect brain development and impair development cognitive function. Additionally, this condition associated with the increased risk for obesity during adulthood. Several studies have shown that the increment risk of obesity and overweight in children with a short stature was due to their metabolic efficiency. Children with stunting have lower resting energy expenditure compared to non stunting children. Additionally, stunted children has higher respiratory quotient and carbohydrate oxidation but lower fat oxidation compared to non-stunting children. These results might explain why stunted children easily become obese, which is due to lower fat oxidation and leading to tendency to store fat.

This review discussed the current status on studies in the nutrigenetic aspects of the relationship between stunting in the childhood and obesity in adulthood. I hypothesized that stunted children are more likely to become obese in their later life because they have lower metabolic rate and higher tendency of fat storage. There are several candidate genes and pathway involved in obesity and I suspected that ghrelin and its receptor growth hormone secretagogue receptor (GHSR) were responsible.

Keywords: stunting, obesity, ghrelin, growth hormone secretagogue receptor (GHSR), gene polymorphism.

INTRODUCTION

Stunting or short stature is a significant nutritional problem especially in developing and underdeveloped countries. In 2010, the worldwide prevalence of stunting in under five years old children was 27%.¹ Although the global trend of stunting declined in the past two decades, several countries still have remaining high prevalence of stunting. It was reported that in India, the prevalence of stunting reached 48%² while in Indonesia the prevalence of stunting was 37.2%.³ It is important to discuss the impact of stunting as a risk factor for obesity because the world prevalence of obesity itself increases remarkably in the past few decades. The increasing rate of obesity is also seen in the developing countries such as Indonesia. The Ministry of Health reported that the prevalence of overweight and obesity in Indonesia is also increasing. In 2013, the prevalence of overweight and obesity in women were 32.9% while in men were 19.7%.³ It is also important to prevent the further increment of obesity because its disease manifestation such as diabetes mellitus and cardiovascular diseases⁴ as well as its significant economic burden.

There are several consequences on the effect of stunting during childhood. First, stunting might affect brain development and impair development of cognitive function.⁵ Second, stunting in childhood associated with the risk factor for obesity during adulthood. Although it is still a controversy, several investigations were leading to the hypothesis that childhood stunting associated with increased risk of obesity. It was before shown that there was an increment in the risk of obesity and overweight in stunted children and adolescents.⁶⁻¹⁰ Children (2-4 years old) with stunting had much higher body mass index (BMI), percent body fat and waist-to-hip ratio compared to the non-stunting children.¹¹ A study in Brazilian children and adolescents showed that there was a connection between malnutrition during childhood (weight and height for-age) and obesity in adolescence and adulthood.¹² The correlation between lower stature and higher incidence of obesity was also seen in a cross-sectional study in Germany.¹³

Several studies have reported that the

increment of risk of obesity and overweight in children with a short stature is associated with their metabolic properties. The possible mechanism has been reviewed before.¹⁴ It was shown that stunted school girls had higher susceptibility to gain weight from a high fat diet compared to non-stunted girls.¹⁵ Hoffman et al.¹⁶ investigated metabolic properties of pre-pubertal boys and girls with and without stunting and showed that children with stunting have lower resting energy expenditure compared to non stunting children. Stunted children has higher respiratory quotient and carbohydrate oxidation but lower fat oxidation compared to non-stunting children. These results might explain how stunted children tend to become obese. This is because they have lower fat oxidation during fasting which lead to tendency to store fat instead of using them to produce energy.

This review discusses current status of research on the nutrigenetic aspect of the relationship between stunting in the childhood and obesity in adulthood. In this paper we hypothesized that the connection between stunting and obesity was due to low metabolic rate and higher tendency of fat storage. There are several candidate genes and pathway that are involved in obesity and we suspected that ghrelin and its receptor namely growth hormone secretagogue receptor (GHSR) were responsible.

GHRELIN AND LIPID METABOLISM

Ghrelin is a stomach derived hormone composed with 28 amino acids. This peptide is not only has orexigenic effect but also involved in human lipid metabolism. Because ghrelin was associated with promotion of feeding and adiposity, several studies showed this protein level was associated with body weight.¹⁷⁻¹⁹ In human, ghrelin level reduced in obesity and raised in anorexia nervosa.^{20,21} In animal model, ghrelin or ghrelin receptor knockout mice model were protected from diet-induced obesity.^{22,23}

Ghrelin works through activation of growth hormone secretagogue receptor 1a (GHSR-1a). This receptor is highly expressed in hypothalamus region that regulate feeding and body weight homeostasis.^{24,25} It has been investigated that the effect of ghrelin was via the

orexigenic neuropeptide agouti related protein (AGRP) and neuropeptide (NPY) in the activity-regulated cytoskeleton associated protein (ARC). Additionally, ghrelin also affect body fat through regulation of two important lipid metabolism pathways: *de novo* lipogenesis and fatty acid oxidation.²⁵

