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Type 1 Diabetes Mellitus and Co-Morbidities

Adriana Franzese, Enza Mozzillo, Rosa Nugnes,
Mariateresa Falco and Valentina Fattorusso
*Department of Pediatrics, University Federico II of Naples
Italy*

1. Introduction

Co-morbid conditions are relatively frequent in Type 1 Diabetes Mellitus (T1DM). They can severely affect clinical management of the disease, especially in pediatric age. Furthermore, these conditions could present very interesting etiopathogenetic mechanisms.

2. Associated autoimmune conditions

2.1 Genetic associations

Patients with type 1 diabetes (T1D) have an increased risk of other autoimmune conditions, such as autoimmune thyroid disease (AIT), celiac disease (CD), Addison's disease (AD) and vitiligo. These diseases are associated with organ-specific autoantibodies: AIT with thyroid peroxidase (TPO) and thyroglobulin autoantibodies (TG), CD with endomysial (EMA) and transglutaminase (TTG) autoantibodies, and AD with adrenal autoantibodies. Using these autoantibodies, organ-specific autoimmunity may be often detected before the development of clinical disease, in order to prevent significant morbidity related to unrecognized disease (Barker, 2006). The probable mechanism of these associations involves a shared genetic background (Myśliwiec et al., 2008; Smyth et al., 2008).

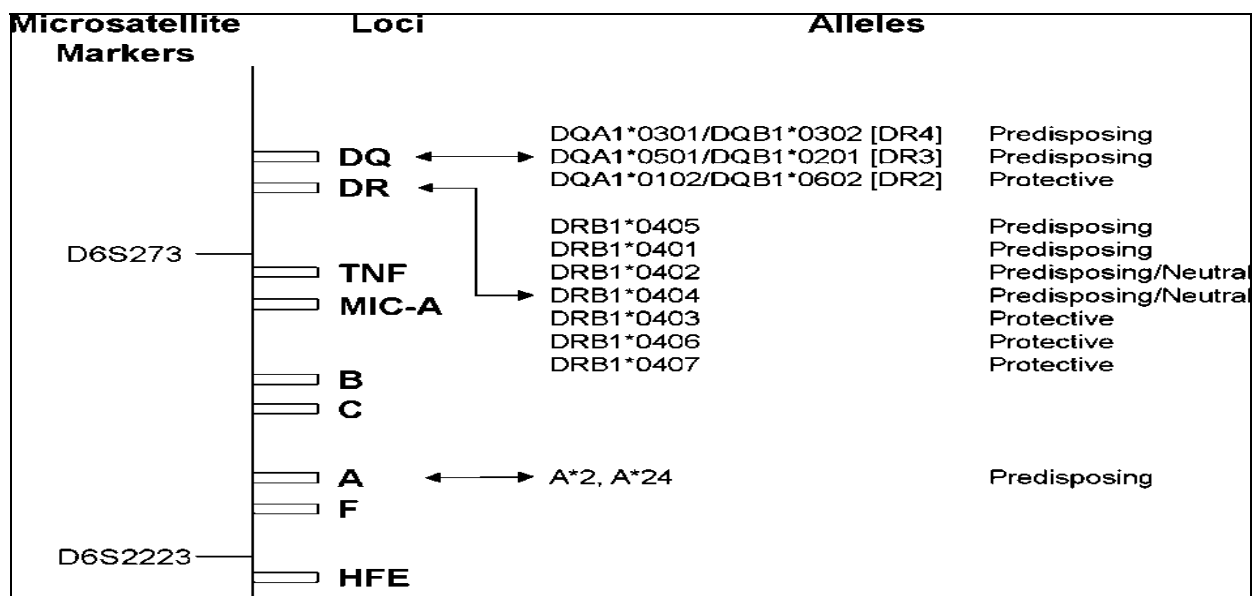
The majority of autoimmune endocrinopathies, including T1D, are inherited as complex genetic traits. Multiple genetic and environmental factors interact with each other to confer susceptibility to these disorders. Genetic risk factors associated with T1D, ATD, CD and AD include HLA genes and non-HLA genes.

2.1.1 HLA genes

The major histocompatibility complex (MHC) has been extensively studied in these diseases. HLA molecules are highly polymorphic and multiple different peptides can be presented to T cells by these molecules. In general it appears that the alleles associated with autoimmunity are not abnormal, but functional variants, that aid in determining specific targets of autoimmunity. The leading hypothesis is that these molecules contribute to determine risk through the peptides they bind and present to T-lymphocytes, either by influencing thymic selection, or peripheral antigen presentation. (Ide & Eisenbarth, 2003).

HLA DR4 and DR3 are strongly associated with T1D and approximately 30-50% of patients are DR3/DR4 heterozygotes. The DR3/DR4 genotype confers the highest diabetes risk with a synergistic mode of action, followed by DR4 and DR3 homozygosity, respectively. The

HLA-DQ (particularly DQ 2 and DQ8) locus has been found to be the most important determinant of diabetes susceptibility. Approximately 90% of individuals with T1D have either DQ2 or DQ8, compared to 40% of the general population (Ide & Eisenbarth, 2003). So, the highest-risk human leukocyte antigen (HLA) genotype for T1D is DR3-DQ2, DR4-DQ8. DR3-DQ2 shows a strong association with CD; homozygosity for DR3-DQ2 in a population with T1D carries a 33% risk for the presence of TTG autoantibodies (Bao et al., 1999). Moreover, in families with multiple members affected with T1D and AIT, DR3-DQ2 has been linked with AIT and T1D (Levin et al, 2004). AD has been associated with the presence of a rare subtype of DR3-DQ2, DR4-DQ8 in which the DR4 subtype is DRB1*0404. This subtype is found in less than 1% of the general population compared with 30% of the population with AD (Barker et al., 2005; Myhre et al., 2002; Yu et al., 1999). A schematic representation of the HLA region and its association with T1D is shown in the Figure 1.



