Introduction

Major depressive disorder (MDD) is highly prevalent among children and adolescents with type 1 diabetes mellitus. The prevalence of MDD among youth with type 1 diabetes (20-27%) is at least two to three times greater than the (5-8%) background rate of MDD reported for non-diabetic youth (**Grey et al., 2002).**

Early-onset MDD is severe, and in combination with diabetes (the third most common chronic disease in childhood), is associated with poorer diabetes control, increased diabetes-related complications, increased frequency of emergency department visitation, hospitalization and greater healthcare costs(**Lawrence et al., 2006)**.

Traditional conceptualization of the increase in MDD prevalence among youth withtype 1 diabetes has relied heavily on the psychologicalburden and non-specific stress of coping with a chronicillness, leading to non-adherence to the diabetes regimen (**Korczak et al., 2011).**

The cause of the association between depressive disordersand inflammatory markers is largely unknown. The relationshipmight be reciprocal. For instance, depressive disorderscan elevate circulating concentrations of IL-6 through

theinfluence of catecholamine release, which in turn stimulatesIL-6 release from adipose tissue.**(Steptoe et al., 2003)**.Alternatively, IL-6 mightcontribute to the development of depressive disorders bystimulating the hypothalamic-pituitary-adrenal axis, whichproduces hormonal products that might cause depression**. (Panagiotakos et al., 2004).**

Cytokines have been implicated in the development of many chronic complications in diabetes mellitus patients, including neurologic and vascular lesions **(Shanmugam et al., 2003).** Chronic hyperglycemia, by inducing the increase of glycated proteins, can stimulate the production of cytokines involved in the activation of the immune system. **(Stentz et al., 2004).**

The pathophysiology of type1 diabetes and MDD suggest plausible mechanismswhereby a biological link between these illnesses mayexist. These include the effects of circulating cytokinesassociated with autoimmune diabetes, the direct impact ofinsulin deficiency on neurogenesis/ neurotransmitter metabolism,the effects of the chronic hyperglycaemic state,the occurrence of iatrogenic hypoglycaemia and the impact of basal hyperactivity of the hypothalamic– pituitary–adrenal axis (**Korczak et al., 2011).**

Aim of the work

The aim is to establish a biochemical relationship between type 1 diabetes mellitus and major depressive disorder.

Type 1 Diabetes

Type 1 diabetes (T1D) is a disorder that arises following the autoimmune destruction of insulin-producing pancreatic beta cells **(Atkinson, 2001).** The disease is most often diagnosed in children and adolescents, usually presenting with a classic triad of symptoms (i.e., polydypsia, polyphagia, polyuria) along- side of overt hyperglycemia, positing the immediate need for exogenous insulin replacement— a medicinal introduction to the disorder whose therapeutic practice lasts a lifetime **(Bluestone et al., 2010).**

These introductory facets having been said, many other etiological and typology-based aspects for this disease remain either unclear or subject to significant debate within the medical research community. Among these are questions related to the percentage of T1D cases that are diagnosed in adults, a figure whose estimates range from a low of 25% to as much as 50% **(Thunandera et al., 2008).**

Indeed, multiple factors contribute to this knowledge void, one being a failure in understanding the percentage of T1D cases that are errantly misclassified as type 2 diabetes (T2D). Specifically, it has been proposed that about 5% – 15% of adults diagnosed with T2D may, in actuality, have T1D **(Palmer et al., 2005).** Were this true, the notion that 90% – 95% of all diabetes cases are diagnosed as T2D would mean that the number of T1D cases is likely far underestimated.

