Review Article

J Mucopolysacch Rare Dis 2015;1(2):44-48
http://dx.doi.org/10.19125/jmrd.2015.1.2.44
pISSN 2465-8936 · eISSN 2465-9452

JMRD
Journal of Mucopolysaccharidosis and Rare Diseases

Obesity and Metabolic Syndrome in Adults with Prader-Willi Syndrome

Su Jin Kim

Department of Pediatrics, Myongji Hospital, Seonam University College of Medicine, Goyang, Korea

Body fat distribution in patients with Prader-Willi syndrome (PWS) is characterized by reduce lean body mass (LBM), increased total body fat mass (FM), and lower percentage of visceral adipose tissue (VAT). Individuals with PWS seem to have a lower risk for insulin resistance with high levels of adiponectin, an anti-atherogenic adipocytokine that is decreased in visceral fat hypertrophy subjects compared to simple obese subjects, both in children and in adults. The mechanism of the reduction in visceral adiposity in PWS is still unclear. It might be related to qualitative intrinsic characteristics of adipocyte or novel genetic influences on the control of fat distribution. However, obesity remains a critical problem, and obesity status plays a crucial role in individual metabolic risk clustering and development of metabolic syndrome (Mets) in PWS children and adults. Long-term growth hormone (GH) treatment after cessation of skeletal growth improved body composition, with an increase in lean body mass and a reduction in total body fat and subcutaneous and visceral fat in PWS adults. Thus, the role of GH is important after childhood because it might attenuate obesity and Mets in PWS adult by adipocyte modification.

Keywords: Prader-Willi syndrome, Obesity, Metabolic syndrome, Adipose tissue

Introduction

Prader-Willi syndrome (PWS) is a genetic disorder associated with chromosome 15 q11–13 deletion, uniparental disomy, or an imprinting abnormality; it is the most frequent cause of syndromic obesity and occurs in 1 in 25,000 live births[1,2]. PWS is characterized by short stature, muscular hypotonia, mild-to-moderate intellectual disability, risk of severe obesity from early childhood due to hyperphagia and endocrine disorders, such as hypogonadism and growth hormone (GH) deficiency[3]. PWS exhibits a unique pattern of body composition with increased body fat predominantly located subcutaneously, but decreased lean body mass[4,5]. The cause of the abnormal body composition is not completely known, but relatively reduced amount of visceral fat protects the patients with PWS from complications to the obesity[3-5]. However, obesity remains a critical problem in PWS teenagers and adults because it leads to severe complications, such as sleep disorder, cardiac or respiratory failure, and physical disability[6]. Obesity status also plays on a crucial role in development of metabolic syndrome (Mets) in PWS children and adults[7-10]. Several studies focused on the metabolic outcomes of PWS adults. PWS patients had a better metabolic profile, such as lower insulin resistance and healthier lipid profile compared with matched primary obese subjects[11]. However, Grugni et al.[8] reported that when matched for body mass index (BMI), PWS adults had the same prevalence of metabolic syndrome (41.4%) and insulin resistance index as obese controls. In this context, we review for the obesity and metabolic syndrome of PWS adults.

Adipose Tissue in Obesity

Adipose tissue (AT) metabolism is a critical regulator of adiposity and whole body energy expenditure. AT cells are surrounded by extracellular matrix proteins whose composition and remodeling is of crucial importance for cell function[12]. The AT expandability hypothesis states that a failure in the capacity for

Received November 12, 2015; **Revised** November 16, 2015; **Accepted** November 20, 2015
Correspondence to: Su Jin Kim
Department of Pediatrics, Myongji Hospital, Seonam University College of Medicine, 55 Hwasu-ro 14beon-gil, Deogyang-gu, Goyang 10475, Korea
Tel: +82-31-810-5421, Fax: +82-31-969-0500, E-mail: sjkim0128@mjh.or.kr

AT expansion, rather than obesity per se, is the key factor linking positive energy balance and type 2 diabetes. All individuals possess a maximum capacity for adipose expansion which is determined by both genetic and environmental factors. Once the AT expansion limit is reached, AT ceases to store energy efficiently and lipids begin to accumulate in other tissues. Ectopic lipid accumulation in non-adipocyte cells causes lipotoxic insults, including insulin resistance, apoptosis, and inflammation[13-16]. The expansion of AT in obesity is linked to an inappropriate supply of oxygen and hypoxia development. AT hypoxia initiates fibrosis, which is further aggravated by inflammation[17]. White AT (WAT) is a major source of energy storage. WAT cells contain few mitochondria and show relatively little metabolic activity. Brown AT (BAT), found mainly in infants and young children, is also present in many adults[18-21]. Subcutaneous ATs (scAT) have a comparatively benign, thermogenic effect, similar to brown fat, and might attenuate adiposity-associated vascular disease[18,22].