(from Pugliese A. and Eisenbarth G.S., Chapter 7, Type 1 Diabetes: Molecular, Cellular, and Clinical Immunology, www.barbaradaviscenter.org)

Fig. 1. The HLA Region and T1D susceptibility. Schematic representation of the HLA region showing microsatellite markers, loci, and alleles associated with T1D susceptibility. Distances between loci are grossly approximated.

2.1.2 Non-HLA genes

Non-HLA genes are also involved in the predisposition to T1D and other autoimmune diseases, such as MIC-A, PTPN22, CTLA-4 (Barker, 2006).

Polymorphisms of MIC-A (MHC I-related gene A) have been associated with T1D, CD and AD. This gene encodes for a protein that is expressed in the thymus and interacts with the receptor NKG2D, which is important for thymic maturation of T cells (Hue et al., 2003). It is hypothesized that the loss of this interaction is a way in which immunological tolerance may be lost. NKG2D also regulates the priming of human naïve CD8⁺ T cells, providing an alternative explanation for associations with autoimmune diseases (Maasho et al., 2005).

The PTPN22 gene is expressed in T cells and encodes lymphoid tyrosine phosphatase (LYP). LYP appears to be important in the signal cascade downstream from the T-cell receptor. A

specific polymorphism, changing an arginine to tryptophan at position 620, has been associated with T1D (Bottini et al., 2004; Smyth et al., 2004) and also other autoimmune disorders, such as rheumatoid arthritis, systemic lupus erythematosus, Graves' disease and weakly with AD. The association with many autoimmune diseases suggests that this gene may be playing a role in susceptibility to autoimmunity in general.

Another non-HLA gene associated with T1D which has a generic role in susceptibility to autoimmunity is CTLA-4 (Cytotoxic T lymphocyte-associated antigen-4) (Vaidya & Pearce, 2004). CTLA-4 gene is an important susceptibility locus for autoimmune endocrinopathies and other autoimmune disorders, including T1D (Ueda et al., 2003). The CTLA-4 gene, which is located on chromosome 2, encodes a costimulatory molecule that is expressed on the surface of activated T cells. It plays a critical role in the T-cell response to antigen presentation, binding costimulatory molecules and inhibiting T-cell activation. (Vaidya & Pearce, 2004). The inhibitory effect of CTLA-4 on T-cell activation has led the investigations into its role in different human autoimmune disorders. Polymorphisms within the CTLA-4 gene have been linked to AIT (Vaidya et al., 1999). CTLA-4 has also been linked to AD and more strongly to subjects affected by AD in association with T1D and AIT compared with AD alone (Vaidya et al., 2000). CTLA-4 has been associated with a wide range of other autoimmune disorders, including primary biliary cirrhosis, multiple sclerosis, CD and rheumatoid arthritis. These observations have suggested that CTLA-4 is a general autoimmune locus, and that the susceptibility polymorphisms within the gene may lead to general defects in the immune regulation, while other tissue-specific (e.g. insulin gene polymorphisms) or antigen-specific (e.g. MHC) genetic factors and environmental factors determine the involvement of particular target organs (Vaidya & Pearce, 2004).

Gene	Associated diseases
MIC-A	T1D, CD, AD
PTPN22	AIT, AD
CTLA-4	T1D, AIT

Table 1. Non-HLA genes associated with T1D and other autoimmune diseases

2.2 Type 1 diabetes and celiac disease

2.2.1 Prevalence and age at starting

Traditional studies, both in children and adults, have shown that CD occurs in patients with T1D with a prevalence that varies from 1,5 to 10 % compared with 0.5 % of the general population (Cronin & Shanahan, 2007; Vaarala, 2000). The mean age at diagnosis of classical CD is commonly around 2-3 years, while the mean age at diagnosis of DM1 is 7-8 years. The age at onset of T1D is younger in patients with the double disease than in those with only T1D (Kaspers et al., 2004). The risk of CD is negatively and independently associated with age at onset of diabetes, with an higher risk being seen in children age < 4 years than in those age > 9 years (Cerutti et al., 2004). In patients with T1D, diabetes is usually diagnosed first, CD precedes diabetes onset only in 10-25% (Cerutti et al., 2004; Valerio et al., 2002), while generally CD diagnosis in T1D patients occurs, trough the screening performed at diabetes onset, in 70-80% of patients with a median age >8 years. Some authors hypothesized that in genetically susceptible patients one disease could predispose to another. Particularly, it has been suggested that untreated (latent or silent) CD could be an immunological trigger and induce diabetes and/or thyroid disorders due to gluten as a driving antigen (Pocecco &

Ventura, 1995). In accordance with this, the prevalence of autoimmune disorders in CD is closely related to age at diagnosis or, in other words, to the duration of exposure to gluten (Ventura et al., 1999) and thyroid-related antibodies tend to disappear during twelve months of gluten-free diet, like CD-related antibodies (Ventura et al., 2000). However, at present, it is unknown whether treatment of CD reduces the likelihood of developing autoimmune disorders, or changes their natural history and actually others found no correlation between duration of gluten exposure in adult CD and risk of autoimmune disorders (Viljamaa et al., 2005).

