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Diabetes Type 1 and 2: What is Behind a Classification?

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1. Introduction

At present, we wonder if the current classification of diabetes agrees with the new advances At the molecular genetic level. Every day we can see an exponential increase of type 1 and 2 diabetes anywhere in the world. On the other hand, although several clinical and biochemical characteristics have been described in order to differentiate between both types of diabetes, this does not seem satisfactory for all cases when facing the patient. These characteristics are: (a) The presence of a strong familiar history of diabetes, obesity, *acanthosis nigricans*, and lack of ketoacidosis and auto-antibodies against antigens of pancreatic b-cells islets supports the diagnosis of type 2 diabetes; (b) In contrast, patients with type 1 diabetes are usually thin and with ketoacidosis; almost 90% of them have auto-antibodies at the onset of the disease.

Nevertheless, in the last decades numerous reports described adults and adolescents (usually from minority groups) presenting ketoacidosis with lack of antibodies and characteristics of type 2 diabetes such as obesity, *acanthosis nigricans* and/or one significant familiar history of diabetes (Pinhas-Hamiel et al., 1997; Pinhas-Hamiel & Zeitler, 1999;).

Until very recently, most children and adolescents diagnosed with the disease were diagnosed as type 1 diabetes; however, there have recently been numerous reports describing an increase in the number of cases of type 2 diabetes in youngsters (Dabelea et al., 1998; Hathout et al., 2001; Neufeld et al., 1998; Pinhas Hamiel et al., 1996; Scott et al., 1997). Epidemiological data suggests that type 1 and 2 diabetes can coexist in the same family (Kolb & Mandrup-Poulsen, 2005; Libman & Becker, 2003).

The potential importance of formulating a specific diagnosis has been emphasized, as this could determine the type of treatment, associated complications, and outcomes (Fagot et al., 2001; Pinhas-Hamiel & Zeitler, 1999). The current criteria for defining diabetes (Asociación Latinoamericana de Diabetes [ALAD], 2010; American Diabetes Association [ADA], 2010) do not always explain neither the evolution of the disease in different patients or the different responses of individuals to treatments. These facts are suggesting the importance

of considering the genetic background of individuals for their categorization and subsequent treatment. A highly controversial topic has recently aroused worldwide: is there a new type of diabetes with mixed characteristics of both types? Different authors have identified this variety as "Double Diabetes" or "Hybrid Diabetes" (Libman & Becker, 2003; Mimbacas et al., 2011; Pozzilli & Buzzetti; 2007; Pozzilli & Guglielmi., 2007); but, are we really facing a new type of diabetes unknown before?, or is it a phenomenon not demonstrated until present due to the use of former inappropriate methodologies or instrumentations? If it is a new expression, why does it appear now? Is there an evolutionary process involved? How?
We will try to discuss these subjects in this chapter.

2. Brief history of diabetes mellitus and the evolution of the classification

In order to understand our point of view we must begin with a brief description of diabetes history and classification. The term diabetes (Greek: διαβητη) was coined by Aretaues of Cappadocia. It is derived from the Greek word διβαινειν, diabaínein that literally means "passing through" or "siphon", a reference to one of diabetes' major symptoms—excessive urine production. In 1675, Thomas Willis added the word mellitus, from the Latin meaning "honey", as a reference to the sweet taste of the urine. Matthew Dobson (1776) confirmed that the sweet taste was due to an excess of a kind of sugar in the urine and blood of people with diabetes. The ancient Indians tested for diabetes by observing whether ants were attracted to a person's urine, and called the ailment "sweet urine disease". The Korean, Chinese, and Japanese words for diabetes are based on the same ideographs (糖尿病), which mean "sugar urine disease".
As stated above, although diabetes has been recognized since antiquity, and treatments of different efficiencies have been known in several regions since the Middle Ages and for much longer in legends, the pathogenesis of diabetes has only been understood experimentally since about 1900 (Patlak, 2002a; 2002b). The endocrine role of the pancreas in metabolism, and indeed the existence of insulin, was not further clarified until 1922, when Banting and Best demonstrated that they could reverse induced diabetes in dogs by giving them a pancreatic islets of Langerhans extract of healthy dogs (Banting et al., 1922). However the precise molecular mechanism of the disease is just beginning to be unraveled. Fortunately, the increasing inventory of human genetic variation is easing our understanding of why susceptibility to the common disease varies between individuals and populations (Rotimi & Jorde, 2010), as we shall see.
In terms of classification, the first distinction between different presentations of the disease, as it is currently known, was clearly established by Sir H P Himsworth, and published in January 1936 (Himsworth, 1936). From its very beginning, the different classifications have undergone changes in the attempt to obtain a better adjustment of the organization of diabetes' nosology (Alberti & Zimmet, 1998): (1) Age, which was the main criterion of the first classification, was quickly abandoned because the different forms can appear at any age, although one is more frequently observed in childhood and youth and the other one in adults (at present, type 1 and 2 respectively); (2) Insulin dependence was the new clinical criterion taken into consideration, because it was easy to use in clinical practice and allowed to consider sub-groups with different pathogenic mechanisms; for several years insulin dependence was an indicator of the auto-immune process.

