Chapter 6

Double Diabetes: The Search for a Treatment Paradigm in Children and Adolescents

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Additional information is available at the end of the chapter

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1. Introduction

Diabetes mellitus is one of the most prevalent chronic diseases in children. Diabetes mellitus is classified into four major types. Type 1, type 2, gestational, and other specific types. Type 1 diabetes (T1D) is caused by autoimmune destruction of the insulin-producing beta cells of the pancreas. Type 2 diabetes (T2D) results from a combination of insulin resistance and beta cell insulin secretory defect. The rising prevalence of childhood obesity has made it more difficult to differentiate between these types of diabetes in children. There is a new expression of diabetes in children known as double diabetes, or hybrid diabetes. This is a clinical state where both T1D and T2D co-exist in the same individual as shown in Figure 1 below.

Childhood obesity is one of the most serious public health challenges of the 21st century [1]. According to the National Health and Nutrition Examination Survey data, about 16% of children and adolescents in the United States have a body mass index (BMI) (kg/m^2) ≥95th percentile for age and gender [2]. Body mass index of >95th percentile is classified as overweight by the Center for Disease Control and Prevention [3,4], and as obesity by European criteria [5].

The prevalence of obesity has tripled in the past three decades [6] among male and female adolescents, and across different racial and ethnic groups [6-8]. There has also been a parallel increase in the prevalence of many obesity-related co-morbid conditions [9] such as T2D, dyslipidemia, hypertension, obstructive sleep apnea, poor quality of life and mortality in adulthood [10-13]. Although obesity is associated primarily with T2D due to insulin resistance, [14], it may also impact T1D morbidity.

T1D is caused by autoimmune destruction of the beta cells of the pancreas leading to insulinopenia. It is sub-classified into 2 main categories- type 1A and 1B [15]. In type 1A, individ-

uals have one or more of the anti-islet cell (including glutamic acid decarboxylase, and insulinoma antigen-2) or anti-insulin antibodies. In type 1B these antibodies are absent, but the clinical and biochemical features are similar to 1A. T2D is characterized by insulin resistance and absence of diabetes-associated antibodies in serum.

A new subset of diabetes, called double diabetes is becoming increasingly prevalent as a result of the epidemic of childhood obesity [16-18]. In double diabetes, elements of both T1D and T2D co-exist. In this condition, individuals with T1D have insensitivity to insulin that is most often associated with obesity; and individuals with T2D have antibodies against the pancreatic beta cells [14] (Figure 1). Unlike T1D and T2D, there is no consensus on the therapeutic modalities for double diabetes.

The incidence of both T1D and T2D is rising in children and adolescents [14]. Data from the EURODIAB study indicate that the overall prevalence of T1D among young people under 15 years is increasing by greater than 3% each year, and by more than 6% a year in children aged up to four years [19].Analysis of the 2002 to 2003 data from SEARCH for Diabetes in Youth, a multicenter study funded by the Centers for Disease Control and Prevention and the National Institutes of Health to examine T1D and T2D among children and adolescents in the United States, showed that annually, about 15,000 youth in the United States are newly diagnosed with T1D, and about 3,700 youth with T2D. The reported rate of new cases among youth was 19 per 100,000 each year for T1D, and 5.3 per 100,000 for T2D [20].

2. Prevalence

The prevalence of double diabetes is unknown [16]. However, reports show that about 25% of children with T1D are either overweight or obese [21]. Other reports show that about 35% of children and adolescents with T2D have at least one diabetes-associated antibody [22]. Some authors estimate that about one in three children and adolescents with newly diagnosed diabetes has double diabetes. Pozzilli et al reported a prevalence of 4.96% in their unpublished Italian cohort [1]. The major difficulty with establishing a prevalence rate for double diabetes is that there are no precise definitions for the different types of diabetes presenting in youth [1]. This is because clinical phenotypes frequently overlap at onset of the disease [1]. For example, obesity and ketoacidosis can be found in both T1D and T2D [23], and the age of diagnosis is now a poorly differentiating factor [24]. In other cases, the clinical features of double diabetes are not apparent at diagnosis but evolve over time [18].