2.2.2 Clinical features and follow up

The classic presentation of CD describes symptoms related to gastrointestinal malabsorption and includes malnutrition, failure to thrive, diarrhea, anorexia, constipation, vomiting, abdominal distension, and pain. This predominance of gastrointestinal symptoms is more common in children younger than three years of age. Non-gastrointestinal or atypical symptoms of CD include short stature, pubertal delay, fatigue, vitamin deficiencies, and iron deficiency anemia and are more commonly observed in older children. The classical presentation of CD can occur in T1D patients, but many patients with CD and T1D are either asymptomatic (silent CD) or present with only mild symptoms (Holmes, 2001a; Ventura et al., 2000). Diagnosis of CD is regularly performed because screening protocols are universally recommended and performed. In patients with overt CD, identifying and treating CD with gluten free diet (GFD) surely confer benefit in reducing complications such as malabsorption, infertility, osteoporosis, poor nutrition, impaired growth and reducing long-term malignancy risks and mortality rates (Collin et al., 2002; Freemark & Levitsky, 2003; Rubio-Tapia et al., 2009), while no evidence exists on long-term morbidity in silent CD. Similarly, children with T1D with evidence of symptomatic CD benefit from GFD (Hansen et al., 2006; Saadah et al., 2004); in symptom-free cases the demonstrated benefit is limited to weight gain and bone mineral density (BMD) changes. (Artz et al., 2008; Rami et al., 2005; Simmons et al., 2007). Recently a 2-year prospective follow up study has provided additional evidence that only in some of the children with T1D and few classical symptoms of CD, identified by screening as being TG+ present, the demonstrated benefit of GFD is limited to weight gain and BMD changes (Simmons et al., 2011); moreover, other authors have reported an improved glycemic control in GFD-compliant celiac patients (Sanchez-Albisua et al., 2005). On the contrary, silent untreated CD has no obvious effect on metabolic control in T1D patients, but could negatively influence weight gain (Rami et al., 2005). In any case, the adherence to GFD by children with T1D has been reported generally below 50% (Acerini et al., 1998; Crone et al., 2003; Hansen et al., 2006; Saadah et al., 2004, Westman et al., 1999). The different viewpoints highlight the need of a long follow up of patients affected by T1D and asymptomatic CD to clarify the role of a GFD. Actually some authors argument against the need to stress GFD in nonsymptomatic T1D patients (Franzese et al., 2007; Van Koppen et al., 2009). However, the wide spectrum of CD include also subjects with positive celiac-related antibodies without diagnostic small-bowel mucosal villous atrophy. This condition is defined as potential celiac disease (pot-CD) (Holmes, 2001b; Paparo et al., 2005; Troncone et al., 1996). Some authors described that the prevalence of pot-CD among patients with T1D recruited from the majority of childhood diabetes care centers in Italy is 12.2 %, with an higher prevalence of females. The prevalence of pot-CD in the CD control population is 8.4 % (Franzese et al., 2011). Case reports and small follow-up studies indicated that only few pot-CD patients may suffer from CD-related symptoms

before the development of villous atrophy (Troncone et al., 1996). No definite consensus exists among experts about to treat pot-CD patients with GFD. No data are available on the natural history of these patients in the long term, nor on the risks they are exposed if left on normal gluten-containing diet, while a recent paper provided evidence that pot-CD children may benefit from GFD treatment (Kurppa et al., 2010).

Other studies have shown intestinal inflammation also in T1D patients without CD-related antibodies and structurally normal intestinal mucosa (Westerholm-Ormio et al., 2003). According to this, our group has observed a gluten-related inflammation either in rectal either in small bowel mucosa of children with T1D (Maglio et al., 2009; Troncone et al., 2003). It can be speculated that gluten could be an optimal candidate to stimulate an abnormal innate immune reaction in intestinal mucosa due to its pro-inflammatory characteristics. It remains a crucial issue to establish to what the extended intestinal inflammation in T1D is gluten-dependent and whether it precedes the occurrence of the disease.

2.3 Type 1 diabetes and autoimmune thyroid disease

2.3.1 Prevalence and age at starting

Antithyroid antibodies have been shown to occur during the first years of diabetes in 11-16.9% of individuals with T1D (Kordonouri et al., 2002). Long-term follow up suggests that as much as 30 % of patients with T1D develop AIT (Umpierrez et al., 2003). The range of prevalence of AIT in patients with T1D is unusually wide (3.4-50%) (Burek et al., 1990; Radetti et al., 1995). Thyroid antibodies are observed more frequently in girls than in boys, often emerging along during pubertal maturation (Kordonouri et al., 2005).

2.3.2 Clinical features and follow-up

Hyperthyroidism is less common than hypothyroidism in association with T1D (Umpierrez et al., 2003), but still more common than in the general population. It may be due to Grave's disease or the hyperthyroid phase of Hashimoto's thyroiditis. The presence of abnormal thyroid function related to AIT in the population with T1D has the potential to affect growth, weight gain, diabetes control, menstrual regularity, and overall well-being. In particular clinical features of hypothyroidism may include the presence of a painless goitre, increased weight gain, retarded growth, tiredness, lethargy, cold intolerance and bradycardia while diabetic control may not be significantly affected. Clinical features of hyperthyroidism may include unexplained difficulty in maintaining glycaemic control, weight loss without loss of appetite, agitation, tachycardia, tremor, heat intolerance, thyroid enlargement or characteristic eye signs. The treatment of hypothyroidism is based on replacement with oral L-thyroxine (T4) sufficient to normalise TSH levels and usually this allows regression of the goitre if present. The treatment of hyperthyroidism is based on the use of carbimazole and beta-adrenergic blocking drugs, if necessary.