Adipose Tissue in Prader-Willi Syndrome

Body fat distribution in patients with PWS is characterized by reduce lean body mass (LBM), increased total body fat mass (FM), and lower percentage of visceral adipose tissue (VAT), with high levels of adiponectin, an anti-atherogenic adipocytokine that decreases with visceral fat hypertrophy[4,23,24]. The development of AT occurs early in PWS infants before the onset of weight gain[25], so PWS can be seen as an exceptional model of early and massive AT development, notably in subcutaneous depots[7].

The mechanisms of reduced LBM in PWS patients are not fully understood. GH deficiency is probably not the only cause, because GH treatment completely normalizes length but does not normalize body composition; muscle weakness and motors problems throughout life may also contribute to the reduced LBM[26]. Sode-Carlsen et al.[10] did not report significant differences between hypogonadal and eugonadal men regarding their body composition measurements, nor differences between men with or without testosterone treatment except for a tendency toward a higher thigh muscle/fat ratio in those receiving testosterone. Furthermore, the mechanism of the reduction in visceral adiposity in PWS is still unclear. It could be related to childhood-onset GH deficiency, defects in hypothalamo-pituitary-adrenal axis activity, or novel hypothalamic or genetic influences on the control of body fat distribution[27]. Lacroix et al.[7] suggested that sc adipocytes in PWS could have a higher capacity to increase in size, without the adverse consequences on the metabolic and inflammatory signals found in primary obesity. They also reported that series of the AT gene, which encodes proteins that are related to insulin resistance (i.e., *SERPINF1*, *CHI3L1*, and *FIBULIN 1*) or low-grade inflammation (i.e., *CD68*, *CD3*, and *IL1β*) were under-expressed in the AT of PWS patients. In addition, they also observed down-regulation of genes involved in extracellular matrix (ECM) remodeling or the promotion of fibrosis such as *LOX*, *LPAR1*, *COL4α1*, and *COL6α1*.

Metabolic Syndrome in Prader-Willi Syndrome

Metabolic syndrome is believed to represent a strong risk factor for the subsequent development of atherosclerotic CVD and type 2 diabetes mellitus (DM)[28]. Insulin resistance is thought to be the cardinal mechanism underlying Mets[29]. However, individuals with PWS seem to have a lower risk for insulin resistance than simple obese subjects, both in children and in adults[5,30]. In this light, the question arises as to whether there is the same pathogenetic relationship between CVD and the development of Mets in PWS as in non-syndromic obesity. Brambilla et al.[31] reported that none of the non-obese PWS children show Mets and obese children with PWS have a similar prevalence of Mets to obese controls; it is thus conceivable that Mets may be involved in the pathogenesis of morbidity and early mortality in PWS. They suggested that the key point seems to be the definition used for Mets estimation, especially for central obesity marker (BMI or waist circumference). It has to be discussed whether BMI or waist circumference really represents abdominal adiposity in subjects with unusual body proportions like those of PWS[32]. However, when the presence of obesity was excluded from the analysis and the frequency of ≥2 altered parameters was considered, a significantly lower frequency in the clustering of metabolic risk factors was still present in the non-obese PWS group as compared to both obese groups, thus confirming the main role played by obesity status in this field. Grugni et al.[8] reported Mets frequency evaluated in a large cohort of PWS adults (87 obese PWS and 85 matched obese control and 21 non-obese PWS). Mets was found in 1/21 (4.8%) non-obese PWS, 36/87 (41.4%) obese PWS, and 39/85 (45.9%) obese controls. Non-obese PWS showed lower frequency for each Mets component as compared with obese PWS and obese controls. Overall, obesity status plays a crucial role in individual metabolic risk clustering in the PWS population.

Role of Growth Hormone

It is well known that long-term treatment with GH in children

and adolescents with PWS improves not only growth velocity, height standard deviation score, and final height, but also the degree of visceral obesity and increased LBM[9,33-35]. However, GH treatment is a relatively new concept in adults with PWS, and knowledge of its long-term effects is limited. In adult GH deficiency, continued GH treatment has already been reported to maintain body composition, improve lipid abnormalities, and reduce the risk of CVD[36]. Considering PWS, Tanaka et al.[37] reported that during GH treatment, although scAT increased, VAT remained low. However, after indications for GH in PWS were no longer met and GH treatment had been discontinued, the degree of obesity was similar to that of the group never treated with GH. Therefore, they surmised that after GH is discontinued, patients experience a marked increase in AT, particularly VAT. In addition, Oto et al. observed that cessation of GH therapy in young PWS patients worsened BMI after 6 months[34]. In 2011, a meta-analysis of eight studies, comprising a total of 134 adults with PWS on GH treatment, was published[38]. All the studies, which ranged from 12 to 72 months, showed that GH treatment improved body composition, with an increase in lean body mass and a reduction in total body fat and subcutaneous and visceral fat[38]. In 2015, Hoybye et al.[33] reported positive effects that GH treatment had on the body composition of men with PWS were also maintained during very long-term treatment (more than 15 years). All things taken together, the concept of continuous GH treatment after cessation of skeletal growth is desirable to maintain good body composition and prevent complication of obesity.