Currently, the classification of Diabetes mellitus (ADA, 2010; ALAD, 2010) contemplates four well-known major groups: (a) Type 1 Diabetes (T1DM), (b) Type 2 (T2DM), (c) Other specific types of diabetes, and (d) Gestational diabetes.
However, on the basis of clinical observations, genetics and molecular research studies carried out in some mixed populations such as those in Latin America (as we shall see below) would point out that this classification is not always adequate; phenotype does not always reflect genotype (Mimbacas et al., 2009).

3. Miscegenated population

In order to support our hypothesis that phenotype is not always a proper indicator of genotype, mainly in miscegenated populations (particularly in multifactorial diseases such as diabetes), we will focus our analysis on the research carried out in our population. We believe that the current classification does not always allow an accurate diagnosis, and therefore the treatment plan is not always the correct one.
Previous research has shown that the Uruguayan population has a particular genetic behavior; in addition to its small size (three millions inhabitants), it presents such a high level of miscegenation that there are individuals that cannot currently identify their ancestors' origin. It has a tri-hybrid origin (Caucasoid, African and Amerindian) but, unlike other Latin-American countries, we do not isolate Amerindian groups (Cardoso et al., 2004; Gascue et al., 2005; Mimbacas et al., 2003, 2004, 2007, 2009; Sans et al., 2011). Thus, this would permit us to think a priori that ethnological factors would (at least in part) cancel each other, therefore eliminating their possible blurring effect on the analysis. When we consider these factors, we can look at our population as an interesting source of information for the study of different issues on diabetes.
Several years ago, we focused our investigation on HLA genes associated with type 1 diabetes; our studies (Mimbacas et al., 2003, 2004) were done both by case-control and parent-cases design. We found a very high frequency of specific alleles (DQB1*0201, DQB1*0302, DR3, DR4) in our population; although the associated alleles were the same as those of the Caucasian population, their frequencies were different; additionally, we also found that almost all of the patients had associated DR3 and DR4 alleles. Continuing with our investigations, we observed that different polymorphisms of other analyzed genes also showed variations when compared with Caucasian populations or with populations from other origin (Fernández et al., 2009; Mimbacas et al., 2007; Soto et al., 2004; Zorrilla et al., 2006).
Conversely, there have been numerous reports describing an increasing number of type 2 diabetes cases in youngsters (Dabelea et al., 1998; Neufeld et al., 1998; Pinhas-Hamiel et al., 1996; Scott et al., 1997). Recently, Lidman and Becker (2003) described the coexistence of types 1 and 2 diabetes in a non-Caucasian individual; afterwards, Pozzili and Buzzetti (2007) described more cases and defined the possibility of a new type of diabetes, proposing more characterization studies in different ethnic groups. In a recent paper (Mimbacas et al., 2011) we described a case report that, according to our criteria, showed this type of presentation of the disease.
In what it has to do with this possibility of a new expression of diabetes, it is important to determine the influence of the genetic and auto-immune factors underlying the consequent destruction of the beta islets, which would pass unnoticed in a classic phenotype.

In the light of an emerging expression of diabetes, and in an attempt to link genetics to the clinic, we continued with our research. On the basis of previous findings and in the clinical evolution of patients, we began to see that in many cases it was very difficult to classify patients into one of the 2 main groups of the current diabetes classification (type 1 or type 2). Another associated observation was that, despite following the international protocols, patients did not always show a good response to treatment.

Therefore, we were interested in testing the hypothesis that genotype does not necessarily result in the disease phenotype. For this purpose, we proposed to determine whether a genetic profile is useful for providing the clinician and the patient with more accurate information, not only for knowing the specific type of diabetes, but also to understand the hyperglycemia pathogenesis and thus treat it more effectively.