3. Etiology and pathophysiology

There are genetic, environmental and behavioral factors that affect the pathophysiological processes of T1D and T2D in such as way to result in double diabetes. Obesity is the central pathophysiological mechanism for double diabetes. Obesity may arise from genetic predisposition or from environmental factors such as the anabolic role of insulin injection in pa-

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tients with T1D who fail to make the necessary healthy lifestyle changes that are recommended for maintenance of normal weight.

3.1. Genetic factors

Unlike T1D where the *MHC* region of chromosome 6 accounts for approximately 40% of the genetic risk of the disease in concert with other genes [25], and in T2D where genome-wide association studies have identified approximately 50 genetic loci associated with T2D in lean and obese individuals [26-28], there are no distinct genes that are unique to double diabetes. However, it is believed that the major genes that are independently associated with susceptibility to either T1D (e.g., the MHC and cytotoxic T lymphocyte-associated antigen-4 (*CTLA-4*) [29] or T2D (e.g., the genes encoding adiponectin (*APM1*) and transcription factor 7-like 2 (*TCF7L2*) [30] can serve as genetic determinants for double diabetes, such that the frequency of the major T1D genetic susceptibility gene (*MHC*) is reduced, whereas the expression of the genes associated with T2D is enhanced [31].

Apart from the principal genetic determinants of T1D and T2D, there are a number of genes that could potentially lead to an outcome of double diabetes by influencing the pathogenetic processes operating in both T1D and T2D [32]. One of such genes resulting from a genetic variance in insulin receptor substrate 1 (*IRS-1*) plays an important role in insulin resistance, a key component of T2D, and also in β cell apoptosis which is associated with T1D [33]. High mobility group A1 (HMGA1) protein, a product of the Hmga1 gene has been identified as a crucial effector in the control of glucose homeostasis, such that impaired HMGA1 function may contribute to the development of specific forms of diabetes [34]. HMGA1-deficient indiviuduals have reduced insulin receptor expression, reduced insulin signaling and decreased insulin secretion similar to the phenotype of T2D [34].

3.2. Environmental and behavioral factors

The epidemic of childhood obesity has led to increased diagnosis of metabolic syndrome and T2D in all children including those with existing T1D [35]. Obese or overweight children have been reported to develop T1D at younger ages than children of normal weight [35]. The SEARCH for Diabetes in Youth Study [36] reported an obesity prevalence rate of 12.6% in US youth with T1D. The study also reported a higher prevalence of overweight status (BMI 85th – 95th percentile) among youth with T1D than in those without diabetes (22.1% vs. 16.1%) ($P<0.05$). Some children with T1D have either a first- or second-degree relative with T2D [1]. Furthermore, weight gain is prevalent in adolescents with T1D after attainment of adult height, which might further impair insulin sensitivity [37].

Therefore, several enviromental factors could lead to the development of double diabetes by their influence on the disease processes of T1D and T2D. Many of the major genetic factors involved in the etiopathogenesis of T2D appear to promote the development of the disease through their influence on obesity and feeding behavior [38]. There is evidence that rapid growth and obesity in early childhood might increase the risk of T1D [35,39]. The strong environmental basis for this obesity pandemic and influence on feeding behavior was recently

outlined in a World Health Organization Technical Report [40] which states that 'Changes in the world food economy have contributed to shifting dietary patterns, for example, increased consumption of energy-dense diets high in fat, particularly saturated fat, and low in unrefined carbohydrates. These patterns are combined with a decline in energy expenditure that is associated with sedentary lifestyle, motorized transport, labor-saving devices at home, the phasing out of physically-demanding manual tasks in the workplace, and leisure time that is preponderantly devoted to physically undemanding pastimes'. However, despite the established association between obesity and the increasing prevalence of T1D, it is unclear how these environmental processes lead to β cell destruction.

