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Genetics of Endothelial Damage Associated to Diabetes Mellitus Type 2

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1. Introduction

Diabetes mellitus (DM) is a serious worldwide public health problem due to its frequency, chronic complications and their high associated costs. This disease is considered a multifactorial pathology that involves insulin resistance and is associated to obesity, dyslipidemia, endothelial dysfunction, inflammation and hypertension (Petersen & Shulman, 2006). Type 2 diabetes (DM2) is one of the most common diseases in the developed world and is recognized now as a global burden (van Dieren et al., 2010). Released in 2000, the initial edition of the Diabetes Atlas estimated the global prevalence of this disease at 4.6%, representing 151 million people, and projected an increase to 333 million people by 2025. On the basis of the most recent evidence, the current Diabetes Atlas has predicted that the number of people with diabetes will have risen to a staggering 438 million or 7.8% of the world`s population in 2030 (Colagiuri, 2010; www.diabetesatlas.org).
The development of DM2 requires the involvement of genetic and environmental factors such as android obesity and sedentary lifestyle that determine hyposecretion of insulin in response to glucose stimulation and a decreased insulin action in peripheral tissues. Most of the complications associated to DM2 are related to pathophysiological alterations of the vascular endothelium, and are the main cause of morbidity and mortality among DM patients. Endothelial dysfunction is the initial event that predisposes the vascular wall to diverse alterations leading to the establishment of so-called cardiovascular complications of diabetes. Known risk factors of diabetic complications such as hyperglycemia, hypertension and dyslipidemia stimulate the production of reactive oxygen species (ROS) in the vascular wall. Hyperglycemia is now considered a key causal factor in the development of chronic complications of diabetes (Giuliano et al., 2008).
The vascular endothelium consists of endothelial cells and is a type of monostratified squamous epithelium that lines the inner surface of all blood vessels including the heart. Its crucial role is to regulate the vascular tone and it also has a structural function. In addition, the vascular endothelium normally inhibits platelet and leukocyte adhesion to the vascular surface and maintains a balance between profibrinolytic and prothrombotic activities

(Sandoo et al., 2010). Under physiological conditions a balance between endothelium-derived relaxing and contracting factors exists, which is altered in diabetes and atherosclerosis, contributing to the progression of vascular damage (Tabit et al., 2010). Endothelial cells, such as capillaries in the glomerulus and renal mesangial cells are more vulnerable to sustained hyperglycemia since they lack the ability to rapidly reduce glucose transport into the cell (Kaiser et al., 1993).

Several routes have been described that are related to vascular damage induced by unregulated blood glucose, such as i) the increased activity of the polyol pathway, causing accumulation of sorbitol and fructose in endothelial cells, ii) the formation of advanced glycation end products (AGE), activation of protein kinase C (PKC) and of the transcription factor NFκB, iii) an increased hexosamine pathway flux, iv) increased oxidative stress, mainly due to an overproduction of superoxide anions by the mitochondrial electron transport chain and v) the increase of inflammatory processes through induction of cytokine secretion by monocytes and adipocytes (Giugliano et al., 2008; Aronson, 2008).

In several cases, vascular damage due to oxidative stress induced by hyperglycemia and / or inadequate metabolic control is not sufficient to explain the severity of micro- and macroangiopathic complications and mortality observed in DM2 patients. Here we review the pathophysiology of diabetic macro- and microangiopathic complications and the impact of genetic variants of several candidate genes that may explain the higher morbility and mortality of these patients.

2. Diabetic complications

Chronic complications of DM type 1 (DM1) and DM2 are basically the same. Many studies indicate that there are genetic factors associated to the development of chronic complications of DM and that these factors differ from those involved in the development of diabetes. In this work we will analyze the importance of genetic variants of genes associated to an increased risk of vascular damage in DM.

In both DM1 and DM2 the most common macrovascular complications are cardiovascular disease (CVD), cerebral vascular and peripheral vascular disease. In diabetic microangiopathy, hyperglycemia induces biochemical and molecular changes in microvascular cells that ultimately progress to retinal, renal and neural complications and extends to other complications, including advanced periodontal disease (Roy et al., 2010). It is known that already from initial stages (glucose intolerance) the patient is under an important risk of chronic complications, mainly macrovascular coronary damage and also microvascular complications, where retinopathies, neuropathies and diabetic nephropathy (DN) are the most frequent and devastating.

2.1 The genetic factor in the chronic complications of DM

Factors involved in the etiology of DM2 are different from those that lead to chronic complications. Not all diabetic patients will develop complications or with the same severity. Prospective studies suggest that hyperglycemia and hypertension are important, but not sufficient for the development of chronic complications, requiring genetic susceptibility. As has been suggested, genetic variants exist that could explain these differences. We will analyze the importance of genetic variants of genes associated to an increased risk of vascular damage in DM, with a special emphasis on the endothelial isoform of nitric oxide synthase (NOS) superoxide dismutase (SOD), catalase and aldose reductase, among others.

Single nucleotide polymorphisms (SNPs) are small genetic changes or variations of a single base found in the sequence of DNA and are defined as polymorphisms when they are present at 1% or more within a population. Most of these are not in coding sequences, since only 3 to 5% of the human DNA sequence encodes proteins. Within a gene, SNPs can be located in promoter regions, exons, introns or untranslated (5'UTR and 3'UTR) regions (Figure 1). The frequency of each SNP is highly variable between different populations within a single species. There are an estimated 5 to 10 million SNPs in the human genome and each SNP is named with a specific code (NCBI, http://www.ncbi.nlm.nih.gov/snp). The discovery of relevant polymorphisms is complicated by the sheer number of SNPs encountered in genes and in non-coding sequences. During the first years, association studies usually started tackling non-synonymous SNPs, i.e. SNPs that change one amino acid to a different one. Later, polymorphisms that modulate mRNA processing started gaining importance, since at least 15% of point mutations are related to human genetic disease caused by RNA splicing defects (Wang et al., 2005). The disproportionate effort invested in studying SNPs which turned out to be neutral or irrelevant to the disease, lead to the development of specialized algorithms designed to select significant SNPs (bioinformatic analysis). Although there are millions of SNPs deposited in public SNP databases, only a small proportion of these are functional polymorphisms that contribute to disease phenotypes. Thus, prioritizing SNPs based on their phenotypic risks is essential for association studies. Yuan et al. (2006) designed a decision tree for prioritizing a SNP based on its functional effects, according to 13 phenotypic risks and putative functional effects, such as changes at the transcriptional level, pre-mRNA splicing and protein structure.