Conclusion

PWS has unique adipocyte distribution, characterized by increased body fat predominantly located subcutaneously. However, the mechanism of the reduction in visceral adiposity in PWS is still unclear. It might be related to qualitative intrinsic characteristics of adipocyte or novel genetic influences on the control of fat distribution. Nevertheless, obesity and Mets in PWS adults are crucial problems that lead to higher mortality. The role of GH is important after childhood because it might attenuate obesity and Mets in PWS adults by adipocyte modification.

References

1. Butler MG. Prader-Willi Syndrome: Obesity due to Genomic Imprinting. Curr Genomics 2011;12:204-15.
2. Whittington JE, Holland AJ, Webb T, Butler J, Clarke D, Boer H. Population prevalence and estimated birth incidence and mortality rate for people with Prader-Willi syndrome in one UK Health Region. J Med Genet 2001;38:792-8.
3. Burman P, Ritzen EM, Lindgren AC. Endocrine dysfunction in Prader-Willi syndrome: a review with special reference to GH. Endocr Rev 2001;22:787-99.
4. Goldstone AP, Thomas EL, Brynes AE, Bell JD, Frost G, Saeed N, et al. Visceral adipose tissue and metabolic complications of obesity are reduced in Prader-Willi syndrome female adults: evidence for novel influences on body fat distribution. J Clin Endocrinol Metab 2001;86:4330-8.
5. Hoybye C, Hilding A, Jacobsson H, Thoren M. Metabolic profile and body composition in adults with Prader-Willi syndrome and severe obesity. J Clin Endocrinol Metab 2002;87:3590-7.
6. Goldstone AP, Holland AJ, Hauffa BP, Hokken-Koelega AC, Tauber M, speakers contributors at the Second Expert Meeting of the Comprehensive Care of Patients with PWS. Recommendations for the diagnosis and management of Prader-Willi syndrome. J Clin Endocrinol Metab 2008;93:4183-97.
7. Lacroix D, Moutel S, Coupaye M, Huvenne H, Faucher P, Pelloux V, et al. Metabolic and adipose tissue signatures in adults with Prader-Willi syndrome: a model of extreme adiposity. J Clin Endocrinol Metab 2015;100:850-9.
8. Grugni G, Crino A, Bedogni G, Cappa M, Sartorio A, Corrias A, et al. Metabolic syndrome in adult patients with Prader-Willi syndrome. Nutr Metab Cardiovasc Dis 2013;23:1134-40.
9. Coupaye M, Lorenzini F, Lloret-Linares C, Molinas C, Pinto G, Diene G, et al. Growth hormone therapy for children and adolescents with Prader-Willi syndrome is associated with improved body composition and metabolic status in adulthood. J Clin Endocrinol Metab 2013;98:E328-35.
10. Sode-Carlsen R, Farholt S, Rabben KF, Bollerslev J, Schreiner T, Jurik AG, et al. Body composition, endocrine and metabolic profiles in adults with Prader-Willi syndrome. Growth Horm IGF Res 2010;20:179-84.
11. Talebizadeh Z, Butler MG. Insulin resistance and obesity-related factors in Prader-Willi syndrome: comparison with obese subjects. Clin Genet 2005;67:230-9.
12. Lagathu C, Christodoulides C, Tan CY, Virtue S, Laudes M, Campbell M, et al. Secreted frizzled-related protein 1 regulates adipose tissue expansion and is dysregulated in severe obesity. Int J Obes (Lond) 2010;34:1695-705.
13. Virtue S, Vidal-Puig A. Adipose tissue expandability, lipo-