Several mechanistic models have been proposed to explain this phenomenon. Some reports have linked high titers of glutamic acid decarboxylase autoantibody to an increase in body mass index (BMI) [41] which suggests that increased BMI might favor the development of an autoimmune response towards β cells. This is in line with other reports indicating that a combination of obesity and insulin resistance speeds up the process of beta cell destruction [35,42]. Other proposed mechanisms for beta cell destruction include the the role of upregulation of autoimmune response by obesity-associated inflammatory cytokines, and hyperleptinemia-associated T-cell activation [43,44].

Other researchers have proposed the following mechanism for obesity-induced insulin resistance : (a) the liberation of large amounts of non-esterified fatty acids by visceral fat which stimulate neoglucogenesis in the liver and diminish glucose uptake in the muscles; (b) the association of obesity with increased activity of the sympathetic nervous system, which in combination with direct release of tumor necrosis factor, resistin and other adipocytokines contribute to insulin resistance; (c) the role of the accummulation of local intramyocellular triglycerides on muscle insulin senstivity [45].

In additon to the above mechanistic models, several hypotheses have been advanced to explain the association between obesity and rising prevlaence of T1D. The most prominent of these hypotheses is the accelerator hypothesis which states that T1D and T2D are the same disease state set in different genetic backgrounds [46]. It originally proposed three major factors as the basis for the development of diabetes: genetic predisposition, insulin resistance and intrinsic rate of beta cell loss. The accelerators have now been reduced to two without altering the premise of the hypothesis [46]. The first is insulin resistance which is believed to accelerate β-cell apoptosis while rendering them more immunogenic. It posits that insulin resistance is the primary driver for the development of diabetes in a susceptible individual and argues that insulin resistance increases through weight gain as does the rate of onset of diabetes [47]. The second accelerator is the hierachy of responsive genes whose reactivity modulates the gradient of β-cell declining function [46].

The central premise of the accelerator hypothesis is based on studies reporting rising incidence of obesity [6,48] and T1D in children [49,50]. These findings were strengthened by reports of an association between weight gain and an increased risk to develop diabetes mellitus [51-53], as well as several reports from Europe indicating that an increasing number of children are being diagnosed with T1D at an earlier age [54-58]. This hypothesis proposes a direct cause and effect relationship between obesity and the development of both T1D and

T2D, and states that as the population becomes heavier (fatter), diabetes appears earlier, thus suggestive of a true acceleration rather than an incidental risk association [59].

The accelerator hypothesis is controversial because studies designed to prove its validity have reached various conclusions [35,60-65]. Reports from the United Kingdom indicated a relationship between younger age at diagnosis of T1D and higher body mass index (BMI) in Middlesbrough [35], and Plymouth [64],but not in Birmingham [61]. Other European studies of large cohorts of German and Austrian children with T1D supported the hypothesis [62,63], although studies from Spain and Australia [66,67] did not. Two studies have been conducted in the United States to examine this hypothesis. Dabelea et al [65] tested the hypothesis in six centers in the US (Cincinnati, Colorado, Hawaii, Seattle, South Carolina, Southern California) and found a significant relationship between BMI standard deviation score (SDS) and age at diagnosis only among patients with low C-peptide values at diagnosis. Evertsen et al [50] reported a significant inverse relationship between age at diagnosis and BMI SDS in their Wisconsin cohort. Thus, there is no consensus on the validity of the hypothesis among children and adolescents with T1D in the United States.

4. Clinical features

Traditionally, a patient with the classic symptoms of diabetes which include polyuria, polydipsia, and polyphagia who also has a family history of T2D, obesity, acanthosis nigricans and lack of both ketosis and diabetes-associated autoantibodies is considered to have T2D [68]. On the other hand, patients with T1D are usually thought to be thin, may present with ketosis, and have diabetes associated autoantibodies. [18] Patients with double diabetes possess the features of both T1D and T2D which could present siimultaneously at the time of diagnosis, or develop sequentially over time [18].