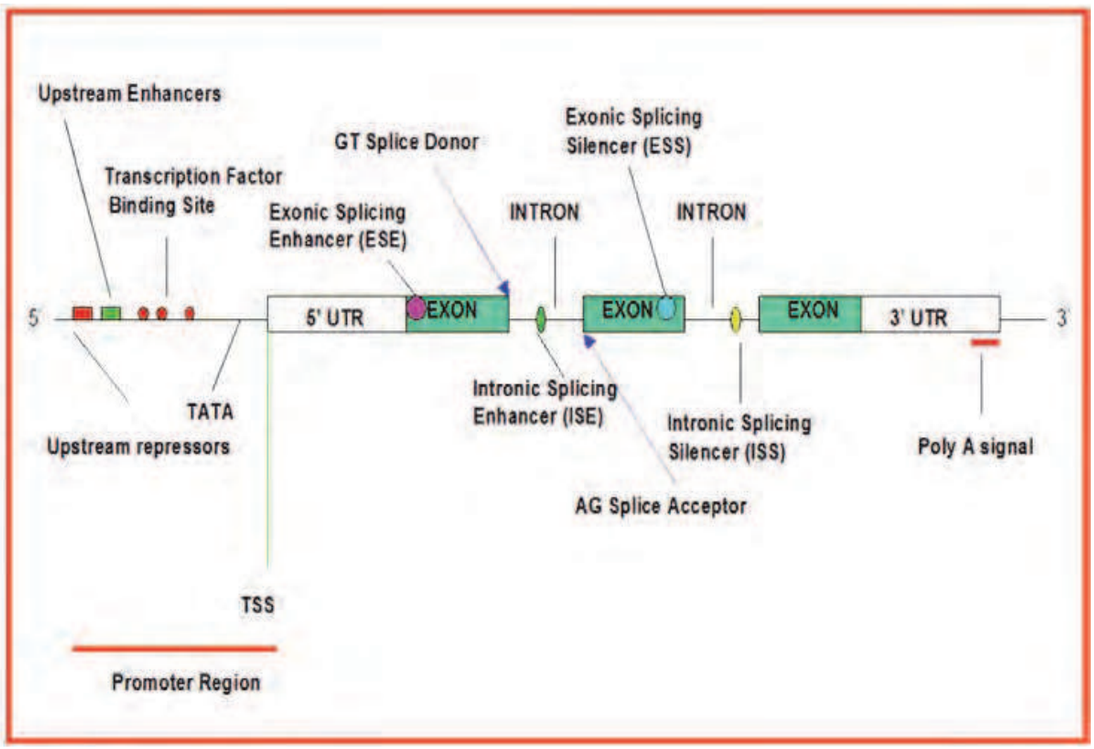

Fig. 1. General structure of a prototype mammalian gene (taken from A. Chattopadhyay, Ph.D., Genetic Variation Resources, Health Science Library System, U. of Pittsburgh, USA).

Missense mutations or non-synonymous polymorphisms may alter protein structure, however apparently silent polymorphisms and point mutations in introns or untranslated regions that do not seem to affect protein structure, can also alter gene function (Kimchi-Sarfaty et al., 2007). For instance, mutations affecting mRNA processing can be located in introns (but also in exons), resulting in exon skipping or creating new splice sites (Baralle & Baralle, 2005). Therefore it is clearly of interest to examine polymorphisms that might appear neutral for translation, but which may alter sequences inactivating regulatory elements that participate in mRNA processing.

2.2 Macroangiopathic complications

DM is preceded by glucose intolerance (pre-diabetes), in which there are already pronounced macrovascular complications. The increase in cardiovascular risk includes coronary heart disease (CHD), stroke and peripheral artery disease. The severity of these complications is significantly greater than the risk observed in the non-diabetic population and corresponds to the first cause of mortality in diabetic patients. In the past 40 years coronary mortality in the general population has decreased, but to a lesser extent in diabetic patients.

The frequency of CHD in diabetics is directly related to the prevalence of the disease in the general population, high in certain ethnic groups and low in others (Japan and China), which relates to its genetic basis. Environmental influences are also important, since the frequency of the disease increases when low-risk individuals are transferred to areas of high prevalence.

Coronary artery disease is the leading cause of death in both DM1 and DM2, hyperglycemia being directly a risk factor for mortality. There is evidence of a direct positive correlation between plasma glucose levels expressed as glycated hemoglobin (HbA1c) and the prevalence and incidence of CVD (Stettler et al., 2006). In DM2 patients the risk is increased even before the appearance of diabetes, in the pre-diabetic state and during the prior period of insulin resistance. These stages are characterized by the presence of a number of other cardiovascular risk factors, such as hypertension, central obesity, atherogenic dyslipidemia, pro-inflammatory and pro-thrombotic states, along with an increase of oxidative stress. All these elements are part of the Metabolic Syndrome (Hunt et al., 2004) and may contribute to the frequent presence of macroangiopathy in DM2 at diagnosis (Stratter et al., 2000). Most studies report a frequency of CHD between 2 and 4 times higher than the general population. The famous Framingham study found that diabetes doubled the risk of CHD in men and tripled in women. Even after correction for age, the risk remained significantly higher after adjusting for all other classical factors such as hypertension, smoking, dyslipidemia and left ventricular hypertrophy (Kannel & McGee, 1979). All the above have led to the inclusion of DM as an independent risk factor. Diabetes and myocardial infarction are similarly strong predictors of total mortality in men. Higher mortality from noncardiovascular causes is observed in those with diabetes only, whereas prior myocardial infarction is more strongly predictive of coronary mortality than diabetes at any age and level of cardiovascular risk factors. The difference in coronary mortality is most evident in the first 10 years of follow-up (Vaccaro et al., 2004). DM in women eliminates the relative protection compared with men before the onset of CHD. Also, high risk determinants occur 15 years earlier in the life of DM individuals compared to control subjects without DM. All the above data and results of prospective studies, such as the San Antonio Heart Study that compared non-DM individuals who had suffered a myocardial infarction and DM patients without previous myocardial infarction, showed that mortality from CHD and non-fatal

heart attacks in DM patients without CHD was similar to that of non-DM individuals with a previous myocardial infarction (Haffner et al., 1998). This led to consider DM as a CHD equivalent. Further data have weakened this statement and have considered that the diagnosis of DM is not equivalent to coronary disease, unless when added to other cardiovascular risk factors (Pignone et al., 2010; ADA, 2011). In DM1, the situation is even more serious, as mortality from CHD at age 55 is between 4 to 8 times higher than for the non-diabetic population (Nathan et al., 2009). In time overall CVD mortality has declined between 24-28% since 1975 in the USA, and has stabilized since 1990, but remains the leading cause of death. There is still an unfavourable difference in black males compared to white males and women, and also in diabetics *versus* non-DM individuals (López et al., 2006). This can be attributed in part to genetic factors.