toxicity and the Metabolic Syndrome--an allostatic perspective. Biochim Biophys Acta 2010;1801:338-49.
14. Vidal-Puig A. Adipose tissue expandability, lipotoxicity and the metabolic syndrome. Endocrinol Nutr 2013;60 Suppl 1:39-43.
15. Moreno-Navarrete JM, Escote X, Ortega F, Serino M, Campbell M, Michalski MC, et al. A role for adipocyte-derived lipopolysaccharide-binding protein in inflammation- and obesity-associated adipose tissue dysfunction. Diabetologia 2013;56:2524-37.
16. Alligier M, Gabert L, Meugnier E, Lambert-Porcheron S, Chanseaume E, Pilleul F, et al. Visceral fat accumulation during lipid overfeeding is related to subcutaneous adipose tissue characteristics in healthy men. J Clin Endocrinol Metab 2013;98:802-10.
17. Buechler C, Krautbauer S, Eisinger K. Adipose tissue fibrosis. World J Diabetes 2015;6:548-53.
18. Cypess AM, Lehman S, Williams G, Tal I, Rodman D, Goldfine AB, et al. Identification and importance of brown adipose tissue in adult humans. N Engl J Med 2009;360:1509-17.
19. Virtue S, Vidal-Puig A. Assessment of brown adipose tissue function. Front Physiol 2013;4:128.
20. Peirce V, Vidal-Puig A. Regulation of glucose homoeostasis by brown adipose tissue. Lancet Diabetes Endocrinol 2013;1:353-60.
21. Carobbio S, Rosen B, Vidal-Puig A. Adipogenesis: new insights into brown adipose tissue differentiation. J Mol Endocrinol 2013;51:T75-85.
22. Gaggini M, Saponaro C, Gastaldelli A. Not all fats are created equal: adipose vs. ectopic fat, implication in cardiometabolic diseases. Horm Mol Biol Clin Investig 2015;22:7-18.
23. Haqq AM, Muehlbauer MJ, Newgard CB, Grambow S, Freemark M. The metabolic phenotype of Prader-Willi syndrome (PWS) in childhood: heightened insulin sensitivity relative to body mass index. J Clin Endocrinol Metab 2011;96:E225-32.
24. Hoybye C. Endocrine and metabolic aspects of adult Prader-Willi syndrome with special emphasis on the effect of growth hormone treatment. Growth Horm IGF Res 2004;14:1-15.
25. Eiholzer U, Blum WF, Molinari L. Body fat determined by skinfold measurements is elevated despite underweight in infants with Prader-Labhart-Willi syndrome. J Pediatr 1999;134:222-5.
26. Reus L, Zwarts M, van Vlimmeren LA, Willemsen MA, Otten BJ, Nijhuis-van der Sanden MW. Motor problems in Prader-Willi syndrome: a systematic review on body composition and neuromuscular functioning. Neurosci Biobehav Rev 2011;35:956-69.
27. Lloret-Linares C, Faucher P, Coupaye M, Alili R, Green A, Basdevant A, et al. Comparison of body composition, basal metabolic rate and metabolic outcomes of adults with Prader Willi syndrome or lesional hypothalamic disease, with primary obesity. Int J Obes (Lond) 2013;37:1198-203.
28. Bruce KD, Hanson MA. The developmental origins, mechanisms, and implications of metabolic syndrome. J Nutr 2010;140:648-52.
29. DeFronzo RA, Ferrannini E. Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. Diabetes Care 1991;14:173-94.
30. Krochik AG, Ozuna B, Torrado M, Chertkoff L, Mazza C. Characterization of alterations in carbohydrate metabolism in children with Prader-Willi syndrome. J Pediatr Endocrinol Metab 2006;19:911-8.
31. Brambilla P, Crino A, Bedogni G, Bosio L, Cappa M, Corrias A, et al. Metabolic syndrome in children with Prader-Willi syndrome: the effect of obesity. Nutr Metab Cardiovasc Dis 2011;21:269-76.
32. Brambilla P, Bosio L, Manzoni P, Pietrobelli A, Beccaria L, Chiumello G. Peculiar body composition in patients with Prader-Labhart-Willi syndrome. Am J Clin Nutr 1997;65:1369-74.
33. Hoybye C. Growth hormone treatment of Prader-Willi syndrome has long-term, positive effects on body composition. Acta Paediatr 2015;104:422-7.
34. Oto Y, Tanaka Y, Abe Y, Obata K, Tsuchiya T, Yoshino A, et al. Exacerbation of BMI after cessation of growth hormone therapy in patients with Prader-Willi syndrome. Am J Med Genet A 2014;164A:671-5.
35. Kuo JY, Ditchekenian V, Manna TD, Kuperman H, Damiani D, Setian N. [Prader-Willi syndrome: metabolic aspects related to growth hormone treatment]. Arq Bras Endocrinol Metabol 2007;51:92-8.
36. Hoffman AR, Kuntze JE, Baptista J, Baum HB, Baumann GP, Biller BM, et al. Growth hormone (GH) replacement therapy in adult-onset gh deficiency: effects on body composition in men and women in a double-blind, randomized, placebo-controlled trial. J Clin Endocrinol Metab 2004;89:2048-56.
37. Tanaka Y, Abe Y, Oto Y, Itabashi H, Shiraishi M, Yoshino A, et al. Characterization of fat distribution in Prader-Willi

syndrome: relationships with adipocytokines and influence of growth hormone treatment. Am J Med Genet A 2013;161A:27-33.
38. Sanchez-Ortiga R KA, Tritos NA. Effects of recombinant human growth hormone therapy in adults with Prader-Willi syndrome: a meta-analysis. Clin Endocrinol (Oxf) 2011;77:86-93.