Features of Double Diabetes in Child or Adolescent with Pre-existingType 1 diabetes: The signs and symptoms typical of T2D can develop gradually in a child or adolescent with pre-existing T1D. The rate of the development of these features of increased metabolic load depends on the individual's genetic makeup and his or her degree of weight gain. These patients are usually overweight or obese and require a high dose of insulin to maintain euglycemia because of obesity-related insulin resistance [31,69]. Some of these patients may have hypertension, dyslipidemia, and poor diabetes control. Female adolescent patients may have polycystic ovarian syndrome.

Features of Double Diabetes in Child or Adolescent with Pre-existing Type 2 diabetes: The presence of increased 'autoimmune load' as marked by the presence of diabetes-associated autoantibodies in a child or adolescent with all of the typical clinical features of T2D - excess body weight, acanthosis nigricans, high blood pressure, dyslipidemia, polycystic ovary syndrome, positive family history of T2D, belonging to ethnic/racial minority group – is consistent with a diagnosis of double diabetes [31,69].

5. Diagnosis

There is the need to formulate universal diagnostic criteria to facilitate the recognition of double diabetes either at the time of onset of hyperglycemia or in the course of the disease process. Pozzilli et al [16,31] recently introduced the concept of 'metabolic load' to describe the features of T2D and 'autoimmune load' to describe the features of T1D. They stated that in an obese child or adolescent with hyperglycemia, an increased 'metabolic load' and a reduced 'autoimmune load' are features of double diabetes (Figure 1). Based on this principle, they advanced the following clinical and biochemical guidelines to facilitate the diagnosis of double diabetes:

i. The presence of clinical features of T2D, hypertension, dyslipidemia, increased body mass index with increased cardiovascular risk, compared with children with classical T1D. Family history for T2D and T1D might be present.

ii. The presence of a reduced number of clinical features typical of T1D, such as weight loss, polyuria and polydipsia, development of ketoacidosis; insulin therapy is not the first line of therapy, by contrast to the situation in subjects with classical T1D.

iii. The presence of autoantibodies to islet cells, although with a reduced number and titer compared with T1D, and probably a reduced risk associated with the *MHC* locus compared with subjects with T1D. As compared with T1D, where insulin resistance and obesity are not common features, double diabetes is always characterized by an obese phenotype, with the additional coexistence of β cell autoimmunity.