The influence of cardiovascular risk factors can also be assessed by measuring the effect of treatment of the each particular risk factor and its impact on cardiovascular morbidity and mortality. In this regard, the increased and continued control of glycemia has shown to reduce these parameters in the long term, with strong evidence in DM1 (Nathan et al., 2009) and less evidently in DM2 (Patel et al., 2008; Turnbull et al., 2009).

To summarize, diabetes is an independent risk factor for (CVD), which in some cases is similar to the risk of a previous myocardial infarct. Also, diabetic women suffer loss of their natural gender pre- menopausal protection. Treatment of diabetes and its associated risks improves morbidity and mortality, but is unable to reach normal population levels. Incidence of myocardial infarction and mortality for this cause is decreasing for the general population, but to a lesser extent for diabetic patients.

New biochemical markers of endothelial damage are being investigated as early signals indicating appearance of this macroangiopathic damage, such as cystatin C, high sensitive C-reactive protein (hsCRP), adiponectin and IL-6. Cystatin C is a non-glycosylated protein produced by nucleated cells and functions as an endogenous inhibitor of cysteine proteases and lysosomal proteinases. Patients with increased cystatin C are at a higher risk of developing both CVD and chronic kidney disease and increased concentrations of cystatin C appear to be indicative of preclinical kidney disease associated with adverse outcomes (Taglieri et al., 2009). There is consensus that serum cystatin C is a good marker of impaired renal function. It has been shown that serum levels of cystatin C are a better indicator of incipient DN in patients with DM2 than serum creatinine and creatinine clearance. Cystatin C would provide more information than other parameters of renal function in risk stratification of morbidity and mortality in patients with acute coronary syndrome (García, 2009).

The association of cystatin C with long-term mortality appears stronger than would be expected for the glomerular filtration rate, so a hypothesis has emerged that it could be linked to mortality, independently of renal function (Stevens & Levey, 2005). It has also been postulated to have a predictor character of cardiovascular damage in diabetic patients (Shlipak et al., 2006). We have shown that cystatin C levels are significantly higher in DM2 patients with cardiovascular damage; coronary condition was assessed using extensive MIBI-dipyridamole procedures (Table 1). Diabetics with coronary artery disease have higher levels of cystatin C, which are closely correlated with serum creatinine levels (Wolff et al., 2009). Studies in progress have found that cystatin C levels are significantly different in groups of low and medium risk according to the cardiovascular Framingham scale adapted to the Chilean population (Villalón, 2011).

Cystatin C (mg/ml)			
Patients	**Media**	**Range**	
Controls	0.68	0.55 – 0.75	**p < 0.0001**
DM2-non coronary	0.81	0.71 – 1.08	
DM2-coronary	1.50	0.89 – 2.19	**p < 0.0001**

Table 1. Serum cystatin C values per group (Wolff et al., 2009).

hsCRP is an acute phase protein synthesized by the liver and also by macrophages, and is usually not found in plasma. It is deposited at inflammatory processes, such as at the intima of arteries, at sites of atherogenesis. For several years hsCRP has been used as a marker of inflammation, since it is useful for detecting acute inflammatory processes. More sensitive methods can detect low levels of hsCRP which are needed for the prediction of cardiovascular risk. Blood hsCRP levels may be decreased due to anti-inflammatory treatment or the use of statins and increase in patients with chronic inflammation (Shlipak et al., 2006).

Adiponectin corresponds to 0.01% of total plasma proteins. Its concentration varies between 5 and 10 mg/ml, and women have higher levels than men (Waki et al., 2003). Adiponectin is a protein hormone of 247 amino acids (30 kDa), synthesized in adipocytes (Scherer et al., 1995). Circulating levels of adiponectin are inversely proportional to body mass index (BMI) and the percentage of body fat; its levels are reduced in obesity, DM2 and coronary disease (Weyer et al., 2001). Adiponectin is a hormone with antiatherogenic, anti-inflammatory and anti-diabetic functions. Low adiponectin levels constitute a marker of insulin resistance and increased risk of DM2 (Lorensatti et al., 1999). Adiponectin has been proposed as a marker in the prevention and evolution of vascular disease (Weyer et al., 2001), however adiponectin values show a high degree of dispersion, making the measurement of adiponectin unreliable for individual evaluation of the cardiovascular risk in DM2 patients (Wolff et al., 2009).

Variants in the adiponectin gene have been suggested to contribute to the risk of DM2 and circulating levels of adiponectin In fact, genome-wide scans have mapped a susceptibility locus of the metabolic syndrome and DM2 to chromosome 3q27, where the adiponectin gene is located. Subsequently, several SNPs and haplotypes of the adiponectin gene have been associated with insulin resistance, DM2 and hypoadiponectinemia. No association of the SNP 45 or SNP 276 of the adiponectin gene with adiponectin level or other metabolic variables was found (Salmenniemi et al., 2005), although other authors suggest a significant role of adiponectin gene variants at the same positions in the development of insulin resistance in healthy Greek women (Melistas et al., 2009). Adiponectin levels are high in cases of DN (Jaziri et al., 2010). In two recent studies (DIABHYCAR and SURDIAGENE), the −11391A and +45G alleles were associated with a higher incidence of renal events (Jaziri et al., 2010). Medium- (MMW) and low-molecular weight (LMW) isoforms of adiponectin were more abundant in cases with renal events, indicating that in subjects with DM2 and early renal dysfunction, adiponectin gene variants are determinants of renal risk. The −11391A and +45G alleles may affect renal risk by leading to high circulating adiponectin concentrations, at least those of MMW and LMW isoforms (Jaziri et al., 2010). Also, a promoter polymorphism (-11377C/G) of the adiponectin gene is associated with DN in female DM1 patients (Zhang et al., 2010).