There are studies showing worse diabetes control in patients with a second autoimmunity, including AIT and CD (Franzese et al., 2000; Iafusco et al., 1998). The factors responsible for the worsened control have not been completely elucidated. Thyroid dysfunction could be responsible of variations in absorption of carbohydrates and increased insulin resistance. There are studies showing similar diabetes control in patients with and without a second autoimmunity, in these studies thyroid autoimmunity does not lead to worsening of diabetic metabolic control in children with T1D (Kordonouri et al., 2002; Rami et al., 2005; Sumnik et al., 2006). The thyroid status is not different between diabetic patients with and

without CD: children with both T1D and CD do not have an increased risk of AIT development compared to diabetic patients without CD (Sumnik et al., 2006).

2.4 Type 1 diabetes, Addison disease and polyglandular syndromes

2.4.1 Prevalence and age at starting

Addison's disease (AD) affects approximately 1 in 10,000 of the general population. The autoimmune process resulting in AD can be identified by the detection of autoantibodies against the adrenal cortex (Anderson et al., 1957; Lovas & Husebye, 2002). Up to 2% of patients with T1D have antiadrenal autoantibodies (De Block et al., 2001; Falorni et al., 1997; Peterson et al., 1997).

AD is occasionally associated with T1D in the Autoimmune Polyglandular Syndromes (APS I and II). APS I, also known as autoimmune polyendocrinopathy candidiasis ectodermal dysplasia (APECED), is a rare polyendocrine autoimmune disease caused by mutations of the autoimmune regulator gene (AIRE) on chromosome 21q22.3 (Aaltonen et al., 1994; Ahonen et al., 1990), which is characterized by the association of mucocutaneous candidiasis, adrenal insufficiency, and/or hypoparathyroidism. Follow-up of subjects with this disorder has revealed that many organ systems may be involved in the autoimmune process including the pancreatic β cell. Approximately 20% of subjects with APS-I develop T1D (Barker, 2006). APS II is more common in adults, but is also observed in children in association with autoimmune thyroiditis (Dittmar & Kahaly, 2003). Other less common disorders observed in APSII include Addison's disease, hypogonadism, vitiligo, alopecia, pernicious anemia and myasthenia gravis. Another rare disorder associated with T1D in early childhood is the Immunodysregulation Polyendocrinopathy X-linked Syndrome (IPEX), which is characterized also by severe enteropathy and autoimmune symptoms due to a clear genetic defect (FOX-P3) (Chatila et al., 2000). FOX-P3 is expressed in CD4+CD25+ regulatory T cells; mutations result in the inability to generate these regulatory T cells resulting in multiorgan autoimmunity (Barker, 2006).

2.4.2 Clinical features and follow-up

The condition of AD is suspected by the clinical picture of frequent hypoglycaemia, unexplained decrease in insulin requirements, increased skin pigmentation, lassitude, weight loss, hyponatraemia and hyperkalaemia. The diagnosis is based on the demonstration of a low cortisol, especially in response to ACTH test. Treatment with a glucocorticoid is urgent and life-threatening. In some cases the therapy has to be supplemented with a mineralocorticoid. In asymptomatic children with positive adrenal antibodies, detected on routine screening, a rising ACTH level suggests a failing adrenal cortex and the development of primary adrenal insufficiency (Kordonouri et al., 2009). There are no current recommendations for screening of adrenal autoimmunity.

2.5 Type 1 diabetes and vitiligo

Vitiligo is an acquired pigmentary disorder characterized by a loss of melanocytes resulting in white spots or leukoderma. The association of vitiligo with other autoimmune disorders, including thyroid disease, adrenal insufficiency, gonadal dysfunction, polyendocrine failure, diabetes mellitus, pernicious anemia, myasthenia gravis and alopecia areata, has been well documented (Bystryn, 1997; Handa & Dogra, 2003). This condition is present in about 6% of diabetic children (Hanas et al., 2009). Spontaneous re-pigmentation is rare and

not usually cosmetically acceptable. Treatment is difficult and multiple therapies have been tried with little success. (Ho et al., 2011)

2.6 Type 1 diabetes and collagenopathies

2.6.1 Rheumatoid arthritis

The tendency of autoimmune diseases to aggregate is well known as clusters of autoimmune diseases within families and individuals. Analysis of susceptible genetic loci for the distinct autoimmune disease shows considerable overlap that suggests the possibility of shared pathways in their pathogenesis. Reports on the clustering of T1D, AIT, CD and rheumatoid arthritis (RA) in the same patient are very scarce. The major genetic predisposition to RA is contributed by variants of the class II HLA gene, HLA DRB1. In exploring the overlap between T1D, CD and RA, there is strong evidence that variation within the TAGAP gene is associated with all three autoimmune diseases. Relatively little is known about the TAGAP gene, which encodes a protein transiently expressed in activated T cells, suggesting that it may have a role in immune regulation. So the TAGAP gene, previously associated with both T1D and CD, is also associated with RA susceptibility. Interestingly a number of loci appear to be specific to one of the three diseases currently studied suggesting that they may play a role in determining the particular autoimmune phenotype at presentation (Eyre et al., 2010). The majority of the published case reports are girls. The predominance of females among the affected individuals may reflect that certain genes play role in the pathogenesis as gender-specific factors or the penetrance of multiple risk genes are enhanced in females. In most reported patients, diabetes is diagnosed first, thyroid autoimmunity and juvenile rheumatoid arthritis develop after a period of several months to years. (Nagy et al., 2010; Pignata et al., 2000; Valerio et al., 2000).