For five years we examined a dynamic cohort of clinical histories of diabetes' patients, with a follow up of 86.6% (Mimbacas et al., 2009). At first, patients were classified into two groups: type 1 diabetes and type 2 diabetes according to the American Diabetes Association criteria (ADA, 2004). We analyzed HLADQB1*/DR in all samples and studied the presence of autoantibodies glutamic acid decarboxylase (GADA) and islet cell (ICA). We found surprising results, specifically in patients diagnosed as type 2 diabetes. When we applied the classification grouping the patients as type 1 and type 2 to our data, we found that the phenotype was not correlated with the expected data in all cases. In order to improve our knowledge of the pathogenesis of hyperglycemia and thus implement a more accurate treatment for the patients, we reclassified our sample according to the presence or absence of the genetic and immunological markers (Figure 1).

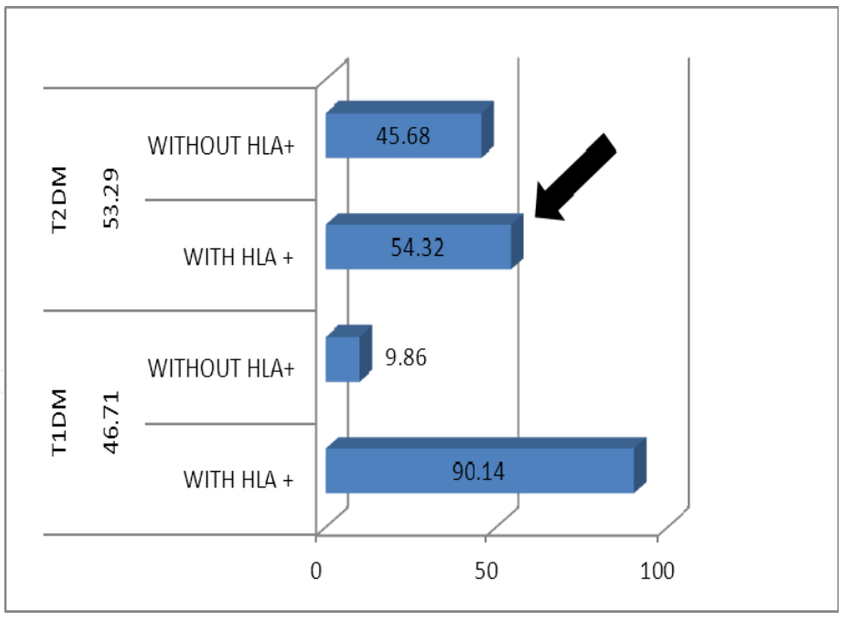

Fig. 1. A high percent of type 2 diabetes have HLA susceptibility gene for type 1 diabetes.

The data obtained shows statistical significant differences, implying that the clinical classification is probably not discriminatory enough for an accurate classification of different types of diabetes (Mimbacas et al., 2009). The methodology implemented in this investigation permitted us to establish that the phenotypic classification did reflect neither the genetic profile nor the immunological disease. The genetic data can help us to provide

an accurate definition of the disease, and would therefore give the physician a better possibility of providing an adequate treatment.

Today, a proper differentiation between the different types of diabetes is becoming an increasingly challenging task. The effect of genetic variables on diabetes has been studied for several decades, but there are only a few consistent risk factors identified up to date.

Most of the large scale studies on candidate genes for diabetes published so far have not performed a combined analysis of both types of diabetes; moreover, there are a high number of published papers dealing with this subject but whose populations are not admixed like the Uruguayan one. Thus, we consider that the Uruguayan population is an interesting one to accomplish epidemiological studies, and that it will therefore contribute to the discussion.

Unfortunately, currently there are a very few researchers using new advanced methodology, such as genome wide association, in non-Caucasian population; nearly 90% of genome scan studies have been carried out in populations of European ancestry (Rotimi & Jorde, 2010).

4. Overweight and obesity mask a genetic profile associated to type 1 diabetes

As stated above, once diabetes diagnosed, proper classification is the first difficulty of this disease in clinical practice, as future treatment will depend on this. This is partly due to a lack of correlation between phenotype and genotype, and to the possible existence of a new form of diabetes, or a different expression, called "hybrid or double". This may pass inadvertently if the corresponding genetic and immunological analyses are not carried out.

Overweight or obesity is one phenotypic trait that is part of the definition of type 2 diabetes. In our study (Mimbacas et al., 2009) we observed that many patients clinically diagnosed as type 2 with positive HLA show overweight or obesity; we therefore suggested looking for a genetic explanation for this apparent contradiction. Overweight or obesity is indicative of insulin-resistance. The primary disorder type 2 diabetes is considered as an insulin-resistant one with an increase in insulin secretion and a decrease in beta cell secretion after several years (Ruiz, 2011).