Adiponectin (μg/ml)			
Patients	**Media**	**Range**	
Controls	9.5	5.5 – 14.1	
DM2-non coronary	8.4	1.4 - 15.1	**NS**
DM2-coronary	6.7	2.6 – 15.4	**NS**

Table 2. Serum adiponectin values per group. (Wolff et al., 2009). NS: Not significant.

IL-6 is relevant to many disease processes such as diabetes (Kristiansen & Mandrup-Poulsen et al., 2005). IL-6 is an interleukin that acts both as a pro-inflammatory and anti-inflammatory cytokine. It is secreted by T cells and macrophages to stimulate the immune response to tissue damage leading to inflammation. Smooth muscle cells in the tunica media of many blood vessels also produce IL-6 as a pro-inflammatory cytokine. IL-6's role as an anti-inflammatory cytokine is mediated through its inhibitory effects on TNF-alpha and IL-1, and activation of IL-1 and IL-10. Elevated plasma IL-6 concentrations are observed in obese, as opposed to non-obese, DM2 patients. Elevated plasma IL-6 concentrations are attributed to the prevalence of obesity and not necessarily associated with DM2 (Hansen et al., 2010).

2.3 Microangiophatic complications

2.3.1 Diabetic Retinopathy (DR)

DR is the leading cause of blindness worldwide. The Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR))(Klein et al., 1989) showed that DR prevalence is over 70% in DM1 patients (with diagnosis of DM under 30 years of age) and 39% in patients diagnosed when over 30 years of age (mainly DM2). The frequency of DR is of 82% in patients with 20 or more years of DM. A variable percentage of DR is already present at DM2 diagnosis (Stratton et al., 2000). It is the most glycemic-control-related diabetic complication, and therefore the diagnosis of DR and glucose levels are the criteria used for diagnosis of diabetes. Both in DM1 and DM2 it has been proved that intensified glycemic control can prevent the development and progression of DR (LeClaire et al., 2006). The general use of more intensive treatment in recent decades has been associated with better prognosis in developed countries like Sweden, Finland and the USA, with a range of 32 - 59% prevalence of DR at 10 years of DM1 debut and a decrease of the extreme forms of DR (Vallance et al., 2008). A similar behavior has occurred in DM2 (Humphrey et al., 1994). Readers are referred to recent reviews on this topic (Jackson & Barber, 2010; Ockrim & Yorston, 2010).

2.3.2 Diabetic neuropathy

Diabetic microvascular pathology comprises a variety of debilitating neuropathies; all of them seem related to the hyperglycemic state (Nassar et al., 2007) for extended periods. This complication is present in 8% of patients at the time of diagnosis and increases to 50% after 20 years of DM; the total prevalence of diabetic neuropathy is between 28 and 34% (Jadzinsky, 2003). This neuropathy can be very painful and is invalidating, as it causes diabetic foot. It develops as a consequence of vascular and metabolic factors which lead to endoneural hypoxia and decreased blood circulation. An association of diabetic neuropathy

with glucose control in both DM1 and DM2 has been proved, as well as the beneficial effect of intensified treatment, as shown in the Diabetes Control Complications Trial (DCCT) and United Kingdom Prospective Diabetes Study (UKPDS) (Nathan et al., 2009; Stratton et al., 2000). The trend of recent years has been favorable, despite the fact that the risk of amputation of lower extremities remains significantly higher than in the general population (11% at 25 years after diagnosis) (Bojstig et al., 1994). The neuropathies developing in patients with diabetes are known to be heterogeneous by their symptoms, pattern of neurologic involvement, course, risk covariates, pathologic alterations and underlying mechanisms. An update on classification, definitions, diagnostic criteria, and treatments of diabetic neuropathies has been published recently (Tesfaye et al., 2010).

2.3.3 Diabetic Nephropathy (DN)

This complication is also a frequent microangiopathic complication of DM, occurring in 20-40% of patients after 10 years of natural evolution. Despite current treatments, 20% of DM2 patients develop renal failure. DN is the leading cause of End Stage Renal Disease (ESRD), chronic hemodialysis and renal transplantation worldwide. Before the intensified treatment approach, 25 to 45% of DM1 patients had diabetic kidney disease (DKD) and the majority of them progressed to ESRD. This situation has improved significantly in recent decades, as the cumulative incidence of DKD at 20 years of diagnosis has dropped to 8.9% and 2% of ESRD, according to the monitoring studies of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) studies. In DM2 patients a significant decrease in the incident of DKD in the Caucasian population in the USA has been recently observed, with a decrease from 32 to 15 x1000 patient /year in the cohorts of 1991-1994 and 1999-2002, respectively (Nathan et al., 2009). This improvement may be explained by the intensified glucose control (DCCT, UKPDS) (Adler et al., 2003) and by early screening, more aggressive management of other risk factors such as hypertension, the use of inhibitors of the angiotensin converting enzyme (IACE) and of hypolipidemic drugs. However, disparities still exist despite these improvements, as African-Americans, Mexican-Americans and Pima Indians present 3-6 times higher frequencies of DKD and ESRD than Caucasian populations. Specifically, Pima Indians have a very high prevalence of DKD (50%) and ESRD (15%) at 20 years of follow-up (Pavkov et al., 2006). Some of the differences may be attributed to social and economic factors, but genetic and ethnic factors cannot be out ruled (Cowie et al., 1989; Adler, 2004; Brancati et al., 1992).

2.3.4 Periodontal Disease (PD)

PD is a chronic infection of the gums which is characterized by a loss of attachment between the tooth and the jawbone. PD affects the general population; however it is more frequent in obese, pre-diabetic and diabetic individuals. Its treatment might permit better metabolic control and should be implemented in the routine care of diabetic patients. Chronic periodontitis is a highly prevalent inflammatory disease, associated with bacterial infection and characterized by attachment loss, alveolar bone loss, periodontal pockets and gingival inflammation, all of which can lead to tooth loss, without the proper treatment.