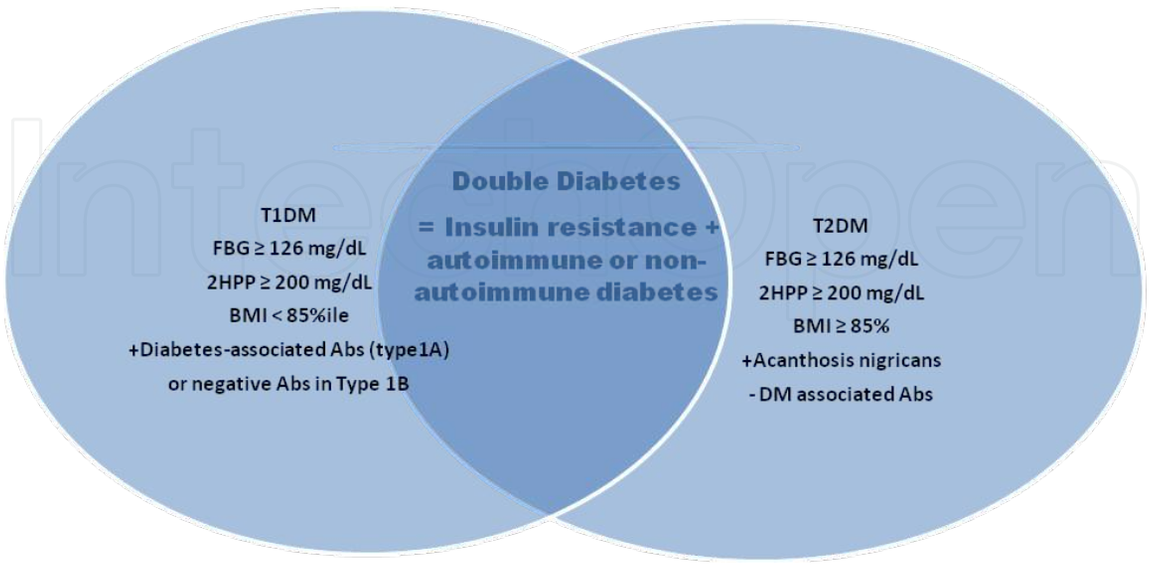

Figure 1. The relationship between T1D, T2D and Double Diabetes, TID = type 1 diabetes, T2D = type 2 diabetes, FBG = fasting blood glucose, 2HPP = 2 hour post prandial glucose level; BMI = body mass index; Abs = antibodies

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6. Treatment

There is no consensus on the best therapeutic regimen for double diabetes. However, because insulin resistance is central to the pathophysiological mechanism of double diabetes, optimal management of this condition necessitates the addition of insulin sensitizers to the patient's therapeutic regimen under appropriate clinical circumstances [18]. Intensification of lifestyle modification strategies should be encouraged to maintain normal weight and attenuate insulin resistance. Finally, because these patients require increased doses of insulin to maintain euglycemia, it is necessary to develop an insulin titration regimen that would ensure adequate glycemic control.

6.1. The burden of poor glycemic control in children and adolescents

The availability of insulin analogs and diabetes monitoring devices has improved diabetes care around the world. However, according to recent studies, the prevalence of poorly-controlled diabetes in youth is still high [70]. This poor glycemic control predisposes the youth to acute and chronic complications of diabetes.

A report by the SEARCH for Diabetes in Youth Study group showed that a high proportion of youth with diabetes had high HbA1c values, with 17% of the youth with TIDM, and 27% of those with T2D showing poor control, defined as HbA1c ≥ 9.5% [70]. The American Diabetes Association target values for HbA1c in relation to age are as follows: 7.5-8.5% at age < 6 years, <8% at age 6-12 years, <7.5% at age 13-18 years, and <7.0% at age 19+ years [68]. Thus only a minority of children and adolescents meet the recommended glycemic targets.

The physiological factors that contribute to poor glycemic control in youth are in part related to the hormonal changes in puberty. Puberty is associated with relative insulin resistance, reflected in a two- to threefold increase in the peak insulin response to oral or intravenous glucose [71]; insulin-mediated glucose disposal is approximately 30% lower in adolescents than in prepubertal children or young adults [72]. This physiologic insulin resistance of puberty is of minimal consequence in the presence of adequate beta-cell function [73]. The cause of this physiologic resistance is likely the transitory increased activity of the growth hormone-insulin growth factor axis, as well as sex steroids, which coincides with the physiologic insulin resistance of adolescence [74] and act as counter-regulatory hormones. As a result of these physiological changes, insulin dosages are often increased to overcome the resistance to insulin, but metabolic control still frequently worsens during the later stages of pubertal development [37].

6.2. Alternative therapeutic strategies

The increasing insulin resistance and deterioration of glycemic control in adolescents create a great need for alternative therapeutic strategies in adolescents with T1D. One such strategy is the addition of a drug that improves insulin sensitivity such as metformin, a biguanide that acts principally by increasing insulin sensitivity in the liver by inhibiting hepatic gluconeogenesis and thereby reducing hepatic glucose production [75]. Other minor mecha-

nisms include decreasing fatty acid oxidation and intestinal glucose absorption [76], and increasing peripheral insulin sensitivity by enhancing glucose uptake in the muscles [77]. Metformin has mainly been used in adult patients with T2D and several studies have shown beneficial effects on body weight, blood lipid levels and metabolic control [78-80]. Randomized controlled trials with metformin in adolescents with T2D reported an improvement in fasting plasma glucose level [81]. However, there have been conflicting reports from studies in adolescents with T1D [75-77,82,83]. The benefit was transient in one study [83] and negative in another [82]. The main drawback of these studies was the small sample size and lack of reporting on long term benefit and safety of adjunctive therapy in many of them [84].