On the other hand, the importance of a study on insulin resistance lies in the fact that the underlying process would be a cardiovascular risk factor per se (Howard et al., 1996; Yip et al., 1998).

Despite evidence of a genetic influence, bibliography suggests that the genetic contribution to insulin resistance is the result of several gene variants that are relatively common in the population, each one with only a moderate influence, but with much more stronger effects when they interact. The heterogeneous and polygenic nature of insulin resistance has made the identification of these gene variants a challenging task. However, once these insulin-resistance susceptibility gene variants are identified, they will have far-reaching implications for our comprehension of the molecular and pathophysiologic basis of insulin resistance, type 2 diabetes and related clustered traits, and thus for the treatment and prevention of these endemic disorders (Mercado et al., 2002).

From the molecular point of view, Insulin-Resistance is caused by different metabolic pathways with gene-gene and gene-environment interactions. In order to begin our study, we selected some of the genes found within these pathways; the first selected gene was the Peroxisome Proliferator-Activated Receptor (PPARγ2) gene, which is in turn one of the strongest candidate genes contributing to the susceptibility of type 2 diabetes, especially the

Pro12Ala polymorphism (de Dios & Frechtel, 2011). The PPARγ gene is a key regulator of lipid metabolism and energy balance, and it is implicated in the development of insulin resistance and obesity. It is a member of the nuclear hormone receptor family involved in adipocyte differentiation and gene expression regulation, and it is a transcriptional factor involved in adipogenesis and regulation of adipocyte gene expression. PPARγ plays a role in insulin signaling, insulin resistance and the development of type 2 diabetes mellitus (Chawla et al., 1994; Auwerx, 1999; Zhang et al., 2007)

A splice variant of this gene contains a common amino acid polymorphism, Pro12Ala (carrier frequencies 8–20%, depending on the population) that, depending on the cell lines, reduces the ligand-induced activity of the PPARγ protein by 30–50% (Altshuler et al., 2000; Deeb et al., 1998; Hansen et al., 2006). This missense mutation (involving a C to G substitution at nucleotide 34) results in the exchange of a proline for an alanine in position 12 of the PPARγ2 protein (Yen et al., 1997). This polymorphism has been associated with a reduced risk of development of a type 2 diabetes mellitus (Altshuler et al., 2000; Stumvoll et al., 2001). Many studies have suggested that the mechanism of reduction of the risk of type 2 diabetes mellitus by this polymorphism involves enabling greater insulin sensitivity. The Pro12Ala polymorphism produces a PPARγ2 protein with lower transcriptional activity (Deeb et al., 1998; Kang et al., 2005). The Diabetes Prevention Program (DPP) found that the Ala12 allele influences central obesity and that it is associated with the differences seen in the different treatment groups regarding polyunsaturated fatty acid intake (DPP, 2008).

In recent years, research has identified PPARs as pivotal actors in the transcriptional control of the Uncoupling Protein genes (UCP) (Villarroya et al., 2007). Thus we selected this one as a possible second gene responsible for IR. UCP-2 are mitochondrial transporters present in the inner membrane of the mitochondria of several cells (Das & Elbein, 2006; Villaroya et al., 2007). Their main function is the uncoupling of oxidative phosphorylation in the respiratory chain, preventing the formation of ATP from the energy released by substrate oxidation, and promoting its dissipation as heat.

The UCP would be in charge of the so-called adaptive thermogenesis, i.e. the generation or dissipation of heat to certain stimuli, such as overeating, cold and exercise, thus regulating temperature and body weight. Other functions have been described, in the case of UCP-2, that takes part in the regulation of insulin secretion (inhibiting its secretion by lowering the ATP synthesis through uncoupling), in immunity, and decreased oxidative stress. Their presence in different tissues, together with their energy dissipating role, could be crucial in explaining not only the genesis of obesity, but certain co morbidities (diabetes mellitus type 2) and their treatment.

A common polymorphism (-866G/A) has been associated with obesity, insulin secretion, and type 2 diabetes (Bell et al., 2005; Freeman and Cox, 2006). In what it has to do with the genetic-environmental interaction, several evidences indicate a fatty acid-dependent activation of UCP-2. Direct analysis of regulation of the promoter of the UCP-2 gene in muscle cells indicated that PPARγ and their ligands induce promoter activity (Aubert et al., 1997), while PPAR activators induce UCP-2 mRNA expression in brown adipocytes. Adipose tissue contains large amounts of endogenous triglycerides, which are capable of causing the local generation of free fatty acids after lipolysis. PPAR receptors can provide a mechanism for responsiveness of UCP-2 expression to intracellularly-derived fatty acid.