The raised ghrelin level increased mRNA expression of enzyme involved in *de novo* lipogenesis such as lipoprotein lipase (LPL), fatty acid synthase (FAS) and stearoyl-CoA desaturase (SCD 1). Ghrelin also induced reduction in carnitine palmitoyltransferase 1 (CPT 1) expression, an important protein that involved in regulation of fatty acid oxidation. The end process of this reaction is that the body tend to store fat and not using it for energy usage²⁵ and because ghrelin level increased during fasting period, this metabolic process make sure that our metabolism is in higher energy efficiency. This is an human adaptation towards low food supply to decrease negative energy balance.²⁶

GHRELIN IN STUNTING AND OBESITY

The role of ghrelin on growth in childhood and development of stunting are still controversial. In the early investigation of the physiology of ghrelin in human, it was stated that ghrelin level is varied depend on stage of development of the children. Ghrelin level during pre-pubertal stage was higher than those in pubertal stage.²⁷ Interestingly, ghrelin level was negatively correlated with growth stimulating hormones such as insulin like growth factor-I (IGF-I) leading to an assumption that reduction ghrelin level during late puberty is responsible for acceleration of growth within the period. However, in the study they did not found the correlation between ghrelin level and height in healthy children and adolescents.²⁷

In order to further investigate the role of ghrelin on growth and stature, a study was done to compared ghrelin level in children with constitutional delay of growth (and puberty) (CDGP) (height standard deviation score/SDS < -2), familial short stature (FSS) (height SDS < -2) and normal height (height SDS > -2 and < 2)(28). In the study they showed that children

with CDGP and FSS had a much higher ghrelin compared to normal height children.²⁸ However, these findings were different with the finding from Sen et al.²⁹ In the study they showed that there were no significant differences in fasting ghrelin level or postprandial ghrelin level in children with CDGP compared to normal children, although there is a trend that children with CDGP had higher ghrelin level compared to normal children.

The association between ghrelin and obesity is controversial and to date there is no exact evidence on whether ghrelin induces obesity or the state obesity induces disturbance in ghrelin production/action. One of the earliest reports on ghrelin level in human obesity was done by Tschöp et al.²⁰ They compared the plasma ghrelin concentration of obese and normal weight individuals and found that ghrelin concentration in obese Caucasian was significantly lower compared to those in their normal weight counterpart. The result from this study was different with those found Cruz-Domínguez et al.³⁰ who showed that ghrelin concentration in obese individuals (with BMI >30 and <40) was significantly higher compared to their normal counterpart.

There were some explanations about the differences between studies. First, it seems that ethnicity has a role in the level of ghrelin since Tschöp et al.²⁰ suggested that Caucasians have a significantly higher ghrelin level compared to the Pima Indians. Second, the degree of insulin resistance or diabetes mellitus between obese individuals seems also have an influence on regulating ghrelin production. This was due to the fact that obese individuals with diabetes mellitus had a significantly lower ghrelin level compared to those without diabetes mellitus.³⁰

Additionally, it is very important to acknowledge that to work properly, ghrelin requires enzyme activation and sufficient receptor sensitivity. Ghrelin should undergo an O-n-octanoylation process before activating GHSR. This process is mediated by an enzyme called ghrelin O-acyl transferase (GOAT) with the acyl originated from medium-chain fatty acids.³¹⁻³³ In addition to GOAT, GHSR is also an important part that regulates the phenotypical

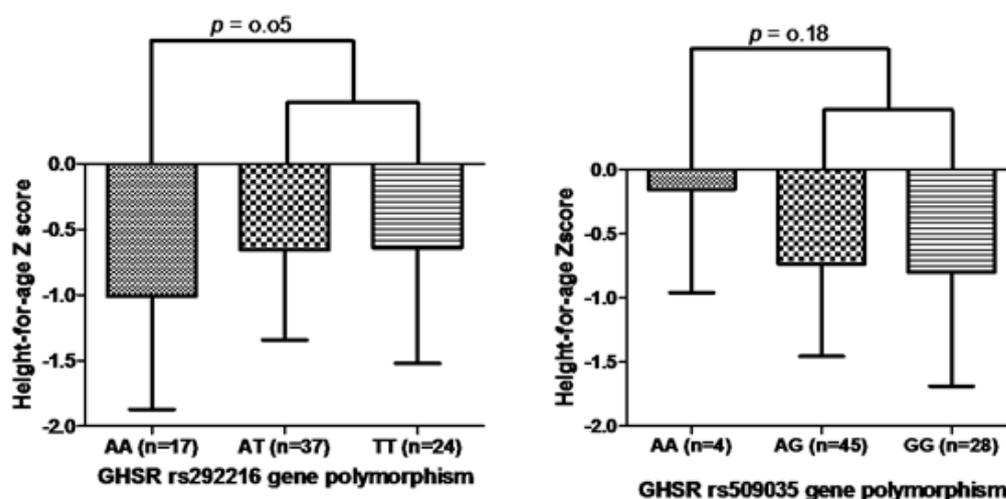
function of ghrelin. This is supported by the report showed that ghrelin antagonists and GHSR gene knockout model has ability to reduce ghrelin induced physiological function.^{23,33,34}