Evidence for the coexistence of insulin resistance and insulin deficiency in childhood-onset T1D adults has been demonstrated by the insulin-glucose clamp technique [85,86]. Furthermore, two randomized, placebo-controlled trials have investigated the role of adjunctive metformin therapy in adolescents with T1D. In a randomized placebo controlled trial in children with T1D who were treated for 3 months with adjunctive metformin, Sarnblad et al [77] reported a significant decrease in A1c from 9.6% to 8.7%($p<0.05$) in the metformin group, compared to 9.5 to 9.2% (p=NS) in the placebo group. In another study, Hamilton et al [75] reported an HbA1c 0.6% lower in the metformin group than in the placebo group ($P<0.035$), after 3 months of therapy. Mean HbA1c at the end of the study was decreased by 0.3% in the metformin group, while it increased by 0.3% in the placebo group (p=0.03). Both studies reported no difference in mean body mass index and serum lipids in the metformin versus placebo group after 3 months of therapy. Hamilton et al [75] reported no significant changes in mean insulin sensitivity, measured by frequently sampled glucose after intravenous glucose tolerance test, after 3 months of metformin therapy in the metformin versus placebo group. Sarnblad et al [77], using hyperinsulinemic euglycemic clamp study, demonstrated no significant change in insulin sensitivity after 3 months between the groups, but they did report an increase in insulin sensitivity in the metformin group during the study ($P<0.05$). Hamilton et al [75] reported a significant change in the mean daily insulin dose in the metformin group in comparison to the placebo group after 3 months of metformin therapy of -0.14 vs. 0.02, P=0.01. However, Sarnblad [77] did not find a significant difference in the daily insulin dosage between the metformin and placebo groups after 3 months of therapy (1.1 vs. 1.3).

The two randomized, controlled studies by Hamilton and Sarnblad did not categorically recruit children and adolescents with double diabetes. This is important because this sub-set of diabetic youth is known to be insulin resistant and may require a careful titration of insulin doses. Adjunctive metformin therapy to achieve glycemic control may also be more effective in this subset of diabetes patients.

Furthermore, even though these randomized controlled trials were designed to investigate the effectiveness of adjunctive metformin therapy compared to insulin therapy alone, they were not designed to compare metformin adjunctive therapy to protocol-driven, optimized insulin therapy. Neither study demonstrated a strong head-to-head comparison of adjunctive metformin to patient-directed, treat to target insulin regimen to ensure optimal insulin

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delivery during the study. Such a comparison is critical because poor glycemic control contributes to insulin resistance [87] as there is an inverse relationship between glycemic control (as determined by HbA1c) and insulin sensitivity (estimated by glucose infusion rate during euglycemic-hyperinsulinemic clamp) [88].

6.3. The need for an insulin titration regimen for double diabetes

In general, patients with double diabetes are overweight or obese and the resultant insulin resistance increases their insulin requirement [1]. However, in addition to requiring a high insulin dose, evidence suggests that many patients often do not have insulin doses titrated sufficiently to achieve target levels of glucose control [89,90]. These patients remain on suboptimal doses of insulin and fail to reach treatment targets [91]. In a recent study Blonde et al [91] demonstrated the efficacy of algorithm-guided, patient titration of once daily long acting insulin in normalizing HbA1c in adult patients with T2D. They conducted a 20-week, randomized, controlled, open label, multicenter, parallel-group study comparing the safety and efficacy of insulin detemir administered once daily in combination with oral antidiabetic agents when titrated to two fasting plasma glucose targets (3.0-5.0 mmol/L versus 4.4.-6.1 mmol/L) for the treatment of T2D in adults. In that study, fasting plasma glucose level decreased throughout the first 8 weeks of the study and then generally remained flat for each treatment group. The combined treatment groups achieved a mean HbA1c level of 6.9% at the end of the study. There were significant reductions in HbA1c in both titration groups: in the 3.9-5.0 mmol/L fasting plasma glucose target group, HbA1c values decreased from a baseline mean of 8% to 6.8% at 20 weeks. In the 4.4-6.1 mmol/L fasting plasma glucose target group, HbA1c values decreased from a 7.9% at baseline to 7.0% at 20 weeks. Overall rates of hypoglycemia episodes were low and were comparable between treatment groups: 7.73 and 5.27 events/subject/year for the 3.9-5 mmol/L and 4.4-6.1 mmol/L groups, respectively. Mean weight changes from baseline to the end of the study were small and did not differ significantly between groups.