2.6.2 Scleroderma, systemic lupus erythematosus

The association of T1D with Systemic Lupus Erythematosus (SLE) and Scleroderma is rare but reported in literature (Inuo et al., 2009, Zeglouli et al., 2010). Some authors found a significant association between DQ2 allele and the presence of anti-SSA antibodies, while others described an association between CD and the presence of A1B8DR3 haplotype, which seems to be frequent in SLE and in Scleroderma (Black et al., 1983; Mark, 2000; Sollid & Thorsby, 1993). In human, the CTLA-4 and PD-1 genes significantly contributed to the development of various autoimmune diseases in different genetic backgrounds (Inuo et al., 2009). It has been suggested the involvement of CTLA-4 and PD-1 (inhibitor receptors of CD28) to the development of T1D, SLE or other autoimmune diseases.

Juvenile scleroderma is present in 3% of scleroderma cases, SLE in children is present in 9% of cases of SLE; one case of a 15 years girl with CD and SLE and Scleroderma has been reported (Zeglouli et al., 2010).

2.7 Screening for associated autoimmune disorders

Since Type 1 Diabetes is associated with the presence of additional autoimmune disease, such as AIT, CD and AD, which are associated with the production of organ-specific antibodies, it is possible to screen patients with T1D by means of these ones. However, only a subset of the subjects with organ-specific antibodies develops clinical disease. The frequency of screening and follow up of patients with positive antibodies remain controversial. The current American Diabetes Association (ADA) recommendations are to

screen for CD-associated antibodies at diagnosis of T1D and in presence of symptoms. The International Society of Pediatric Adolescent Diabetes (ISPAD) recommends to screen for CD at the time of diagnosis, annually for the first five years and every second year thereafter. More frequent assessment is indicated if the clinical situation suggests the possibility of CD or the child has a first-degree relative with CD. Respect to the screening for thyroid disease, current recommendations from the ADA are for screening TSH after stabilization at onset of diabetes, with symptoms of hypo- or hyperthyroidism, and every 1–2 yr thereafter. ISPAD recommends to screen by circulating TSH and antibodies at the diagnosis of T1D and, thereafter, every second year in asymptomatic individuals without goitre or in the absence of thyroid autoantibodies. More frequent assessment is indicated otherwise, subjects with positive TPO autoantibodies and normal thyroid function are screened on a more frequent basis (every 6 months to 1 yr). There are no current recommendations for screening of adrenal autoimmunity (Barker, 2006). Authors observed that the prevalence of adrenal antibodies in diabetic patients with thyroid antibodies compared with those without thyroid antibodies is increased (5,1 vs 0,6%) (Riley et al., 1981). It is possible conclude that routine screening for AD in children with T1D is not warranted unless there is a strong clinical suspicion or family history of AD (Marks et al., 2003)

Celiac disease	Transglutaminase antibodies	Yearly
Thyroiditis	TSH, FT4, thyroid antibodies	Yearly
Addison disease	Cortisolemia, adrenal antibodies	Screening if AD in family
Collagenopathies	Specific auto-antibodies	No screening

Table 2. Autoimmune diseases associated with T1D, recommended systems and frequency of the screening

3. Associated non-autoimmune conditions

3.1 Type 1 diabetes and growth

Type 1 diabetes and other chronic diseases are well known to adversely affect linear growth and pubertal development, this can include a wide spectrum of different conditions, from poor gain of weight to Mauriac Syndrome (MS); MS classically involves hepatomegaly, growth impairment, and Cushingoid features in poorly controlled diabetic patients. Although MS, the most important expression of growth alteration due to severe insulin deficiency in diabetic patients, is now rare, impaired growth in children with T1D is still reported. This is particularly true in patients with poor metabolic control (Chiarelli et al., 2004; Franzese et al., 2001). Some studies report that poorly controlled patients show a decrease in height standard deviation score over the next few years, while better controlled patients maintain their height advantage (Gunczler & Lanes, 1999; Holl et al., 1998).

Longitudinal bone growth is a complex phenomenon involving a multitude of regulatory mechanisms strongly influenced by growth hormone (GH) (Chiarelli et al., 2004) and by the interaction between insulin-like growth factors (IGF-I and IGF-II), that circulate bounded to specific insulin-like growth factor binding proteins (IGFBPs). IGFBP-3, the major circulating binding protein during post-natal life, is GH-dependent. Insulin is an important regulator of this complex. In fact, adequate insulin secretion and normal portal insulin concentrations are

needed to support normal serum concentrations of IGFs and IGFBPs and indirectly to promote growth. Poor gain of height and weight, hepatomegaly, non alcoholic steatosis hepatitis (NASH) and late pubertal development might be seen in children with persistently poorly controlled diabetes. Similar to healthy adolescents, the pubertal growth spurt represents the most critical phase for linear growth and final height in children with T1D. The pubertal phase is characteristically associated with reduction in insulin sensitivity, which is known to be more severe in patients with T1D, and might negatively influence growth and height gain (Chiarelli et al., 2004). Although the chronological age at onset of puberty and the duration of the pubertal growth spurt is not significantly different between subjects with T1D and healthy adolescents, several studies have shown a blunted pubertal growth spurt which seems to be associated with a reduced peak of height velocity SDS (Vanelli et al., 1992). Although loss of height from the onset of diabetes has been widely reported, an impaired final height has not been reported in children with T1D. In fact, while some studies, especially those performed in the pre-intensive insulin therapy era, showed an impaired final height in children with diabetes (Penfold et al., 1995), more recent studies show a normal or only slightly reduced final height (Salerno et al., 1997).