Thus cross-talk between adrenergic regulation of adipose tissue lipolysis and PPAR induction mechanisms of UCP-2 gene expression may occur, especially in response to noradrenergic stimulus in brown adipocytes (Carmona et al., 1998; Villaroya et al., 2007).

With regard to diabetes, the overexpression of PPARγ causes up regulation of UCP-2 expression and suppresses glucose-stimulated insulin secretion (Ito et al., 2004).
However, there are situations where patients can, due to these genes, present the wild type variant and yet remain with their obesity and IR unchanged. Because of this, we selected another gene that may cause IR on the other metabolic pathway: IRS-1.
IRS-1: Genetic variance in the insulin receptor substrate-1 is thought to play a key role in the insulin resistance that characterizes type 2 diabetes. Transfection studies have demonstrated that the most common IRS-1 variant, Arg972, which involves a Gly 224 Arg substitution at codon 972, impairs insulin signaling via the phosphatidylinositol-3 (PI3)-kinase pathway, and in some (but not all) studies this variant has been found with an increased frequency among type 2 diabetic patients (Almind et al., 1993, 1996; Imai et al., 1994; Sesti et al., 2001; Sigal et al., 1996; Zhang et al., 1996). Interestingly, carriers of the Arg972 substitution have been found to have lower fasting insulin and C-peptide levels than noncarriers (Clausen et al., 1995; Stumvoll et al., 2001), suggesting that this IRS-1 variant might also play a role in the secretory capacity of the beta-cells. Indeed, impaired insulin secretion has also been observed in rat insulinoma (RIN) cells overexpressing the Arg972 IRS-1 polymorphism (Porzio et al., 1999), in human islets naturally carrying the variant (Marchetti et al., 2002), and even in normal glucose-tolerant subjects with the Arg972 variant. These observations raise the intriguing hypothesis that genetic defects in the IRS-1/PI3 kinase pathway might also be involved in the inadequate insulin secretion that characterizes type 2 diabetes. More recent studies suggest that the Arg972 IRS-1 variant also plays a role in beta cell survival.
The human Arg972 islets contain a significantly higher number of apoptotic cells than their wild-type counterparts, and they are also resistant to the antiapoptotic effects of insulin (Federici et al., 2003). It has been speculated that apoptosis plays a crucial role in the autoimmune destruction of beta cells characterizing type 1 diabetes (Mathis et al., 2001). An increase in apoptosis might have pathological consequences in diabetes prone individuals, who have an auto-reactive T-cell repertoire that may be activated by the exposed beta-cell antigens. The Arg972 variant of the IRS-1 seems to play a complex role in the pathogenesis of diabetes, affecting both peripheral insulin sensitivity and the functional capacities of the pancreatic beta-cells themselves. In the light of our findings, it is possible to speculate that the same mechanisms —in the presence of a genetically determined predisposition— might also result in, or contribute to, different clinical manifestations of diabetes.
Once we have identified the genes to be analyzed, we decided to test our hypothesis: there are patients with a complex clinical autoimmune disease masked by insulin-resistance which in turn is genetically determined.
The results of our research, although not published yet, were presented in recent meetings in our country and international events as the "1st Latin American Congress: Controversies to Consensus in Diabetes, Obesity and Hypertension [CODHy]" and the "XIV Latin-American Congress of Asociación Latinoamericana de Diabetes [ALAD]" (Fabregat et al., 2010; Farias et al., 2010; Fernández et al., 2010; Mimbacas et al., 2010; Reyes et al., 2010; Souto et al., 2010).
Indeed, all patients tested (presence of HLA and positive susceptibility to type 1 diabetes antibody) with a body mass index >25kg/m^2 and clinical diagnosis of type 2 diabetes were overweight or obese with mutations in one or more of the analyzed genes. Our results indicated that insulin resistance in patients with complex diagnosis may be explained by the occurrence of a mutation in one or more of the analyzed single nucleotide polymorphisms (SNPs).

5. Importance of genetics for the clinician

In the last 15 to 20 years, clinicians have been concerned with grasping the increasing complexity of this disease, with a gradual worldwide increase of its prevalence that has turned it into a pandemic disease. The latest evidence shows that, despite correcting their lifestyle, we cannot always achieve good metabolic control in patients in complex clinical situations.