Reports from populations in the USA indicate that subjects with DM present increased prevalence, extent, severity and progression of PD with increased risk of alveolar bone loss and are positively associated with attachment loss (Grossi et al., 1994). Conversely, periodontitis predicts the development of both overt nephropathy and ESRD in an American-Indian population with DM2 (Shultis et al., 2007). PD in Central and South

America exhibits a prevalence of nearly 35% (Gjermo et al., 2002). In Chile, a recent study showed that the adult population showed a high prevalence and extension of clinical attachment loss (>6 mm) in adult populations (69% in seniors and 38% in younger subjects). Age, sex (male), education level and smoking were the main risk indicators of severe clinical attachment loss in this population (Gamonal et al., 2010). In a sample of 66 DM2 subjects (55.6±9.3 years of age from Santiago, Chile), we found a frequency of periodontitis of 92%, compared with 75% in a sample of 91 non-diabetic subjects (43.0±14.3 years of age) (V. Araya, et al., manuscript submitted).

Periodontitis is a complex disease and both genetic and environmental factors are involved. Environmental factors play an important role in the expression of periodontitis. These factors include oral hygiene / bacterial plaque, smoking and stress that may exacerbate the inflammatory pathology associated with periodontitis. Since diabetes is a proinflammatory state, increased levels of circulating cytokines suggest a causal role for inflammation in its etiology (López et al., 2009). The activation of the broad axis of innate immunity through up-regulation of proinflammatory cytokines from monocytes and polymorphonuclear leucocytes includes IL-1β, IL-6, IL-8, tumour necrosis factor alpha (TNF-α) and prostaglandin E_2. In diabetic subjects, inappropriate secretion of these cytokines, in terms of either type or quantity, characterizes a dysregulated immune response that leads to the destruction of periodontal tissues in the presence of some Gram-negative bacteria that form biofilm complexes adhering to the tooth surface (Araya et al., 2003; Nassar et al., 2007; Nishimura et al., 2007). The formation of AGEs that bind to AGE receptors on critical target cell surfaces lead to over-secretion of these inflammatory mediators (Mealey, 2006).

As for other inflammatory diseases, nitric oxide (NO) could play a role in the pathophysiology of periodontitis and the presence of inducible NOS (iNOS) in healthy and inflamed human gingival tissue has been demonstrated. On the other hand, the expression of iNOS in gingival tissues and its increase following some dental proceedings have been demonstrated. Moreover, it has been stated that lipopolysaccharide induced macrophages express iNOS (Pan et al., 2010). eNOS mediated NO production is also involved in critical processes relevant to periodontal disease pathogenesis, including inhibition of cyclooxygenase, regulation of osteoblast activity, prevention of the leukocyte adhesion and superoxide anion release from leukocytes, and suppressing T-cell proliferation (Uğar-Cankal & Ozmeric, 2006).

Several studies indicate that different SNPs of specific genes could be associated with diverse forms of periodontitis in different populations. These include the genes that affect the expression of IL-1, IL-6, TNF-α, IL-10, and eNOS; some of these have been evaluated in diabetic subjects. In Chilean type 1 diabetic subjects with and without aggressive periodontitis the TNF-α SNP at position –308 was assessed, but no association between this SNP and periodontitis was found (Pérez et al., 2004). In a different Chilean population, no significant differences in IL-1A -899, -1B +3954, or -1RN genotype frequencies were found between patients with diabetes and patients without diabetes (López et al., 2009). Interestingly, however, periodontitis was significantly associated with some specific IL-1 gene polymorphisms, such as the IL-1A -889 TT, IL-1B +3954 TT and IL-1B -511 CC genotypes (López et al., 2009).

Periodontitis is also a known risk factor for CVD. One study in Pima Indians with DM2, periodontitis was a strong predictor of mortality, isquemic heart disease and DN. The effect of PD is another factor in addition to traditional risk factors for these diseases (Saremi et al.,

2005). There is also emerging evidence of an independent association between periodontitis and the development of DKD (Shultis et al., 2007).

The inflammatory nature of periodontitis can affect metabolic control of diabetes. Several studies in diabetic subjects with periodontitis have shown an improvement of HbA1c (0.9 – 1% decrease) after conventional periodontal treatment with or without the addition of antibiotics; however, many of these changes were not statistically significant (Darre et al., 2008; Taylor & Borgnakke, 2008). In our study, 12 DM2 subjects with severe periodontitis were selected for periodontal treatment. These patients continued without modifications in their antidiabetic therapy. A non-significant decrease in the mean HbAlc (from 8.8±0.7% to 8.0±0.6%) after 6 months of periodontal treatment was found (Araya et al., manuscript submitted). These results are comparable to those described by other authors. Nevertheless, periodontal treatment could have a similar effect of decreasing HbA1c as other glucose lowering therapies. Therefore, although periodontal treatment appears to be less important in improving metabolic control of DM, a significant improvement of periodontitis in these clinical aspects determines a better quality of life in these patients.

To summarize, microangiopathic complications of diabetes lead to various associated complex and invalidating diseases, which severely compromise the specific tissues. Traditionally, diabetic nephropathy, neuropathy and retinopathy were considered the main complications, but recently, PD is being considered an additional diabetic complication, which determines a decreased quality of life of diabetic patients.

2.4 The contribution of specific genes to diabetic complications

2.4.1 Nephrin

The gene for nephrin was initially identified as the gene responsible for congenital nephrotic syndrome of Finnish type, in which individuals suffer massive proteinuria *in utero* and nephrosis at birth severe (Beltcheva et al., 2001). The protein (nephrin) has 1241 amino acids and is a cell adhesion protein of the immunoglobulin family that is expressed in the kidney, but also in the pancreas and the central nervous system (Beltcheva et al., 2003). Nephrin is the central structural and signaling molecule in the slit diaphragm of the kidney (Hauser et al., 2009). Conditions of endothelial injury, such as preeclampsia, hypertension, diabetes and high fat diet were found to induce a loss of nephrin (Hauser et al., 2009). Its extracellular domain plays a fundamental structural role in podocytes, interacting with various proteins such as podocin (Kestilä et al., 1998). These findings indicate that podocyte physiology is strongly linked to vascular endothelial cells via molecular signaling. As podocytes are non-proliferating terminally differentiated cells, apoptosis of podocytes leads to a reduction in nephrin (Hauser et al., 2009). Nephrin in the pancreas is found at the plasma membrane and on insulin vesicles and its expression is decreased in islets from diabetic patients when compared with nondiabetic control subjects (Fornoni et al., 2010). These results suggest that nephrin is an active component of the insulin vesicle machinery that may affect vesicle-actin interaction and mobilization to the plasma membrane (Fornoni et al., 2010).