The Diabetes Control and Complications Trial (DCCT) and other studies have reported increased weight gain as a side effect of intensive insulin therapy with improved metabolic control (DCCT Research Group, 1993). As obesity is a modifiable cardiovascular risk factor, careful monitoring and management of weight gain should be emphasised in diabetes care. Girls seem to be more at risk of overweight and as well of eating disorders.

Monitoring of growth and development and the use of percentile charts is a crucial element in the care of children and adolescents with diabetes. Improvements in diabetes care and management and especially newer insulin schedules based on multiple daily injections or insulin pumps have led to a reduction in diabetic complications and seem to ameliorate growth in children with T1D. Start an intensive insulin regimen since the onset of diabetes might prevent the induction of abnormalities of the GH-IGF-I-IGFBP-3 axis potentially achieving near-normal portal insulin concentrations and thereby leading to normal IGF-I and IGFBP-3 levels and physiological growth in children and adolescents with T1D.

3.2 Type 1 diabetes and eating disorders

Eating disorders (EDs) are a significant health problem for many children and adolescents with T1D similar to that observed in other high risk groups, such as competitive athletes, models and ballet dancers. EDs and subclinical disordered eating behaviors (DEBs) have been described in adolescents with T1D with a higher prevalence than in a non-diabetic population. The start of insulin treatment and the need to comply with dietary recommendations both lead to weight gain, which in turn leads to body dissatisfaction and a drive for thinness. Since the dietary restraint usually requires ignoring internal cues of hunger and satiety, it has been suggested that it may be a triggering factor in the development of cycles of binge eating and purging. The concurrence of T1D and EDs can greatly increase morbidity and mortality. In diabetic subjects, EDs are associated with insulin omission for weight loss and impaired metabolic control. On the contrary, in a five year longitudinal study, the expected relationship between ED and poor metabolic control was not evident, although there was a trend for higher haemoglobin A1c in individuals with an EDs (Colton et al., 2007). This offers hope that early interventions might prevent the worsening metabolic control that is often associated with EDs. In addition subclinical DEBs

among youth with T1D have been associated with increased risk of poor metabolic control and increased prevalence of microvascular complications such as retinopathy and nephropathy (Rydall et al., 1997). Some studies have examined the prevalence of EDs and DEBs in youth with T1D. Prevalence rates vary considerably from study to study possibly due to differences in sample, screening tools, and data collection methods. In a multi-site, cross sectional case-control study, the prevalence of ED meeting DSM-IV diagnostic criteria was about 10% and that of their sub-threshold variants about 14%: both were about twice as common in adolescent females with T1D than in their non-diabetic peers. (Jones et al., 2000). However there are also rare cases in childhood (Franzese et al., 2002a).

3.2.1 Management

Nutritional treatment is one of the main difficulties in managing diabetes in the young. Diabetes clinicians should be aware of the potential warning signs in an adolescent with diabetes as well as assessment and treatment options for eating disorders with concomitant T1D. Clinical approaches should focus on normalizing eating behaviour and enhancing self-esteem based on personal attributes unrelated to weight and eating, with a low threshold for referral for specialized EDs services (Colton et al., 2007). A multidisciplinary team, composed by clinicians, psychologist/psychiatric, dietitian/nutrition therapist, especially one with a background in EDs, is opportune to identify and treat unhealthy EDs and DEBs in T1D. Treatment for adolescents with T1D should include both diabetes management treatment and mental health treatment. The diabetes team and the mental health team have separate responsibilities but work collaboratively to address disordered eating in patients with T1D. Treatment begins with emphasis on nutritional rehabilitation, weight restoration, and adequate diabetes control. Psychotherapy should begin immediately for the patient and family (S.D. Kelly et al., 2005).

3.3 Necrobiosis lipoidica diabetorum

Necrobiosis lipoidica diabetorum (NBL) is an infrequent skin affection in pediatric age. The etiology is not clearly understood. The reported prevalence in children varies from 0.06% to 10% (De Silva et al., 1999). The female/male ratio is 3:1 (Hammami et al., 2008). The average age of onset is 30–40 years. In the past, it has been described as a complication of diabetes and associated with microvascular complications (W.F. Kelly et al., 1993), but NBL has been observed also at the beginning of diabetes. NBL typically appears on the anterior lower legs. The lesions are usually bilateral and are characterized by well circumscribed yellow brown inflammatory plaques with raised borders and an atrophic center. Ulceration occurs in up to 35% of cases and is notoriously difficult to treat (Elmholdt et al., 2008). This complication negatively affects quality of life and implies a greater risk for secondary infection. Although NBL is usually observed in diabetic patients, there is some controversy regarding the degree of this association and it has been hypothesized that the strength of this association may have been overestimated in the past. Some authors have studied the effect of glucose control on NBL and found no correlation with glycosylated hemoglobin A1c levels (Dandona et al., 1981), while others found an association with a poor glucose control (Cohen et al., 1996).

3.3.1 Management

There is currently no standardized effective treatment of NBL. A wide variety of treatments have been used over the years in adults. These include: topical, systemic or intra-lesional

steroids, aspirin, cyclosporin, mycophenolate, becaplermin, excision and grafting, laser surgery, hyperbaric oxygen, topical granulocytemacrophage colony-stimulating factor and photochemotherapy with topical PUVA (Hanas et al., 2009). A recent study suggests the use of TNF inhibitors in selected patients for treatment of NBL (ulcerative forms) unresponsive to prior conventional therapies (Suárez-Amor et al., 2010). NBL in children can be hard to manage and may be associated with a long-term risk of malignant transformation to squamous cell carcinoma. Systemic therapies, such as corticosteroids and azathioprine are immunosuppressive and immunomodulatory and could facilitate malignant transformation (Beattie et al., 2006). Therefore, although NBL is not clearly related to poor metabolic control, we believe that the diabetic control may also be useful. Effective primary prevention strategies and new treatment options are needed to adequately control the disease and its progression.