There is a population, which is probably formed by most of our patients, with clinical features where their phenotype is a good reflection of their genotype; but we are finding with increasingly frequency clinical cases that are difficulty to classify with the current criteria.

In these cases, a high percentage of patients had severe difficulties with their metabolic control. It is precisely here where we need to carry out a proper genetic diagnosis, and eventually an immunologic one, to allow us a broader view of their pathology. Several clinical observations and systematic studies have shown that classical type 1 diabetes, whether in children, late onset in adults, or individuals over 65, can coexist in the same individual with "classic" type 2 diabetes where insulin secretion deficiency and insulin resistance are detected simultaneously (Serrano Rios, 2009). This group of patients is usually referred to a diabetes specialist because the primary care physician cannot decide about or control them. Once reached this stage and after correcting the variables that affect proper metabolic control, such as nutritional plan and regular physical activity, we can see that many of these patients keep having a poor metabolic control. These patients are usually overweight and / or obese with a very erratic response to anti-diabetic drugs alone or in combination, both between them and with insulin.

Complying with the algorithms, we almost always end up giving insulin to our patients, but in many cases this is probably done too late. This was analyzed by many authors that described as final: “therapeutic inertia”. They are usually described as patients with a poor adherence to the treatment plan. Also, on average they start insulin treatment before the classical diabetes type 2 patients.

Thus, we are planning to deepen into genetic typing, in order to see if it may help us to understand the etiopathogenesis of these patients, and why they do not have the expected response to the drug treatment.

As stated above, these patients surprisingly had a genotype that does not agree with their phenotype. This was what allowed us as clinicians to begin to understand these facts and to find an explanation (albeit partial) of the poor outcome of each patient.

What are the issues that the clinician should consider for further study of certain patients?

a. Obese patients showing good response to insulin during intercurrence: many of these patients had an intercurrent disease, and with the temporary insulin treatment they achieved a good control (especially in early stages of diagnosis) that may be explained by an improvement in glucotoxicity and / or moderate insulinopenia. In these patients the insulin will be removed based on these myths: (1) Insulin is "ineffective"; (2) Insulin injection increases cardiovascular diseases and hyperinsulinemia; and (3) Insulin causes weight gain. The reluctance we see in these patients insulin is based on misguided or questionable in view of the genetic results we are finding and the matching clinical trials.
b. Poor response to insulin sensitizers: in particular thiazolidinedione but also biguanides.
c. Poor response to secretagogues: it is usually attributed to glucotoxicity, but how much influence does drug response have?

d. Obese patients without dyslipidemia or other elements of metabolic syndrome.
e. Overweight or obese type 2 diabetes patients with hypoglycemia episodes, especially at night.
f. Type 2 Diabetic patients with microangiopathic complications preceding or concomitant to the macrovascular complications.

Already, Nolan and Murphy (2001) posed an approach to the phenotypic and metabolic characterization of insulin-resistant patients, impaired glucose tolerance, or type 2 diabetes, and the use of glutamic acid decarboxylase antibodies (GADA), genetic markers, and models to estimate the insulin-resistance should be considered. These authors discuss the utility of using genetic markers based on population studies for type 2 diabetes mellitus. In what it has to do with the poor response to treatment, we must remember that both therapeutic inefficiency and drug toxicity, which have been seen in some individuals, have been frequently observed. Due to the presence of some drug metabolizing enzymes, drugs can participate as inhibitors or inducers of these enzymes, thereby their variation in activity between individuals. This variability in enzyme activity may reflect the existence of mutations in their genes.

6. Conclusion: What is happening?

The above mentioned points will lead us to review the different mechanisms that may have taken place in the evolutionary processes leading to the current status of this disease. We will consider some possible situations.

a. Researchers are considering the way natural selection is currently operating in humans. The concept of "the survival of the strongest individual" perhaps is no longer valid in the 21st century. Quintana Murci et al. (2007), at the Pasteur Institute (Paris), have looked for answers regarding the mechanisms of human evolution by comparing whole genomes of different populations. They analyzed more than 2.8 million genetic markers in different populations from different ethnic groups collected in the HAPMAP project. They found that 582 genes were subject to "strong selective pressures" during the last 60,000 to 10,000 years. Some of these genes are strongly associated to external features (e.g.: hair, skin color); others are to the response to pathogenic agents or drugs; and others to diseases with different incidences between populations, like diabetes, obesity, or hypertension. Barreiro pointed out that "it is the first time that it can be demonstrated, concerning the whole genome that natural selection participates in the differentiation of the populations" This work is not only useful to satisfy our curiosity, but also to aid in the identification of genes implied in different diseases (Barreiro et al., 2005; 2008).