Our group is conducting a randomized control trial to explore the role of protocol-driven treat-to-target regimen in children and adolescents with double diabetes. Given the rising prevalence of obesity in the general population we speculate that many children with T1D will eventually develop double diabetes. Thus, it is timely to devise an appropriate management protocol to treat this burgeoning sub-population. Our aim is to primarily study this group of patients to determine the role of protocol-driven, treat-to-target regimen alone or in combination with metformin therapy in their care. Metformin is approved by the Food and Drug Administration for use in children with T2D, and recently it has been recommended that metformin added to insulin therapy might be used in clinical practice in adolescents with T1D who are poorly controlled and show evidence of insulin resistance (double diabetes) as noted in T2D [84]. Given the conflicting reports on the efficacy of adjunctive metformin therapy in adolescents with T1D, this double blind, randomized, placebo controlled trial will demonstrate the effect of meformin on HbA1c reduction under optimized insulin titration regimen. Secondly, we will investigate whether a titrated insulin regimen alone would have a superior-, or similar effect to combined metformin and titrated insulin regi-

men in children and adolescents with double diabetes and how this modality of treatment compares to standard insulin therapy.

Blonde et al [91] demonstrated that self-titration regimens facilitate empowerment of patients, allowing them to become more involved in their treatment, which can result in improved glycemic control. Patient-directed insulin titration is increasingly important as health care practitioners often do not have the resources to advise patients with the frequency needed to effectively titrate their insulin doses to maintain euglycemia. Optimal patient empowerment through self-titration regimens is critical for the motivation to reach treatment targets.

7. Prognosis

The coexistence of both T1D and T2D in an individual should in principle denote an increased risk for the complications of both diseases [32]. Therefore, it is possible that these individuals are at higher risk for the microvascular and metabolic complications of T1D and the macrovascular complications of T2D [18]. This is supported by investigations by Orchard et al [85,92], in the Epidemiology of Diabetes Complications Study, who reported that patients with T1D who have a positive family history of T2D were at greater risk for cardiovascular disease than those who did not. Furthermore, data from the Diabetes Control and Complications Trial (DCCT) show that weight gain and central obesity are associated with insulin resistance, hypertension, and dyslipidemia in T1D [93], and data from Epidemiology of Diabetes Interventions and Complications (EDIC) Study show that central obesity is an independent risk factor for incident microalbuminuria in individuals with T1D [94]. However, both DCCT and EDIC follow up studies show that intensive diabetes therapy results in a uniform, major reduction in (and significant protection from) microvascular disease [95], even in overweight or obese T1D patients [92]. Thus, there is the need to devise a consensus treatment regimen that would ensure the best glycemic and metabolic outcome for patients with double diabetes.

8. Conclusions

The global pandemic of obesity in children and adolescents has resulted in a new expression of diabetes mellitus known as double diabetes. The entity encompasses the autoimmune load of T1D and the metabolic load of T2D. There is no consensus on the best therapeutic modality for this new expression of diabetes mellitus. However, optimal therapeutic options must address the coexistence of both metabolic and autoimmune components of diabetes mellitus in the patient. There have also been calls to revise the current classification of diabetes mellitus to take into account the surging prevalence of double diabetes in children and adolescents.

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