GHSR GENE POLYMORPHISM IN STUNTING AND OBESITY

The role of single nucleotide polymorphism (SNP) of GHSR on GHSR activity and obesity has been extensively studied in the past ten years. Inoue et al³⁵ screened for genetic mutations of GHSR gene in Japanese patients with familial short stature and growth hormone deficiency. In the study they discovered 4 mutation points that were connected with GHSR activity including Δ Q36 (106-108 del CAG), P108L (323C>T), C173R (517T>C), and D246A (737A>C). Most of the mutations have a significant impact on constitutive signaling activity of GHSR. This was done through various mechanism including intracellular retention; reduction in binding activity to ghrelin; and impaired agonist- and inverse agonist – stimulated receptor signal. Those data then supported by findings done by Pugliese-Pires et al³⁶ who showed that transfection with a plasmid encoding Ser84Ile mutation induce reduction of GHSR expression at the surface of HEK293 cells.

There were some reports on clinical phenotypes of GHSR gene polymorphism especially on individual's stature and obesity. The reports on genetic association between GHSR polymorphism, stature and obesity have been reviewed elsewhere.³⁷ A large cohort study conducted by Riedl et al(38) in Australia followed 1362 children from birth to 10 years old. In the study they showed that there were 2 important SNPs including SNPs in rs482204 and rs562416. TT genotype in rs482204 vs TC/CC was associated with greater stature across the entire observation period while TT genotype in rs562416 vs TG/GG was correlated positively with tall stature at 3, 8, and 10 years old. These associations were not seen in French population.³⁹ In our study, we showed that GHSR gene polymorphisms were slightly to be associated with stature in obese adolescent girls.⁴⁰ (Figure 1)

Despite the fact that only limited studies reporting the relationship between GHSR gene polymorphism and obesity, few of the results were tend to be controversial.³⁷ It was showed that GHSR gene knock out model had a different properties in energy intake and adiposity.²³ GHSR-null mice were failed to response to ghrelin signal thus eat less food and store less fat compared to the wild type mice. One of the



In this study we analyzed two SNPs in GHSR include rs292216 and rs509035. In our previous study we showed the trend that AA genotype in GHSR gene rs292216 were more likely to have lower Z score compared to those with AT and TT. Because all subjects were adolescents, height was analyzed using a height-to-age Z score. p-value was obtained from t-test by comparing mean height-for-age Z score between AA genotype and AT+TT genotype.

Figure 1. The association between height-for-age Z score and GHSR gene polymorphism in obese female adolescents.

earlier investigations on SNP in GHSR and obesity in human was done by Baessler et al.⁴¹ who showed that SNPs and haplotypes within GHSR gene region were associated with obesity. Interestingly, this result cannot be replicated by studies from European region.⁴¹ Gueorguiev et al.⁴² showed that GHSR gene polymorphism rs572169 was significantly associated with obesity but the significance the diminished after corrected for multiple comparisons.

In this review, author proposed an idea that ghrelin plays an important role in the connection between stunting in childhood and obesity in adulthood. This was based on trend that stunted children and obese adults possessed similar pattern on ghrelin concentration and GHSR sensitivity. Author also proposed that GHSR gene polymorphism was previously reported to induce lack of ghrelin sensitivity. Unfortunately, today there was no study that clearly demonstrated that GHSR gene polymorphism is induces stunting in children and obesity in adulthood by affecting individuals ghrelin concentration.

In the future, it will be interesting to clarify the role of GHSR gene polymorphism and ghrelin sensitivity on stunting children followed until adults. Since ghrelin appears to have role in development of short stature in children, developing a treatment targeting ghrelin and its receptor pathway could be potential to be done in the future. This is probably could be used as one of the treatment for stunted children to prevent future development of obesity.

CONCLUSION

In summary, author supported the idea that stunted children were at higher risk of obesity in their adult life. This was due to the shifting in their metabolic properties which are likely to store fat and not using fat for the source energy. Ghrelin was believed to have a role in this metabolic property because studies showed that there is disturbance in ghrelin concentration in stunted children. The disturbance of ghrelin sensitivity was associated with GHSR gene polymorphism and because GHSR gene polymorphism is associated ghrelin sensitivity, author suggested that this gene can explain the connection between stunting in childhood and obesity in adulthood.

CONFLICT OF INTEREST AND FUNDING DISCLOSURE

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