Is poor metabolic control inevitable in adolescents with type 1 diabetes?

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INTRODUCTION

Numerous studies provide evidence that metabolic control deteriorates during adolescence in those with type 1 diabetes compared to younger children and adults[1-4]. Recently, in an evaluation of 2873 children and teens with type 1 diabetes from 17 countries, adolescents were found to have higher HbA1c levels than younger children, and fewer (29 versus 41%) could be considered in "good" metabolic control defined by HbA1c levels <8%[3]. Furthermore, in the Diabetes Control and Complications Trial (DCCT), the adolescents achieved HbA1c levels that were, on average, 1% higher than those in the adults in both the conventional and intensive treatment cohorts[1]. Of note, in all of these studies, higher HbA1c levels were reported even though the teens were receiving a higher insulin dosage (in units/kg) than prepubertal or adult subjects[1,3].

This article explores the biologic/physiologic and psychologic/psychosocial factors that may account for rising HbA1c levels during adolescence. We conclude that insulin resistance of puberty is an important factor which contributes to, and is a consequence of, poor metabolic control.

NORMAL ADOLESCENCE

During adolescence there is rapid physical, emotional and psychological growth. Teens move from complete dependence on parents to a more independent lifestyle. This occurs on the background of major changes in the hormonal mediators of puberty, i.e. activation of the hypothalamic-pituitary-gonadal axis, and amplification of the GH-IGF-I axis.

Teens with type 1 diabetes face additional challenges: they must acquire the knowledge and skills to take over their own diabetes care, specifically administration of insulin injections, monitoring of blood glucose levels, insulin dose adjustment, avoidance or treatment of hypoglycemic episodes and meal planning. Adolescence is the time when specific psychologic stresses emerge, such as weight and shape concerns that may, in teenage girls, develop into full-blown eating disorders. It is also the time of emergence of risk-taking behaviours such as experimentation with tobacco, alcohol and drugs.

The hormonal changes of puberty may impact negatively on diabetes control. Historically, diabetes health care professionals have presumed that the deteriorating metabolic control during puberty is largely the result of the psychosocial upheaval and noncompliance with self-care routines that accompanies adolescence. However, there is good evidence that the insulin resistance of puberty contributes significantly to this metabolic deterioration. We believe that there is a complex interplay between physiologic and psychosocial factors that make excellent glycemic control difficult, but not impossible, for adolescents with type 1 diabetes.

"Biologic" factor: Insulin resistance of puberty

Type 1 diabetes in adolescents is often characterized by higher HbA1c levels, higher insulin dose requirements and the potential for excessive weight gain (perhaps more so in the girls than boys)[1-5]. This triad of findings suggests that the administered insulin is less effective in maintaining glycemic control (i.e. insulin resistance), but does allow normal growth and sometimes excessive weight gain (i.e. normal anabolic effect of insulin during puberty). This results from dysfunction of a usually adaptive process (i.e. the normal insulin resistance of puberty) due to the presence of diabetes.

Insulin resistance is a component of normal puberty. Moran and colleagues performed euglycemic- hyperinsulinemic clamp studies on 357 nondiabetic children at various stages of puberty and found that insulin sensitivity decreased significantly in early to mid-puberty, improving again with the completion of sexual maturation[6]. The maximal decrease in insulin sensitivity was about 20% in mid-puberty and at all stages of puberty, girls were more insulin resistant than boys[6].

Amiel and Bloch and their colleagues studied prepubertal, pubertal children and adults with and without type 1 diabetes using the euglycemic-hyperinsulinemic clamp[7,8]. In both studies, puberty was associated with decreased insulin sensitivity compared to both the prepubertal and adult subjects. Of note, the subjects with diabetes showed a 33-42% lower insulin sensitivity at all ages compared to their non-diabetic peers[7]. In another, slightly larger study matching for BMI, pubertal stage and glycemic control, Arslanian et al found a 43% decrease in the insulin-mediated glucose utilization rate in 15 female adolescents with type

1 diabetes compared to 12 male counterparts[9]. Thus, the normal insulin resistance of puberty appears to be exaggerated to a greater degree in the teen with type 1 diabetes and perhaps more so, in females.