Well defined since the XV century, clinical knowledge on diabetes gradually increased, and in the end two major distinct types of this pathology were described (1 and 2). In order to understand the current increase of chronic diseases, it is necessary to consider the important relationship between human feeding and human evolution. The regular offer of food that seemed to help human evolution so greatly in the past is also generating a great amount of diseases and their corresponding incapacities (like hemiplegics, aphasia, amputations, etc.). This fact is a true evolutionary paradox (Insua & Fuks, 2003).

Initially, we must consider the importance of the neutralization of positive selective pressure introduced by the availability of nutrients as consequence of human civilization. A good

example of the relationship between nutritional factors, diabetes, and population genetics is Szathmary's hypothesis (Marrodán, 2000) for explaining the high incidence of diabetes in several Amerindian populations (USA and Canada), either in reservations or in those adapted to western life.

Diabetes is a genetic-based disease whose manifestation is partly favored by excessive carbohydrate consumption. Possibly, several individuals with a specific genotype would produce insulin faster when faced with higher glucose levels than others; and they would also store this glucose as glycogen or fat more efficiently. This genotype would have been positively selected in a nutritional environment where periods of abundant or shortage of foods oscillate in a critical form. But this capacity for a faster answer to carbohydrate stimulus has a biological cost when food intake is constant. Under this situation, genes increasing insulin production are no longer beneficial to the individual because their carriers become obese, exhausting the physiological capacity of the pancreas, and leading to the subsequent development of diabetes (Marrodán, 2000; Harris, 2002). Variations in diabetes or obesity genes imply that adaptation to fasting was also an important selective agent. Quintana-Murci et al. (2007) pointed out that insulin-regulating genes have been positively selected. Thus, for instance, the ENPP1 gene has a mutation protecting against obesity and type II diabetes. This variant is present in 90% of non-African individuals and it is almost absent in African ones.

The susceptible genotype may have been selected in these populations because unusually frequent fasting periods may have taken place during the initial colonization of 'new worlds'. The abovementioned non-insulin dependent diabetes mellitus has shown a strong genetic component that may include a 'thrifty' genotype(s) (Neel 1962; Zimmet et al., 1990).

The 'thrifty' genotype(s) may have once allowed founding populations to survive both 'feast' and 'famine' conditions for several generations. Individuals carrying these genes would have had an increased efficiency for energy extraction (nutrition) from environmental scarce resources. During times of abundance those individuals with this predisposition would store more energy than those lacking it. When the progress of human civilization assured continuous fat-rich and fiber-poor diets, and a sedentary lifestyle, the 'thrifty' genotype(s) became disadvantageous, leading to obesity, increased insulin resistance, beta cell misbalance, and finally diabetes (Wendorf, 1991; 1992).

What was a selective advantage in past environments is currently, for most people in industrialized countries, an undesired condition. The result is obesity, diabetes, and the metabolic syndrome. For many years, diabetes was considered as a lethal or near-fatal disease by death simply by complications or by difficulties in the reproductive stages, both for men and women. More recently —the use of insulin is a landmark in this subject— reproductive problems and some of their related complications have been solved.

In conclusion, evolutionary or Darwinian medicine considers that many contemporary diseases are associated to incompatibility between current human lifestyles and environments, and those under which human biology was shaped. As the observed difference between the incremental rates of both civilization and evolution is so great, most human evolutionary changes took place when our ancestors were gatherer-hunters. Thus, many characteristics and conducts that had adaptive value in the past may currently have non-adaptive value. Medicine has always tried to improve and look for the patient's cure. It really improved people's health, but in this process populational issues that are beyond the epidemiologic point of view were overlooked. This medical conduct may be explained by

the lack of information, or misinterpretation, of the importance of the genetic components of the disease. But this disregarding could be considered also as having iatrogenic elements: we improve the current patient's quality of life, but on the other hand we hamper that of future persons. This process implies the emergence of currently unknown entities. New discoveries have allowed life extension for affected people, with the subsequent appearance of new pathological complications that were not seen before simply because affected individuals passed away before their onset.

b. Are we witnessing a new type of diabetes, called "double o hybrid" by some authors? We believe that the phenomenon we are watching is simply another expression of the multifactorial nature of this disease. When we analyze populations with an ethnic mixture or of different ethnic origins, we begin to get a glimpse of the products of genetic admixture. This leads us to find a higher proportion of problematic patients that are difficult to classify because, when examining their phenotype, they are affected by certain genes that are masked by others. Hence, we can see families where, according to traditional classification, both entities (type 1 and type 2) coexist. This fusion would be associated with a new and intermediate phenotype (Tuomi, 2005). There are a few studies identifying patients where both type of diabetes overlap (Libman &. Becker, 2003; Pozzilli & Guglielmi, 2009); moreover, Pozzilli and Gugliemi (2007) place this entity in the middle of the double "rainbow" (made up of type 1 and type 2 diabetes).

