Abstract
The relationship between diabetes mellitus and depression is not always recognized. About one third of the patients with diabetes have some degree of depression, which favours a poor metabolic control. On the other hand, late complications of diabetes further aggravate depression.
Depression can increase up to 37% the risk for developing type 2 diabetes mellitus when compared to non-depressed subjects. Even when there is not an identifiable etiopathologic factor, changes in different hormonal systems (cortisol, insulin, growth hormone, etc.), neurotransmitters (serotonin), and the activated autonomous nervous system play a relevant role.
Treatment must be adjusted according to guidelines established for each entity present to achieve complete well-being of the person.

Introducción
In the past few years, it has been recognized an interaction between diabetes mellitus and depression. Even being two separate entities, they have an intimate relationship over their natural history. Prevalence studies have shown that depression favours the development of diabetes mellitus, and that a high percentage of people with diabetes usually suffer from depression as well. That is why we have decided to make an analysis of the existing evidence that relate diabetes mellitus and depression, answering the following questions:

1) Is there an association between diabetes and depression?
In the United States, about 7% of the population, or 20 million people, have diabetes. Depression affects 10% of the adult population, and women have a twofold higher prevalence of depression than men. One-third of people having diabetes are undiagnosed and therefore untreated. This is also a problem in depression. In a meta-analysis of 42 published studies including 21,351 adults, the prevalence of major depression in people having diabetes was 11 % and the prevalence of clinically relevant depression was 31%.1
Overall, studies have shown that individuals with depression are more than twice as likely to have diabetes as individuals without depression. Furthermore,
there are indications that depressive states are more common in diabetes than in other diseases with comparable physical and psychological suffering.\(^2\)

Although this is the first and simplest question of this paper, its answer is not conclusive. The definitions and methods of diagnosis for both depression and diabetes are different among studies. There is a paucity of well-conducted and well-powered prospective and rigorously designed studies as was recognized in November of 2002 by The Depression and Bipolar Support Alliance.\(^3\) Five years later, the continued lack of data and clear awareness of the problem of diabetes and depression in the medical and scientific communities is one of the reasons for this work.

2) **How serious is the co-morbidity of diabetes and depression?**

The burden of co-morbid depression on patients with diabetes is profound. There is strong evidence that the coexistence of diabetes and depression is associated with poor diabetes outcomes. The impact of diabetes on depression outcomes has received little attention. In a large meta-analysis that included individual who had type 1 or type 2 diabetes, depression was associated significantly with poor control.\(^4\) Patients having diabetes with co-morbid depression suffer increased morbidity, mortality, and health care costs, and decreased work productivity and quality of life.\(^5\) Unsurprisingly, much of this morbidity and mortality is related to cardiovascular disease. Adoption of appropriate self-care behaviors (regular exercise, dietary intake, home blood glucose monitoring, etc) is an integral part of good diabetes care, yet very difficult for the depressed person with diabetes to do.\(^5\)

We are not aware of any consensus conference or position statement by the ADA alone or in cooperation with any of the psychiatric associations focusing on the problem of diabetes and depression.

3) **What is the temporal relationship between diabetes and depression?**

Depression is often regarded as a co-morbid condition that results from the daily burden of having diabetes and its complication. However, it appears that the reality is different.

A meta-analysis of nine longitudinal studies suggested that adults with depression have a 37% increase in risk of developing type 2 diabetes compared with those who are not depressed.\(^6\) In some of these studies, the risk persisted even after adjusting for body weight, BMI, physical activity, family history of diabetes, socioeconomic status, and education\(^7\) and is stronger in females.\(^8\) Thus, depression appears to be an independent risk factor for diabetes similar in magnitude to the combined risk of smoking and lack of exercise.

The metabolic syndrome and obesity are both risk factors for the development of diabetes. In a longitudinal study women with a history of major depressive episodes were twice as likely to have the metabolic syndrome compared with those having no history of depression.\(^9,10\) The relationship between depression and the metabolic syndrome remained after controlling for age, race, education, smoking, physical inactivity, carbohydrate consumption and alcohol use. Interestingly, men with a history of depression were not significantly more likely to develop the metabolic syndrome.\(^9\)

The association between obesity and depression is well recognized.\(^10\) However, most studies do not show conclusively whether obesity leads to depression or vice versa. It is almost certain that the association works in both directions. However, data from three longitudinal studies including more than 10000 subjects indicate that depression in childhood and adolescence may lead to adolescence or adult obesity.\(^11\)

Furthermore, the National Longitudinal Alcohol Epidemiology Survey found that, among subjects age 18 or older, a BMI of 30 or greater was positively associated with past depression only in women.\(^12\)

Thus, it appears that depression is a predictor of obesity, the metabolic syndrome, and diabetes. However, recognizing the heterogeneity of these conditions, it is possible that those processes can be bidirectional.

4) **Is there a mechanistic link between diabetes and depression?**

Depression, obesity, the metabolic syndrome, diabetes, and macrovascular disease are called “complex diseases”. They are polygenic diseases in which susceptibility genes are in constant interaction with the environment, resulting in expression of a given phenotype. Thus, it is very unlikely that any mechanistic links among these diseases would be simple and obvious.