3.4 Osteopenia

Children and adolescents with T1D can show several impairment of bone metabolism and structure, resulting in a higher risk of decreased bone mass and its related complications later in life. Consequently an assessment of quality of the bone through non-invasive methods (phalangeal ultrasonography) seems to be opportune in the care of diabetic patients, specially the ones with clusters of autoimmune diseases to define a possible involvement of the bone (Lombardi et al., 2010).

Bone impairment in multiple autoimmune diseases might be considered not only a complication due to endocrine or nutritional mechanisms, but also a consequence of an immunoregulatory imbalance.

3.4.1 Metabolic causes

Alterations of bone mineral density (BMD) are especially observed when diabetes is associated with CD and/or AIT. Bone loss, described in patients with T1D, AIT or CD is usually viewed as a complication of these diseases and is related to duration of diabetes and quality of metabolic control. The exact mechanisms accounting for bone loss in these diseases have been variably explained by metabolic derangements due to the impaired hormonal function in T1D or AIT (McCabe, 2007), or calcium malabsorption and secondary hyperparathyroidism in untreated CD patients (Selby et al., 1999). Alterations of homeostatic mechanisms might explain an imbalance of osteoclast activity leading to osteopenia (Lombardi et al., 2010; Wu et al., 2008).

3.4.2 Immune causes

Bone remodeling involves complex interactions between osteoclasts and other cells in their microenvironment (marrow stromal cells, osteoblasts, macrophages, T-lymphocytes and marrow cells) (Kollet et al., 2007; Teitelbaum, 2007). Besides their role in calcium mobilization from bone and initiation of bone remodeling, osteoclasts are now considered as the innate immune cells in the bone, since they are able to produce and respond to cytokines and chemokines. Some authors found altered levels of plasma Osteoprotegerin (OPG) in children with T1D. Osteoprotegerin is a circulating secretory glycoprotein and is a member of the tumor necrosis factor receptor (TNFR) family. It works as a decoy receptor for the cytokine receptor activator of NF κ B ligand (RANKL). RANKL and OPG are a key agonist/antagonist cytokine system: RANKL increases the pool of active osteoclasts thus

increasing bone resorption, whereas OPG, which neutralizes RANKL, has the opposite effect. Alterations or abnormalities of the RANKL/OPG system have been implicated in different metabolic bone diseases characterized by increased osteoclast differentiation and activation, and by enhanced bone resorption (Galluzzi et al., 2005). Therefore, bone could be an additional target of immune dysregulation.

Cytotoxic T lymphocyte-associated antigen-4 (CTLA4), a well-known susceptibility gene for autoimmune disorders, might also represent a possible link between immune system and bone. In animal studies CTLA4 expressed on T regulatory (Treg) cells impairs osteoclast formation (Zaiss et al., 2007). Therefore the failure of Treg cell function in clustering of multiple autoimmune diseases could represent a mechanism to explain both the occurrence of poly-reactive autoimmune processes and the increase of bone resorption in the same individuals.

In patients affected by both T1D and CD, the risk of developing osteopenia is probably influenced by the compliance to gluten-free diet. Osteopenia occurs more frequently in patients with diabetes and CD with poor compliance to GFD. Interestingly, recent observations indicate also an imbalance of cytokines relevant to bone metabolism in untreated celiac patients' sera and the direct effect of these sera on *in vitro* bone cell activity. In particular the RANKL/osteoprotegerin (OPG) ratio was increased in patients not on gluten-free diet. Actually, the only presence of a second disease, either AIT or CD, do not seems to increase the frequency of osteopenia, provided a good compliance to GFD in CD patients, while the association of three autoimmune diseases significantly increases the occurrence of osteopenia (37.5%). In addition, poor compliance to GFD of CD patients could increase the occurrence of osteopenia more in patients with three autoimmune diseases (80%) than in those with two autoimmune diseases (18.8%) (Valerio et al., 2008).

3.5 Gastropathy

Gastrointestinal motility disorders are found in a consistent proportion of children with T1D and are associated with significant morbidity: they are usually associated with dyspeptic symptoms, such as nausea, vomiting, fullness and epigastric discomfort, and could be an important cause of morbidity in diabetic patients. Gastroparesis has been shown to be significantly correlated with a poor metabolic control in a population of T1D children with gastric electrical abnormalities. (Cucchiara et al., 1998). Furthermore it is conceivable that delayed gastric emptying may cause a mismatch between the onset of insulin action and the delivery of nutrients into the small intestine (Rayner et al., 2001). Diabetic children with unexplained poor glycemic control should be investigated for abnormalities in gastric motility (Shen & Soffer 2000). On the other hand, hyperglycaemia itself can affect the neuromuscular mechanisms regulating gastrointestinal motility and delay the gastric emptying process (Jebbink et al., 1994). Therefore, it is of great importance to try to reverse abnormalities of gastric motility and improve gastric emptying in patients with T1D and gastroparesis by the use of domperidone in children with T1D. (Franzese et al., 2002b).