Attempts to distinguish T1D cases from those with T2D have also resulted in a proposed new disease classification, Latent Autoimmune Disease of Adults (LADA) (Leslie et al., 2008). However, over this past decade, the lack of firm diagnostic criteria for LADA, taken together with other notions (e.g., genetic similarity between those with T1D and the so-called LADA patients), have dramatically decreased, but not eliminated, enthusiasm for adopting this presumed "new" disease entity as a novel category for diabetes **(Rolandsson, 2010).** To be clear, such confusion over disease classification in settings of diabetes is not new because many terms (e.g., insulin-requiring diabetes, juvenile diabetes, insulin-dependent diabetes mellitus, etc.) have been used over the years to describe what now referred to as T1D; each term eventually being replaced, to a large extent, as improvements occurred in our understanding of the pathogenesis and natural history of this disease. For T1D, expert panels formed under the auspices of the American Diabetes Association (ADA), as well as the World Health Organization (WHO), were instrumental in defining criteria for the diagnosis of and selecting the terminology for what considered T1D and T2D **(American Diabetes Association, 2010).**

Beyond a lack in understanding the boundaries for age on T1D, another facet subject to considerable debate relates to T1D heterogeneity, both in terms of patient disease course as well as pathogenic mechanisms that underlie the disorder's

formation. As noted above, T1D is considered, with near uniformity, to represent a disorder "autoimmune" in nature—meaning that patients often express features reflective of an immunological contribution to their disease pathogenesis (e.g., autoantibodies, genes associated with immune-related genetic susceptibly, etc.).Yet, not all T1D patients possess these characteristics; leading some to the proposed classification of type 1A (autoimmune) diabetes **(Eisenbarth, 2007)** for the 70% – 90% of T1D patients having these immunological self-reactive properties, with type 1B (i.e., idiopathic) representing the remainder whose specific pathogenesis remains unclear **(Imagawa et al., 2000).**

Other potential factors of influence, either toward the age of T1D disease onset, its heterogeneity, or diagnosis, would include, but not be limited to, the growing problem of obesity (both childhood and adult) and health care provider recognition, as well as an increasingly diverse genetic admixture due to migration and/ or social changes **(Knip et al., 2005).** These examples of influential changes likely reflect a series of additional variables (e.g., pathological studies of pancreata that are suggestive of various patterns of islet histology among supposed T1D patients, alterations in what comprises genetic susceptibility for the disorder) that require consideration when one ponders the pathogenesis as well as the clinical presentation of this disease **(Atkinson, 2012).**

EPIDEMIOLOGY: INCIDENCE AND PREVALENCE

Type 1 diabetes is without question one of the most common chronic diseases of childhood **(Karvonen et al., 2000).** Here too, a variety of epidemiological notions (i.e., dogmas) appear, at least on their surface, firm in their proposition, whereas other concepts are less sure **(Gale, 2005).**

First, it does appear that two peaks of T1D presentation occur in childhood and adolescence—one between 5 and 7 year of age, with the other occurring at or near puberty (Harjutsalo et al., 2008). Beyond this, although many autoimmune disorders disproportionately affect women, T1D appears to affect males and females equally; but controversy does exist whether amodest excess of T1D cases occurs in males in early age or signs of autoimmunity are increased with male gender **(Weets et al., 2001; Krischer et al., 2004).** In addition, the incidence of T1D varies as a function of seasonal changes, higher in autumn and winter and lower in the summer months **(Moltchanova et al., 2009).** The pathogenic mechanisms that underlie these seemingly sure observations are unclear, but, interestingly, some studies assessing the development of T1D-associated autoimmunity (i.e., the formation of autoantibodies characteristic for the disease) in the months to years before the onset of symptomatic T1D also show a degree of synchronization, akin to the aforementioned seasonality, supporting a theoretical role for an environmental agent driving the pathogenesis of the disorder. **(Kukko et al., 2005).**

Less clear to this field of investigation is knowledge related to several variances that occur with respect to the incidence and prevalence of T1D, across both geographic populations as well as within different racial/ethnic groups. To begin, for years, data regarding the incidence and prevalence for T1D were far more predominant from studies performed in Europe rather than in the United States, where such information (in the latter instance) was largely dependent on extrapolation of data obtained from a small and limited number of somewhat localized studies (e.g., Alleghany County Pennsylvania, Colorado Diabetes Registry) rather than whole-country data **(Libman et al., 1998).**

However, this situation has been subject to an improvement with the formation of the SEARCH for Diabetes in Youth Consortium within the United States, a multicenter study whose goals include identifying the number of children under the age of 20 with diabetes (either T1D or T2D), to understand the influence of race/ethnicity on the disease, and to address how T1D and T2D differ in this U.S. population **(Dabelea et al., 2011).**