Nephrin is a good indicator of both of genetic and acquired renal disease and animal studies have shown that nephrin loss causes proteinuria (Pätäri-Sampo et al., 2006). In fact, a decrease in nephrin mRNA correlates with the presence of proteinuria in renal biopsies of patients with DM2 (Toyoda et al., 2004). More important still, in DM1 patients with DN, nephrin appears in the urine, proving an association between the presence of this protein in the urine (nefrinuria) and kidney damage. Normal controls have no nefrinuria (Pätäri et al., 2003).

Over 300 polymorphisms in the nephrin gene *(NPHS1)* gene have been described. The Finn-Diane Study 3 examined non-synonymous SNPs (E117K, R408Q and N1077) in the *NPHS1* gene in Finnish patients with DM1 without finding association between these variants and DN (Pettersson-Fernholm et al., 2003). Another study found several polymorphisms in a Japanese population, specifically in exon 3 (C294T), exon 17 (C2289T) and intron 5 (-61C/G) of the nephrin gene to be associated with DM2 (Daimon et al., 2006).

We analyzed Chilean patients with diabetes type 1 and type 2, to determine if the frequency of an intronic SNP (rs466452, located in intron 24) of the nephrin gene differs in diabetic patients and control individuals, since bioinformatic analysis suggested that this genetic variant could produce alterations in the processing of the nephrin transcript. No association was found with the degree of renal damage (normo, micro and macroalbuminuric diabetic patients), either in DM1 or DM2 patients, as the distribution of genotypes was not significantly different between these groups. The molecular analysis of nephrin transcripts obtained from a renal biopsy of a patient with DM2 however indicated that no change in splicing of this gene had occurred (González et al., 2009). Results of this study strongly advocate the importance of validating results obtained from bioinformatic analysis.

In another study we identified purine-rich GAGA boxes in the nephrin gene promoter, which Kennedy and Rutter (1992) described as important transcriptional regulation elements of insulin expression. We conducted a genomic study of 100 individuals in Chile, in search of the presence of polymorphisms in this element and its possible association with DN in DM2 patients. Sequence analysis of 20 healthy individuals, 20 patients with non-diabetic nephropathies, 20 non-diabetic subjects with coronary disease, 20 normoalbuminuric DM2 patients without coronary disease and 19 macroalbuminuric DM2 patients with coronary disease, indicated that the GAGA elements did not present polymorphisms, suggesting a lower level of heterogeneity than surrounding regions (González et al., 2007).

To summarize, in association to chronic diabetic complications, polymorphisms studied in the nephrin gene include genetic variants present in the promoter (GAGA boxes), coding (E117K, C294T, R408Q and N1077) and non-coding regions (intron 24), do not differ in the frequency found in control subjects and diabetic patients with nephropathy.

2.4.2 eNOS

NO is a major mediator in vascular biology, regulating regional blood flow and blood pressure. Changes in NO production and of the enzymes that synthesize NO may contribute contribute to the aetiology of vascular pathologies (Bruckdorfer, 2005). NO is an important cellular signaling molecule and in DM, over-production of NO might play a role in the development of DN, while reduced NO production may be related to the development of DR and diabetic neuropathy, where VEGF (vascular endothelial growth factor) levels are increased in a counter-regulatory manner. NO is an endogenous vasodilator involved in inflammatory and autoimmune response, and in the pathophysiology of diabetic vascular disease. There are three isoenzymes of NOS that catalyze the production of NO from L-arginine: endothelial NOS (eNOS encoded by the gene *NOS3*), neuronal NOS (nNOS, gene *NOS1*) and the inducible isoform (iNOS encoded by *NOS2*). In this section, greater attention will be focused on eNOS, considering its relevance to angiopathies. Studies have provided evidence for altered NO metabolism and impaired endothelial function in diabetes, probably due to polymorphisms in the eNOS gene (Channon & Guzik, 2002).

The enzyme eNOS is essential for the vasodilation control in physiological conditions, producing NO which reacts with free radicals. Any anomalies in the function of this enzyme will alter physiological levels of vascular NO. It is known that vascular damage has a genetic component, and the search of polymorphisms of the gene that codifies for eNOS and its metabolites (nitrite, nitrate and oxidized proteins) would allow identifying individuals with a greater risk of presenting vascular damage.
Several eNOS polymorphisms have been studied in different populations, analyzing their association to vascular damage, such as Glu298Asp and T-786C in the regulatory region of the *NOS3* gene. We analyzed two eNOS polymorphisms in groups of DM2 patients and nondiabetic controls, one SNP corresponding to rs6947833 which changes Cysteine 991 to Serine and the SNP rs891512 in intron 23 which changes G at position 24943 to A. Our results suggest that these SNPs are not associated with DM2 (Seelenfreund et al., unpublished results).

eNOS genotype	type 2 diabetic patients	control subjects
Number	93.0	76.0
GG (%)	74.2	75.0
GA (%)	22.5	18.4
AA (%)	3.3	6.6
Allele frequency		
G (%)	85.5	84.2
A (%)	14.5	15.8

Table 3. Genotype frequencies (%) and allele distribution at the rs891512 polymorphism according to study groups. Differences in genotype and allelic frequencies were not significant for any group.

2.4.3 Antioxidant enzymes: Superoxide dismutase (SOD) and catalase

Chronic extracelular hyperglycemia in diabetes stimulates ROS production and increased oxidative stress plays an important role in the development of diabetic complications (Brownlee, 2005). Hyperglycemia-induced ROS activate many pathways of diabetic tissue damage, including production of superoxide anions by the mitochondrial electron transport chain. As a result of the high glucose levels inside diabetic cells, more donors (NADPH and $FADH_2$) are produced and increases in electron transfer occur, thereby generating superoxide. The excess of ROS production in the diabetic cell (superoxide, hydrogen peroxide and reactive nitrogen species such as NO) oxidize proteins, nucleic acids and membrane lipids and thereby damage cellular structure and function (Shi et al., 2009).
SOD, catalase and glutathione-S-transferases are enzymes that protect against the damage caused by oxidative stress by scavenging free radicals. SOD and catalase directly eliminate ROS. SOD, which catalyzes the dismutation of the superoxide anion into hydrogen peroxide and molecular oxygen, is one of the most important antioxidant enzymes. SOD enzymes are classified into three groups: cytosolic CuZn-SOD, mitochondrial Mn-SOD, and extracellular Ec-SOD (Zelko et al., 2002). Catalase is present as a dumbbell-shaped tetramer of four identical subunits in peroxisomes and removes hydrogen peroxide molecules that are by-products of the SOD reaction (Goyal & Basak, 2010).