The insulin resistance of puberty in nondiabetic children is a normal physiologic regulator of the pubertal growth spurt and is likely an evolutionary adaptive response. Increased activity of the GH-IGF-1 axis and possibly, increased secretion of sex steroids, during puberty may account for decreased insulin-mediated glucose uptake[8,10-12]. Nondiabetic teens do not develop hyperglycemia as they are able to increase insulin secretion sufficiently to overcome the resistance[13]. Caprio and colleagues demonstrated that the insulin resistance of puberty relates only to the effects of insulin on glucose regulation and not to its effects on protein synthesis and lipogenesis[14]. The specificity of the effects of insulin resistance on glycemia and the resulting relative hyperinsulinemia provide an adaptive, growth promoting, anabolic effect during puberty.

In type 1 diabetes, the insulin resistance of puberty increases insulin requirements, more so in girls than in boys[3]. The result of this is greater peripheral hyperinsulinemia and more protein and lipid deposition. This accounts for the more rapid weight gain and higher body mass index in teens with type 1 diabetes compared to their peers.

Chronic hyperglycemia also decreases insulin dependent glucose uptake in peripheral tissues and may be a consequence of noncompliance with one or more of the important aspects of the diabetes treatment regimen[15]. Thus, the interplay of psychosocial disturbance and physiologic events will lead to hyperglycemia, exaggerated insulin resistance and deterioration in metabolic control.

Psychosocial factors

Many studies have examined family functioning, coping abilities and levels of anxiety and depression in teens with diabetes. In addition, the frequency and severity of disordered eating patterns and substance abuse in this population has led to recognition of how these behaviours might impact on metabolic control.

Impact of chronic disease

Kovacs and her colleagues, followed a cohort of children from the onset of their diabetes[16]. They reported that 45% of the group had a period of "pervasive noncompliance" during adolescence. This was defined as noncompliance with at least two of the three cornerstones of diabetes management, namely insulin injections, self-monitoring routines and meal planning. Furthermore, noncompliance during adolescence was highly predictive of major psychiatric disorder (affective disorder, conduct/substance abuse disorder or anxiety disorder) during early adulthood[16].

Jacobson et al also studied psychological adjustment to diabetes. At 10 year follow-up, diabetic subjects reported lower perceived competence and self-esteem which may predispose them to risk for future depression or adaptation difficulties[17]. A prospective 2-year study of newly diagnosed children and adolescents with diabetes showed an increased risk of depression at study end, as compared to a nondiabetic, age-matched, healthy control group[18].

Family functioning and autonomy issues

A review of more than 30 studies on social support and health outcomes of adolescents with type 1 diabetes found that supportive, cohesive families with low levels of conflict were more likely to have adolescents with strong adherence and good metabolic control than families without such cohesion[19]. A four year longitudinal study examined family milieu and diabetes control at various time points also confirmed that strong family cohesion can help protect the young adolescent from poor glycemic control[20]. At 10 year follow up, these same authors found that patients with irregular clinic follow up in the first few years after diagnosis were most likely to experience poor metabolic control, episodes of ketoacidosis and retinopathy[21]. In addition, families with irregular follow up were more disadvantaged in terms of social or demographic markers and had increased parental separation/divorce.

Eating disorders in adolescent females with type 1 diabetes

We believe that there is evidence to support the notion that specific features of diabetes and/or its management may lower the threshold for expression of eating disturbances in teenage girls:

1) There is often rapid weight gain following the initiation of insulin treatment and increased weight as a consequence of improved metabolic control[1]; 2) Dietary restraint is an integral part of diabetes management; and 3) Insulin omission or dose manipulation is a unique method of weight control through induced glycosuria[22].

Although results from smaller studies are inconclusive, a recent large three-site study showed definitively that girls with diabetes have a two-fold greater risk of developing eating disorders than their non-diabetic peers[23]. Clinical diagnosis of eating disorders could be made in up to 10% of the teenage girls with diabetes compared to only 4% of their nondiabetic peers and an additional 7-15% of diabetic girls meet criteria for subclinical eating disorders[23-27]. Both overt and subclinical eating disordered behaviour may have a significant impact on metabolic control and diabetes-related complications.

The most common weight control behaviours in these girls include binge-eating (60-80% of adolescent females admit to binge eating) and intentional underdosing insulin in 12-40%[28-31].