In addition to this United States–based effort, years ago, at a global level, the WHO formed the Multinational Project for Childhood Diabetes known as the DIAMOND Project, an effort that followed the highly successful and often cited EURODIAB effort **(EURODIAB ACE Study Group 2000; DIAMOND Project Group 2006).**

Among the most significant findings the SEARCH effort has noted thus far, approximately 215,000 youth less than the age of 20 have diabetes (both T1D or T2D), representing ~0.26% of all people within this age group **(Dabelea et al. 2007)**. During 2002–2005, 15,600 youth were diagnosed with T1D annually in the United States. Interestingly, among youth <10 year in age, the rate of new T1D cases was 19.7 per 100,000 each year, whereas for those >10 year of age, the rate was 18.6 cases per 100,000. In terms of ethnicity, SEARCH showed that non-Hispanic whites showed the highest rate of new onset T1D (24.8 per 100,000 per year among those <10 year of age) **(Dabelea et al., 2011).**

At a global level, the incidence and prevalence rates for T1D are exceptionally interesting because they vary quite dramatically, with more than a 350-fold variation in incidence among reporting countries **(Patterson et al., 2009).** Although clear exceptions to this rule exist, it does remain noteworthy that the incidence of T1D is positively related to distance north of the equator (i.e., the so-called North–South Gradient) **(Karvonen et al., 2000).** In terms of extremes, T1D is uncommon in China, India, and Venezuela, where the incidence is only 0.1 per 100,000 per year. In contrast, the disorder is far more common in Finland, with recent incidence rates of more than 60 cases per 100,000 per year being noted, and to a slightly lesser degree, Sardinia, with rates approximating 40 per 100,000 per year. Rates of more than 20 cases per 100,000 per

year are observed in Sweden, Norway, Portugal, Great Britain, Canada, and New Zealand **(Maahs et al., 2010).**

Interestingly, wide variations in incidence have been noted to occur between neighboring areas in both Europe and North America. For example, Estonia, separated from Finland by <75 miles, has a T1D incidence less than one-third that of Finland. Puerto Rico has an incidence similar to the mainland United States (i.e., 17 per 100,000 per year), whereas neighboring Cuba has an incidence of less than three cases per 100,000 per year. The mechanisms underlying these variances are unknown but, have largely been ascribed to the all-encompassing bin of "environment." **(Atkinson, 2012).**

Beyond current rates of T1D frequency, for reasons that remain unknown, the incidence of T1D has apparently been increasing throughout the world, for decades **(Gale, 2002b).** For example, Sweden and Norway have reported a 3.3% annual increase in T1D rates, whereas Finland has observed a 2.4% annual rise in incidence **(Patterson et al., 2009),** and to be clear, like examples exist across the globe. These increases have largely been ascribed to some unknown change in environmental constituents because notions of genetic alterations or improvements in delivery rates of offspring from T1D mothers could not in and of themselves explain these rates of increase **(Soltesz et al. 2007).** After years of reports suggesting increases, at least one country, Sweden, has quite unexpectedly noted that its incidence rates may have reached a

"plateau" **(Berhan et al. 2011).** If confirmed in other populations, this would be cause for optimism because current incidence rates, if they were to continue on their existing path, would suggest a near doubling of T1D cases over the next decade **(Patterson et al. 2009).**

It is also important to note that these increases in incidence rates have not occurred equally across all age groups; that is, the most profound elevations in incidence rates have been observed in the youngest individuals (i.e., those <5 year of age) (DIAMOND Project Group, 2006), as well as in young children from countries with historically high incidence rates (e.g., children <5–7 year of age in Norway). Finally, T1D appears to have seen an increase in populations whose genetic susceptibility for the disease, in previous generations, would have been considered "lower." Put another way, less genetic predisposition to T1D (i.e., class II alleles of the major histocompatibility complex, or MHC) appears to be required in order to develop the disease now, versus decades ago. This notion finds support with at least two studies, one in Europe, the other in the United States **(Steck et al.,2011).**

