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An Update on Prader-Willi Syndrome with Diabetes Mellitus

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Prader-Willi syndrome (PWS) often develops type 2 diabetes mellitus (T2DM) related to severe obesity. The prevalence of T2DM in adults with PWS (7–20%) exceeds greatly the prevalence in the general population (5–7%). It is uncommon for pre-pubertal children with PWS to develop overt diabetes or glucose intolerance. GH therapy and genotype did not influence the development of altered glucose metabolism. It has been assumed that T2DM in PWS develops as a consequence of morbid obesity and concomitant insulin resistance. However recent studies suggest the relationship between morbid obesity and T2DM development is more complex and appears to differ in PWS subjects compared to non-PWS subjects. PWS patients had relatively lower fasting insulin levels and increased adiponectin levels compared with BMI-matched obese control despite of similar levels of leptin. So PWS children may be protected to some extent form of obesity-associated insulin resistance. Although there's no data, it seems logical to approach diabetes management including weight loss and increased exercise, using similar pharmacological agents as with non-PWS obesity-related diabetes such as metformin or thiazolidinedione, with the introduction of insulin as required. On the other hand, several recent T2DM in PWS case reports suggest favorable outcomes using Glucagon-like peptide 1 (GLP-1) analog with regard to ghrelin reduction, control of glucose and appetite, weight loss and pre-prandial insulin secretion. The role of GLP-1 agonist therapy is promising, but has not yet been fully elucidated.

Keywords: Prader-Willi syndrome, Diabetes mellitus, Obesity

Introduction

Prader-Willi syndrome (PWS) is a complex multisystem genetic disorder that arises from lack of expression of paternally inherited imprinted genes on chromosome 15q11-q13[1]. PWS is characterized by infantile hypotonia, followed by progressive obesity and hyperphagia in childhood. They often develop type 2 diabetes mellitus (T2DM) related to severe morbid obesity. Obesity is a critical problem in PWS and the yearly mortality rate for obesity induced complication is about 7%[1]. In this mini review, we discuss an update on PWS with disorder of glucose metabolism, including epidemiology and management of PWS patients with T2DM.

1. Altered glucose metabolism in PWS

While PWS individuals show high plasma ghrelin levels related to uncontrolled appetite, they display low visceral adiposity and relative hypoinsulinemia[2]. The inappropriate suppression of insulin secretion and hyperphagia lead to hyperghrelinemia might bring on hyperglycemia[3]. Meanwhile the finding of a selective reduction of visceral fat in adult PWS has been supported to explain a lower insulin resistance, in comparison to matched obese population[4]. PWS individuals may be less likely to develop T2DM than non-syndromic subjects with comparable obesity. In fact, the lower fasting insulin and HOMA-IR were shown in not only PWS children but also PWS adults[5,6]. However, recent study suggested further investigation with hyperinsulinemic- euglycemic clamp due to failure to reprove this identification[7].

It has been assumed that T2DM in PWS develops as a result of

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morbid obesity and concomitant insulin resistance, especially in PWS adults. Additionally, there's age factor and unique beta-cell dysfunction among tentative associated risk factors with T2DM in PWS. GH therapy and genotype did not influence the development of altered glucose metabolism. In PWS children, obesity-associated insulin resistance might be protected to some extent because of relative lower fasting insulin levels, increased adiponectin levels and increased insulin sensitivity.

Consequently, the mechanism of the beta-cell dysfunction in PWS remains elusive. One hypothesis is that decreased GH secretion in PWS reduces beta cell growth and response of insulin secretion. The other explanation proposes that reduced vagal parasympathetic tone to the pancreas in PWS individual decreases insulin secretion[8]. Another theory suggests that relative hyperadiponectinemia may promote fatty acid oxidation and elevated inulin sensitivity[9].

2. Epidemiology of diabetes in PWS

The prevalence of T2DM in PWS adults, about 20% exceeds greatly the prevalence in the general population (5–7%)[10]. In one cohort data in UK, the mean age of onset was 20 years and the prevalence was around 25% (16/66)[10]. A large population-based adult cohort study in France has shown similar results such as 25% of T2DM prevalence and mean onset of age of 24 years[11]. Otherwise, in one cohort of 83 PWS patient in South Korea (Samsung Medical center) , the prevalence of PWS with T2DM was reported as 32.5%, which was higher than in other European countries, while the mean onset of age, 21.4 years-old, was shown similar finding with others country (unpublished data, 2015 year).

It is uncommon for pre-pubertal children with PWS to develop diabetes or impaired glucose tolerance[12].

3. Management of diabetes in PWS

Although there's no data, it seems logical to approach diabetes management including weight loss and increased exercise, using similar pharmacological agents as with non-PWS obesity-related diabetes such as metformin or thiazolidinedione, with the introduction of insulin as required. However, even though weight reduction is a critical part of T2DM patients' management, many antidiabetic agents including insulin, sulfonylureas, and thiazolidinedione cause weight gain during the management. Therefore, a long acting glucagon-like peptide 1 receptor analog (GLP-1 RA) has been expected in the reduction of weight in obese T2DM.

GLP-1 RA plays many roles in reducing appetite and body weight, slowing gastric emptying, simulating insulin secretion, and suppressing glucagon secretion[13]. In T2DM patient with PWS, GLP-1 RA therapy could bring the favorable outcomes such as; weight control, glycemic control, reduced plasma ghrelin level, increased pre-prandial insulin secretion. Also, PWS diabetic patients showed the difference that it has no gastrointestinal side effects compared with non-PWS T2DM patients. It may suggest that there is not only high tolerance of nausea, pain, but also altered GLP-1 signaling in brain[14]. Several recent PWS case reports suggest that the effect of GLP-1 RA on weight loss may be related to reduction of ghrelin, leading to an improvement of hyperphagia, body mass index, and visceral fat[15]. However the role of GLP-1 RA therapy has not yet been fully elucidated.

Conclusion

T2DM in PWS develops as a consequence of morbid obesity, insulin resistance, and unique beta-cell dysfunction. PWS patients had relatively lower fasting insulin levels and increased adiponectin levels compared with BMI-matched obese control despite of similar levels of leptin. PWS children may be protected to some extent form obesity-associated insulin resistance. The prevalence of T2DM in PWS adults, about 20% exceeds greatly the prevalence in the general population. Approach to management of T2DM in PWS is similar to the non-PWS obesity-related diabetes, including weight loss, increased exercise, and pharmacological agents. Recently, several T2DM in PWS case report suggest favorable outcome using GLP-1 RA with regard to ghrelin reduction, control of glucose and appetite, weight loss and pre-prandial insulin secretion. The role of GLP-1 RA therapy is promising, but is fully needed to establish in a larger number of patients during long-term therapy of GLP-1 RA.

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