There are important implications of these behaviours. HbA1c levels in diabetic girls with clinical and subclinical eating disorders have been shown to be consistently hig-

her than in those with normal eating behaviours[24,25,31,32]. Furthermore, 4 year longitudinal study from our centre documented that girls with persistent eating disorders maintained higher HbA1c levels compared to those without disordered eating behaviours (9.9% vs. 8.3%)[33]. In addition, those with eating disorders had a higher prevalence of retinopathy[33]. The association of eating disordered diabetics and microvascular complications has been confirmed by others[34,35].

Diabetes management

Other potential causes of poor metabolic control during adolescence relate to the technical aspects of insulin delivery. Inaccurate insulin measurement and insufficient mixing of NPH insulin occurs commonly[36,37]. As teens assume more responsibility for their own care, there is generally less supervision by parents and the possibility of dosing errors and using good injection technique may increase.

TREATMENT STRATEGIES

Psychosocial

Psychosocial interventions in teens with type 1 diabetes have been reported infrequently, and tend to look at short-term outcomes[38-40]. All have been group interventions based on frequent meetings over a period of a few months to discuss diabetes management, trouble-shoot common problems and provide a forum for support and guidance. A recent review of these interventions indicates that these studies have a small to medium sized beneficial effect on diabetes management[41]. The most effective interventions appear to be guided by theoretical principles that provide a rationale for the content of the intervention, along with outcome assessments[41].

A randomized, controlled study examined the effect of coping skills training (CST) in a group of adolescents embarking on intensive diabetes management (IDM)[42]. After 12 months, both control and CST groups had improved metabolic control, however, the group who received CST had an addition 1% decrease in HbA1c compared to the control IDM group with no increase in hypoglycemic episodes. In addition, the CST group scored significantly better on diabetes self-efficacy and quality of life scores.

There is very little information on effective treatment or prevention of eating disorders among young diabetic females. We compared a six-session group psychoeducational therapy to standard diabetes treatment and showed a significant improvement in eating attitudes and less dieting and binge eating episodes at the end of treatment[43]. These improvements were maintained at 6 and 12-month follow-up, however, there was no decrease in frequency of insulin omission for weight control or HbA1c. A case series reported 6 subjects who received cognitive behavioural treatment for bulimia nervosa, with minor modifications made for diabetes[26]. This series showed improvements in the eating habits and glycemic control in these patients.

Pharmacologic

Intensified diabetes management with multiple daily injections of insulin or use of insulin pumps, frequent blood glucose monitoring and careful nutritional planning has been shown to improve metabolic control and decrease the microvascular complications of diabetes in both adults and adolescents[44]. The Diabetes Control and Complications Trial enrolled 195 adolescents between the ages of 13 and 17 years[1]. Teens randomized to intensive therapy had significantly lower mean HbA1c levels than their conventionally treated counterparts (8.2 versus 9.8% respectively). However, HbA_{1c} in the adolescents were about 1% higher in both the conventional and intensive therapy groups compared to the adult subjects participating in the study[1].

Other pharmacologic strategies such as the use of IGF-1 or insulin sensitizing agents, such as metformin or thiazolidinediones, remain experimental, but warrant extensive analysis for both safety and efficacy in this group.

SUMMARY

Both psychosocial and physiologic factors contribute to the deterioration in metabolic control in the adolescent with diabetes. With the assumption of greater independence by these teens, there is more opportunity for decreased compliance with diabetes management. Family functioning also has a significant impact: those from families with high conflict level, weak cohesion, inadequate family structure and impaired communication are at greater risk for poor metabolic control. It is not clear if diabetic adolescents experience an increased frequency of depressive and anxiety disorders compared to their nondiabetic peers, however, there is good evidence that when a psychological disturbance is present, there is coexisting poor metabolic control.

There is a higher prevalence of clinical eating disorders in teenage girls with diabetes than in the general population. Insulin omission is a unique method of weight control.

A number of intervention strategies such as behavioural therapy using coping skills training, have been successful in the short term. Long term outcome studies are required to determine if these benefits are maintained. In young female diabetics with eating disorders, research strategies such as cognitive behaviour therapy are needed to determine if improvement in metabolic control can be achieved and maintained. Finally, newer treatment strategies, such as the use of metformin, and possibly other insulin sensitizing agents, such as the thiazoladinediones, may improve the insulin resistance of puberty. Improving insulin sensitivity may have beneficial effects on glycemic excursions, making it easier to adjust insulin, lower insulin doses, re-

duce the risk of unwanted weight gain, and improve metabolic control.

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