NATURAL HISTORY OF TYPE 1 DIABETES

Over the past three decades, the ability to understand the natural history of T1D has improved dramatically through the combined use of genetic, autoantibody, and metabolic markers of the disease **(Atkinson, 2005).** Indeed, in the mid-1980s, a

model was developed that attempted to integrate each of these three features. This model for the natural history of T1D suggests that genetically susceptible individuals with a fixed number of β cells are exposed to a putative environmental trigger, which induces β-cell autoimmunity. This process, marked by the development of islet reactive autoantibodies, portends the development of activated autoreactive T cells capable of destroying β cells, resulting in a progressive and predicable loss in insulin secretory function. With this model, clinical (i.e., symptomatic) T1D does not present until >80%–90% of the β cells have been destroyed, and there is a marked gap between the onset of autoimmunity and the onset of diabetes. **(Eisenbarth, 1986).**

Clearly, this model has served the community well over the years, providing a road map for investigations that have transformed the understanding of the natural history for this disease. However, recently, some aspects of the classical model have been modified to update knowledge gains (Fig. 1) **(Atkinson, 2001).**

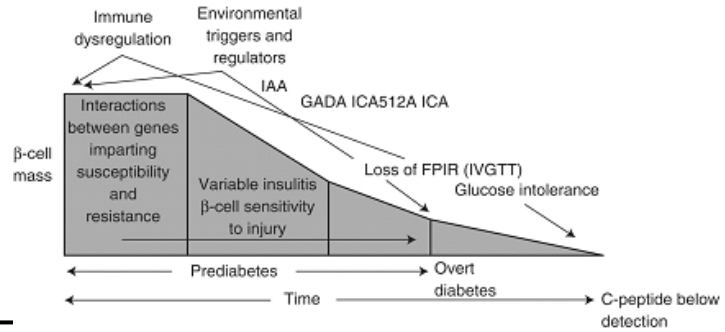

Figure (1): Model of the pathogenesis and natural history of type 1 diabetes. The modern model expands and updates the traditional model by inclusion of information gained through an improved understanding of the roles for genetics, immunology, and environment in the natural history of T1D **(Atkinson and Eisenbarth, 2001).**

For example, there are data to suggest that pancreatic β cells may persist in some individuals with T1D for an extended period of time (i.e., never reaching zero in many established T1D patients) **(Meier et al., 2005).** In addition, the degree of β-cell destruction required for symptomatic onset is also of growing question, with recent studies suggesting that 40%–50% β-cell viability may be present at the onset of hyperglycemia **(Akirav et al., 2008),** an aspect that may be related to subject age, among other factors (e.g., body mass index, physical activity, etc.) **(Matveyenko, 2008).** This may explain why, despite persistent autoimmunity, insulin secretory function can remain stable for long periods of time in persons with T1D. That said, a loss of first-phase insulin response is usually followed by a period of glucose intolerance and a period of clinically "silent" diabetes **(Sosenko et al., 2010).** Finally, the "slope" reflective of β-cell loss in the pre-diabetic period has also recently been subject to considerable debate, with some proposing that the disorder may see its symptomatic onset only following a period of relapsing/remitting like autoimmunity (Fig. 2) **(Von Herrath et al., 2007).**