The "accelerator hypothesis" is a theory that shares this vision. It is a singular, unifying concept, which states that type 1 and type 2 diabetes are the same insulin-resistance disorder set against different genetic backgrounds. This hypothesis does not deny the role of autoimmunity, only its primacy in the process. It distinguishes type 1 and 2 diabetes only by tempo, the faster tempo reflecting the (inevitably) earlier presentation in the more susceptible genotype (Wilkin, 2009).

Recognition that susceptibility arises through the combination of multiple genetic pathways influencing hazardous factors in a nonlinear manner suggests that a 'decanalization' process contributes to the epidemic nature of common genetic diseases. The evolution of the human genome, combined with a marked environmental and cultural perturbation in the past two generations, might lead to the uncovering of cryptic genetic variations that are a major source of disease susceptibility (Gibson, 2009).

This would be also favored by others processes such as an increase of life expectancy and fertility of affected individuals, the globalization phenomena, and increased admixture of different ethnic groups when compared with the past. The last phenomenon is clearly seen in Latin America and mainly in the Uruguayan population as it was stated above.

Regardless of all the arguments presented in this chapter, we think that it is extremely important to introduce the genetic risk profile into the present diabetes classification criteria. This will clearly improve our capability of distinguishing between different types of diabetes or specific presentations.

The effects of genetic traits in diabetes had been studied for decades, but few consistent risk factors have been well established. Currently, most of large scale studies on candidate genes do not combine the analysis of both types of diabetes. Establishing the association between genotype and phenotype would allow a deeper insight into the pathogenesis of the disease. Screening of associated anomalies and the possibility of anticipating future outcomes would be consequently improved.

While for many countries, especially in Latin-America, individual genetic diagnosis can be very expensive to implement, we must realize that we are facing a multifactorial disease.

Thus, although classifications may be useful, they only have relative value. We must keep an open mind to the fact that there are patients that do not fall in any of them, and we must remember that genetics is at the base of diabetes, as there are multiple genes that interact both with the environment and between them. These interactions can result in a somewhat "liar" phenotype. In the preceding sections we saw how mutations in a few genes associated to insulin resistance may mask the presence and/or action of genes causing autoimmune disorders. Moreover, if we take into account the modifications observed with genome scanning, where there are millions of Single Nucleotide Polymorphisms, it is virtually impossible to make a phenotype-based classification.

Although we are aware that understanding the pathogenesis of hyperglycemia or the basis for an effective treatment may be deemed as more important than knowing the type of diabetes we are dealing with, we are currently persuaded that the distinguishing between different types or presentation forms of diabetes based on genetic information is an important task that has turned into our great challenge.

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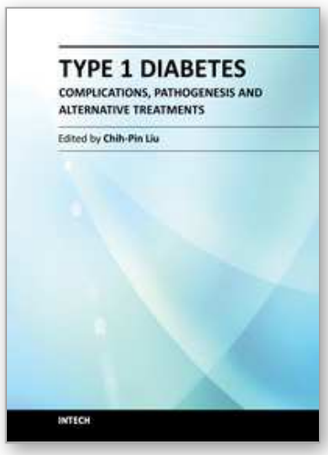

Type 1 Diabetes - Complications, Pathogenesis, and Alternative Treatments

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This book is intended as an overview of recent progress in type 1 diabetes research worldwide, with a focus on different research areas relevant to this disease. These include: diabetes mellitus and complications, psychological aspects of diabetes, perspectives of diabetes pathogenesis, identification and monitoring of diabetes mellitus, and alternative treatments for diabetes. In preparing this book, leading investigators from several countries in these five different categories were invited to contribute a chapter to this book. We have striven for a coherent presentation of concepts based on experiments and observation from the authors own research and from existing published reports. Therefore, the materials presented in this book are expected to be up to date in each research area. While there is no doubt that this book may have omitted some important findings in diabetes field, we hope the information included in this book will be useful for both basic science and clinical investigators. We also hope that diabetes patients and their family will benefit from reading the chapters in this book.

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