3.6 Type 1 diabetes and limited joint mobility

Type 1 diabetes can be associated with other less common disabling conditions of locomotor system: Dupuytren's contracture, stiff hand, carpal tunnel syndrome, and limited joint mobility (LJM). Limited joint mobility is one of the earliest clinically apparent long-term complications of T1D in childhood and adolescence, characterized by a bilateral painless

contracture of the finger joints and large joints, associated with tight waxy skin. Changes begin in the metacarpophalangeal and proximal interphalangeal joints of the fifth finger and extend radially with involvement of the distal interphalangeal joints as well. Involvement of larger joints includes particularly the wrist and elbow, but also ankles and cervical and thoracolumbar spine (Komatsu et al., 2004). The limitation is only mildly disabling even when severe. With rare exception, LJM appears after the age of 10 years. The prevalence of LJM in T1D, evaluated in several studies ranges from 9 to 58% in paediatric and adult patients (Lindsay et al., 2005).

The biochemical basis of LJM may be a consequence of changes in the connective tissue, probably due to alterations in the structural macromolecules of the extracellular matrix. The hyperglycaemia can alterate the glycation of protein with the formation of advanced glycation end products (AGEs), which resist to protein degradation and consequently increase thickness of basal membranes in the periarticular tissues (Shimbargger, 1987). Development of LJM is related to both age and diabetes duration (Cagliero et al., 2002), while others showed that it can be compromised also in a precocious age and with a short duration of diabetes (Komatsu et al., 2004). Of note, fluorescence of skin collagen, which reflects the accumulation of stable AGEs, increases linearly with age, but with abnormal rapidity in T1D and in correlation with the presence of retinopathy, nephropathy and neuropathy (Monnier et al., 1986).

Some authors have showed that there is a clear link between upper limb musculoskeletal abnormalities and poor metabolic control (Ramchurn et al., 2009). It has been observed a reduction in frequency of LJM between the mid-70s and mid-90s in children, most likely due to the improved glucose control during this era (Infante et al., 2001; Lindsay et al., 2005).

3.7 Type 1 diabetes and oedema

Insulin oedema is a well-recognized and extremely rare complication of insulin therapy. It was found to occur equally in both sexes in adults, but a clear female predominance was noted in younger ages. The condition is self-limiting, but a progression to overt cardiac failure and development of pleural effusion has been reported. (Chelliah & Burge, 2004).

The pathophysiology remains vague. Intensive fluid resuscitation in an insulin-deficient catabolic state may lead to extravasation of fluid to the subcutaneous tissue, resulting in peripheral oedema. This may be exacerbated by the increased capillary permeability associated with chronic hyperglycemia. Renal tubular sodium reabsorption is enhanced by insulin therapy via stimulating the Na^+/K^+ -ATPase as well as the expression of Na^+/H^+ exchanger 3 in the proximal tubule. Transient inappropriate hyperaldosteronism has also been suggested to contribute to the fluid retention (Bas et al., 2010). Loss of albumin from the circulation due to increased transcapillary leakage probably contributed to the formation of oedema and the decreased serum albumin, but was not severe enough to account for the magnitude of oedema (Wheatly & Edwards 1985). Cases with normal serum albumin have also been reported.

Clinically, insulin oedema may present with a spectrum of severity until to frank anasarca. Pleural effusions have uncommonly been reported, although some of these patients were elderly and may have had pre-existing cardiac disease. Rarely, the oedema extended from peripheral tissues to serosal cavities with ascites and cardiac failure (Bas et al., 2010). Fluid and salt restriction should be implemented and this may be all that is necessary. Diuretic

therapy may be indicated in more severe decompensated cases. Administration of an aldosterone antagonist such as spironolactone may be considered from a pathophysiological point of view in the presence of inappropriate hyperaldosteronism (Kalambokis et al., 2004). In most instances no specific therapy is needed and spontaneous recovery is noted.

Impaired growth	Poor metabolic control	Monitoring of growth and physical development using growth charts
Eating disorders	Dietary restriction	Ameliorating of nutritional assistance
Necrobiosis lipoidica diabetorum	Parallel dermatopathy	Routine clinical examination of the skin
Osteopenia	Probably even present, but worsened by poor metabolic control/comorbidity	Eventually controlled by Bone ultrasonography/DEXA
Gastropathy	Poor metabolic control	Investigating of dyspeptic symptoms
Limited joint mobility	Parallel condition	Routine clinical examination of the joint mobility
Oedema	Unknown	Clinical examination

Table 3. Non autoimmune associated conditions to Type 1 diabetes, causes and detection

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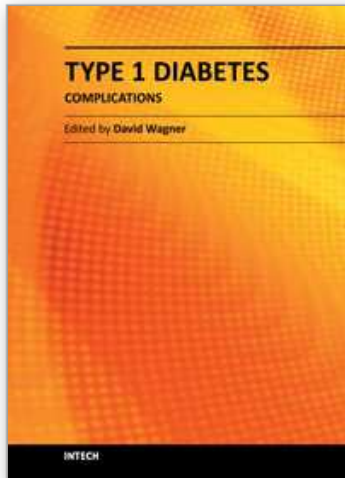
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This book is a compilation of reviews about the complication of Type 1 Diabetes. T1D is a classic autoimmune disease. Genetic factors are clearly determinant but cannot explain the rapid, even overwhelming expanse of this disease. Understanding etiology and pathogenesis of this disease is essential. The complications associated with T1D cover a range of clinical obstacles. A number of experts in the field have covered a range of topics for consideration that are applicable to researcher and clinician alike. This book provides apt descriptions of cutting edge technologies and applications in the ever going search for treatments and cure for diabetes.

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Phone: +86-21-62489820
Fax: +86-21-62489821

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