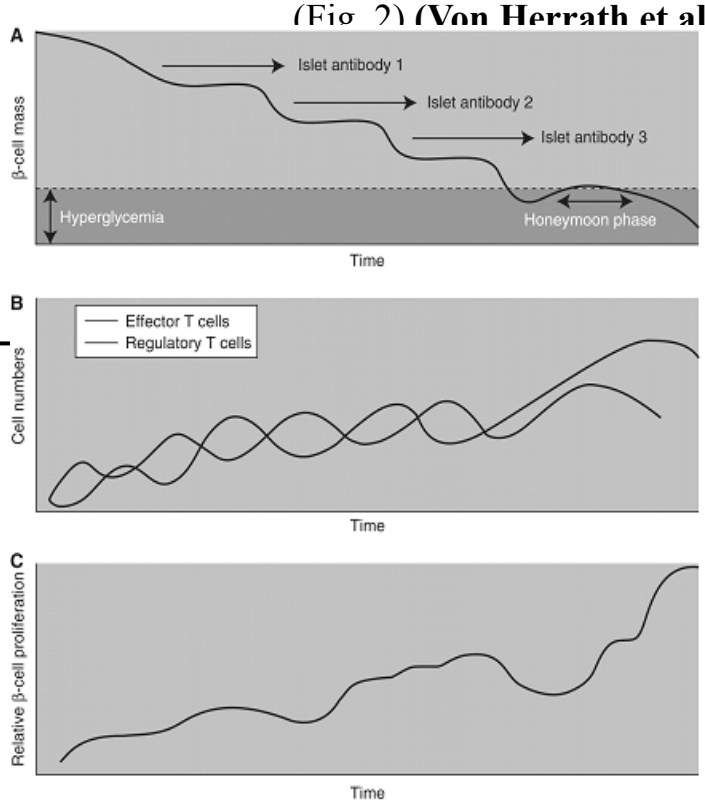

Figure (2): Model for type 1 diabetes as a relapsing-remitting disease. (A) Graph showing the stepwise, nonlinear decline of β-cell mass over time, as well as the development of autoantibodies that are associated with hyperglycemia, that is, the onset of T1D. (B) The immunological response to T1D is cyclic. An increase in the numbers of autoreactive effector T cells is controlled by an increase in the number of regulatory T cells. However, over time, a gradual disequilibrium of the cyclical behavior could occur, leading to the number of autoreactive effector T cells surpassing the number of regulatory T cells, which would no longer be capable of containing autoreactive effector T-cell responses and thereby lead to a decline in pancreatic islet function. (C) β-Cell proliferation increases in a cyclical fashion over time. This figure indirectly depicts the biological trends of the development of T1D, which may be attributed to the cyclical nature of the immunological events that lead to the attack or protection of β cells. Such a phenomenon is usually the result of feedback-loop mechanisms, which, in the case of T1D, could be due to misdirected effector T cells that are not easily controlled by regulatory T cells. The inflammatory process of the pancreatic islets themselves may enhance β-cell proliferation and antigenic presentation, ultimately leading to the generation of more effector and regulatory T cells. In addition, as β-cell mass declines, the pressure on each β-cell to produce insulin increases, which may be sufficient to alter the recognition of β cells by the immune system and to alter their ability to regenerate and increase insulin production **(Von Herrath et al. 2007)**.

An improved understanding of the natural history of pre-diabetes remains critical for directing future studies aimed at the prevention of T1D. Indeed, continued identification of genes controlling disease susceptibility, improved under-standing of autoimmunity/mechanisms underlying loss of

immune regulation, and further identification of environmental agents influencing the disease are all examples of information needed to impact efforts toward the goal of disease prevention; each is discussed below. Likewise, understanding events (e.g., rate of C-peptide loss, the presence of residual β cells, etc.) following symptomatic onset are also of importance because many ongoing efforts are actively seeking to reverse the disorder in those previously diagnosed with the disease **(Atkinson, 2012).**

Genetics

Despite being strongly influenced by genetic factors, T1D does not fit any simple pattern of inheritance and is considered a complex, multifactorial disease **(Noble and Erlich, 2012).** Early familial aggregation and twin studies supported the aforementioned importance for both genetic and environmental risk factors in T1D **(Tattersall, 1972),** because individuals in the United States having a first-degree relative with T1D have an approximately 1 in 20 risk of developing T1D, whereas the general population of the United States have a one in 300 risk **(Redondo et al., 2001).** In addition, monozygotic twins have historically been considered to have a disease concordance rate of 30%–50%, with dizygotic twins having a concordance of 6%–10%. This said, one recent study suggests that were one to follow twins throughout their lifetimes, the percentage reaching concordance for T1D would come exceedingly close to being uniform **(Redondo et al., 2008).** And a strange curiosity remains that 85% of new T1D cases reside in individuals with