Most enzymes involved in defense mechanisms against oxidative stress are polymorphic (Wang et al., 2007). Studies evaluating the association of polymorphic markers in genes encoding antioxidant enzymes regulate the production of ROS. A case-control study indicated that homozygosity for the SOD2 rs4880 Val allele is associated with an increased risk of DN, thus supporting the hypothesis that oxidative stress contributes to this severe long-term complication in diabetic patients (Môllsten et al., 2007). Other studies showed that oxidative stress in DM1 and DM2 can be accelerated not only due to increased ROS production caused by hyperglycemia, but also by the reduced ability of the antioxidant defense system caused at least partly by deleterious SNPs of some scavenger enzymes (Flekac et al., 2008). The presence of the TT (Val/Val) homozygous genotype of the SOD2 gene was associated with poorer diabetes control in comparison with CT (Ala/Val) and CC (Ala/Ala) genotypes. Observed macroangiopathy was associated with significantly lower frequency of the C (Ala) allele of Ala16Val SNP of the SOD2 gene. No differences in genotype frequencies were associated with microangiopathy (Flekac et al., 2008). However, Lee et al. (2006) suggest that this Ala16Val SNP of the SOD2 gene is not related to the pathogenesis of diabetes, but correlates with microangiophathy expressed as microalbuminuria. Other authors found a statistically significant association of the MnSOD Ala16Val polymorphism with DR in a Finnish population (Kangas-Kontio et al., 2010).

Several polymorphisms of the gene coding for catalase have been studied, however in alleles of SNPs located in the promoter region (-21A/T) no statistically significant differences between DM2 patients and controls were found (Flekac et al., 2008). The -262C/T polymorphism in the promoter of catalase gene has also been analyzed in Caucasian-Brazilians with DM2, but no association with DR, DN and ischemic heart disease was found (dos Santos, 2006). Only a weak association was detected between the C111T SNP in exon 9 and a decrease in catalase activity in blood of DM2 patients (Tarnai et al., 2007). These results suggest that genetic variants of the catalase gene do not seem to be involved in the development of vascular complications of DM2.

2.4.4 Aldose reductase

The aldose reductase gene (ALR2) codes for an enzyme involved in glucose-induced pathways and catalyzes the reduction of carbonyl-containing compounds to their respective alcohols. In a two-step metabolic process, the polyol-pathway reduces excess glucose to sorbitol and fructose in insulin-independent tissues (Alexiou et al., 2009). ALR2 is a key regulator, as it is the first and rate-limiting enzyme of the polyol pathway catalyzing the NADPH-dependent reduction of glucose to sorbitol, which is subsequently converted to fructose by sorbitol deshidrogenase, using NAD+ as a co-factor. Both ALR2 and sorbitol deshidrogenase are expressed in human tissues that are sites of diabetic complications and are active when intracelular glucose concentration is elevated. The activation of the polyol pathway produces osmotic stress and oxidative stress, from the accumulation of sorbitol and leads to diabetic lesions in these tissues (Chung et al., 2003; Ramasamy & Goldberg, 2010).

The functional ALR2 gene consists of 10 exons and is located on chromosome 7q35 (Wang et al., 1993). In a 8-year prospective case-control study the association of the z-2 allele of the 5'-(CA)(n) microsatellite and C-106T promoter polymorphisms of the aldose reductase gene with DN in Chinese DM2 patients was assessed. In this cohort, these polymorphisms

independently predicted new onset of renal and cardiorenal end points, with the latter being largely mediated through renal disease. Compared with noncarriers, patients with two risk-confering genotypes had a twofold increased risk of renal and cardiorenal end points (So et al., 2008).

In other studies, the association of these polymorphisms with the risk of albuminuria and retinopathy were analyzed in a Finish population. The C-106T polymorphism of the ALR2 gene was related to the early development of microalbuminuria, but not DR (Sivenius et al., 2004a). However, it has also been reported that the C-106T polymorphism may contribute to an early development of neurophysiologic deterioration in DM2 patients (Sivenius et al., 2004b). In Japanese DM2 patients, the C-106T variant was also associated with diabetic macroangiopathy, were the CT or TT genotype showed association with increased risk of stroke (Watarai et al., 2006).

2.4.5 Other genes

Polymorphisms of several other candidate genes may also be related to the susceptibility of patients to develop complications. For example, cyclooxigenase, which has an important role mediating inflammatory processes in periodontal tissues, appears as a candidate gene related to the development of PD. Two polymorphisms (rs20417 and rs689466) of the COX-2 gene, which codes for the cyclooxygenase enzyme, have been reported to be associated with periodontitis (Schaefer et al., 2010).

Polymorphisms in adhesion molecules have also been reported, such as the K469E polymorphism of the intracellular adhesion molecule 1 (ICAM-1) gene, which is associated with proliferative DR in Caucasian DM2 patients (Petrovic et al., 2008), while the 469KK genotype could be a genetic risk factor for DR (Kamiuchi et al., 2002). ICAM-1 is mainly expressed in endothelial cells and is implicated in the recruitment of leukocytes, especially macrophages in inflammatory situations (Muller, 2011). In spite of the fact that ICAM-1 has a fundamental role in the inflammatory process, is not clear whether this molecule is simply a marker of the inflammatory process or might actually play a causative role in the resultant organ dysfunction.

VEGF appears to play a central role, since it mediates microvascular pathology of DR. VEGF induces early alterations of DR, such as leucotaxis and may be operative in the pathogenesis of diabetic blood–retinal barrier breakdown. At the cellular level, blood–retinal barrier breakdown is associated with endocytic vesicle formation and, to a lesser extent, degenerative endothelial changes (Qaum et al., 2001). In DM1 or DM2 patients with DR, diabetic controls without DR and non-diabetic controls, VEGF SNPs rs699947, rs2010963, rs2146232, rs3025033, rs3025039 gene were genotyped, but no association was found (Kangas-Kontio et al., 2009). Other studies on the -634C/G SNP of the VEGF gene found no association with DR (Yang et al., 2010), however these results are controversial (Zhao & Zhao, 2010). A study of the 936 C/T polymorphism of the VEGF gene in a Korean population suggested that this genetic variant may be an important factor determining plasma VEGF levels and is related with DR, since a higher frequency of the TT genotype was observed in patients with proliferative DR. Additionally, plasma levels of VEGF were significantly higher in the TT genotype. There was no difference in VEGF genotype distribution between the control and diabetic patients based on the state of diabetic neuropathy and DN (Kim et al., 2009).

2.4.6 Genome wide association studies

The classical methods of linkage analysis have been useful to identify loci with strong effects; however they are of limited use for discovering genetic variants with a modest impact on complex diseases. Association studies of candidate genes have also been useful, but they are necessarily biased, since they are based on prior knowledge. In addition, they only rely on coding regions and disregard the possible effect of intergenic sequences.

During the last decade, the completion of the Human Genome Project and the development of high throughput technologies have spurted novel strategies termed Genome Wide Association Studies (GWAS), which allow the unbiased analysis of millions of SNPs in very large cohorts. GWAS of DM2 have lead already to the discovery of over 30 SNPs associated with the development of this disease and more than 20 SNPs associated with glycemic traits (Billings & Florez, 2010; Bonnefond et al., 2010). Until recently, the search for genetic determinants of diabetic complications was also constrained to a small number of candidate genes selected on the basis of their postulated role in cellular pathways linking glucose to tissue damage (Doria, 2010). Current initiatives have centered on kidney disease and cardiovascular disease, but not specifically associated to diabetes (Doria, 2010). Recent reports promise the first results of GWA studies of macroangiopathic diabetic complications (Bowden et al., 2010). To date no GWAS data are available for diabetic retinopathy (Doria, 2010). In the near future, GWAS will generate a large output of valuable information of many novel genetic variants related to the development of micro- and macroangiopathic complications. It is expected that this knowledge will provide unprecedented insights on the pathogenesis of diabetic complications (Doria, 2010).

3. Conclusion

Diabetic complications are an important factor contributing to the high morbility and mortality among diabetic patients. It is well known that genetic factors contribute to the appearance and development of these chronic micro- and macroangiopathic complications, but environmental factors usually trigger their appearance. Among these factors, as a product of hyperglicemia, ROS generate endothelial damage. Several genes have been identified, however research related to the contribution of each gene remains controversial and the importance of different genetic variants to the development of diabetic complications is a field of active research were definite conclusions have not yet been established. Figure 2 shows the main genes contributing to the development of diabetic complications. Although there is a prolific literature on polymorphisms of genes involved in vascular damage, clear results are still lacking and more research is needed in order to define the importance of genetic variants and their incidence in disease outcome. In the next years, most probably the use of GWA studies will identify new susceptibility markers related to diabetic complications.

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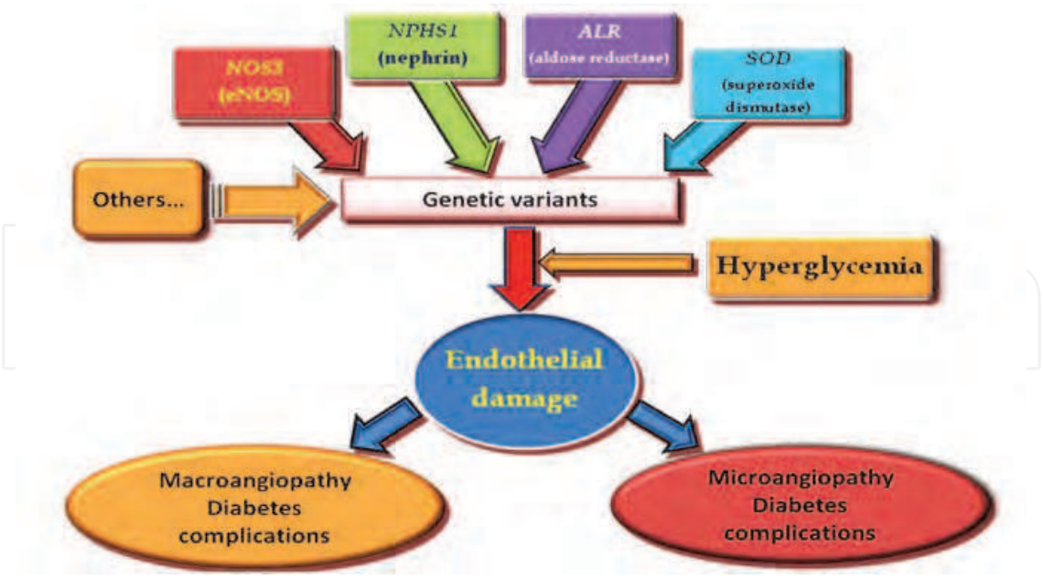

Fig. 2. General overview of genes involved in the development of diabetes complications.

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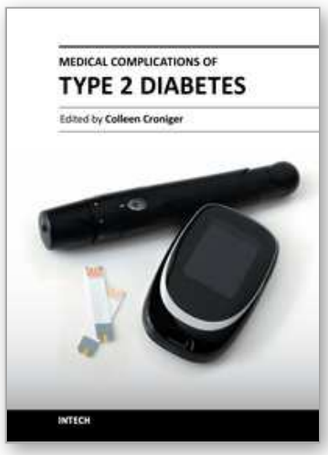

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Obesity and type 2 diabetes are increasing worldwide problems. In this book we reviewed insulin secretion in both healthy individuals and in patients with type 2 diabetes. Because of the risk associated with progression from insulin resistance to diabetes and cardiovascular complications increases along a continuum, we included several chapters on the damage of endothelial cells in type 2 diabetes and genetic influences on endothelial cell dysfunction. Cardiovascular complications occur at a much lower glucose levels, thus a review on the oral glucose tolerance test compared to other methods was included. The medical conditions associated with type 2 diabetes such as pancreatic cancer, sarcopenia and sleep disordered breathing with diabetes were also discussed. The book concludes with several chapters on the treatments for this disease offering us hope in prevention and successful alleviation of the co-morbidities associated with obesity and type 2 diabetes.

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