An established neuro-endocrine abnormality in depression is the hyperactivity of the hypothalamo-pituitary-adrenal (HPA) axis. Increased cortisol production in depression may result in insulin resistance, decreased insulin secretion, and central obesity, which are premonitory of the metabolic syndrome and diabetes. Diminished sex steroids and growth hormone in depression have metabolic consequences similar those of hypercortisolism. Elevated activity of the sympathetic nervous system in depression would result in elevated blood pressure and also abnormalities in insulin action and secretion. The decreased tone of the central serotonin system in depression may increase by a high carbohydrate diet and could facilitate the devel-
opment of obesity and the metabolic syndrome. Finally, the pro-inflammatory state that leads to atherosclerosis is common to depression, obesity, the metabolic syndrome and diabetes. The separate pathophysiology of depression and diabetes are reasonably well understood. The changes that the two co-morbidities together produce are only inferred and not determined experimentally. There are no longitudinal studies, observational or interventional, wherein any of the biomarkers of the two diseases have been studied together.

5) Why is depression so prevalent among people with diabetes?

To the evolutionary biologist, human beings at every stage of their development represent “compromises” in their continual adaptation to their changing environment. Recent developments in evolutionary theory suggest that negative emotions and depression may be evolved strategies that facilitated behavior solutions to problems in the ancestral environment. Is depression a disease, or a “behavior shutdown mechanism”? Major Depression can be thought of in terms of the mismatch between modern and ancestral environments. Although many of the characteristics of the ancestral hunter-gatherer environment remain open to speculation, one can be quite certain that our hominid ancestors used to be much more vulnerable and much less in control of their environment than we are currently. Famine, warfare, drought, disease and infection, extreme weather fluctuations, high predation, authoritarian leaders etc. were likely frequent problems that the individual had little or no control over. As such, one can be quite certain that behavioral activity was much more dangerous than now. Because of lesser control and greater danger, the propensity to shut down in unpropitious situations may very well have been adaptive in ancestral environment. This evolutionary tendency toward depression may well be a disadvantage in modern cultures.

In 1962, the thrifty gene hypothesis was proposed to explain the tendency of certain ethnic groups toward obesity. It postulates that certain genes in humans have evolved to maximize metabolic efficiency to survive famine and that in times of abundance these genes predispose their carrier to diseases caused by excess nutritional intake, such as obesity. Is it possible to unify the behavior shut-down hypothesis with the thrifty gene hypothesis? Studies have shown that depression is more common in women. Depression appears to precede the development of obesity, the metabolic syndrome and diabetes, a relationship that is clearer in women. Thus, it is possible that the phenotype of one of the putative thrifty genes is the shut-down behavior which is energy conserving. Accumulation of adipose tissue is the critical signal for the initiation of puberty. Considering that life expectancy in the ancestral environment was probably measured in the teens, the initiation of menarche a few months earlier than those that did not acquire the “behavior shutdown” phenotype would have given them an extraordinary evolutionary advantage: increased fertility by a significant percentage of their brief life span. Today, given the environment of plenitude, those individuals may have obesity, the metabolic syndrome, or diabetes.

6) Can diabetes and depression be treated?

There are at least three hypotheses to answer this question:

a) “Treatment of depression in people with diabetes is possible and, without any additional intervention in diabetes management, will improve diabetes control”. This hypothesis has been tested by two randomized controlled clinical trials. They demonstrated that depression can be treated in people with diabetes with remission rates similar to those without diabetes. However, improvement of depression was not followed by any changes in diabetes outcomes.

b) The second hypothesis - “Active management of both depression and diabetes is necessary to improve diabetes outcome in people with co-morbid diabetes and depression".

The IMPACT (Improving Mood Promoting Access to Collaborative Treatment) was a randomized clinical trial which included 1801 patients 60 years of age or older with depression of whom 417 had coexistent diabetes. Eighteen primary care clinics from 8 health care organizations in 5 states participated. Two hundred and twelve patients with both co-morbidities were randomized to the usual care and 205 formed the intervention group. In the intervention group a care manager offered education, problem-solving treatment, or support for antidepressant management by the patient’s primary care physician; diabetes care was not specifically enhanced. Outcome measurements were obtained at baseline, 3, 6, and 12 months for the degree of depression, functional impairment, diabetes self-management behaviors and Hemoglobin A1c. At 12 months, patients with diabetes who were assigned to the intervention group had less depression but diabetes outcomes remained unchanged.

The PATHWAYS study was a randomized trial of collaborative care in patients with diabetes and depression. It included 329 patients, 12 months follow up and the setting, intervention, main outcome measures and results are similar to the IMPACT trial.
least five studies have tested this hypothesis. Unfortunately, most of these studies were not sufficiently powered. Thus, it is appropriate to conclude that this hypothesis has not been adequately tested.

Three randomized, placebo-controlled, double-blind trials in people with diabetes and depression using Nortriptyline (14 placebo, 14 active, 28 weeks);21 Sertraline (73 placebo, 78 active, 52 weeks);22 and Fluoxetine23 (27 placebo, 27 active, 8 weeks) demonstrated statistically significant improvement in depression but not in glucose control.

An open label observational study without a controlled arm showed improvement of both depression and glucose control by Bupropion.24 Given the nature of the study design, the conclusion of this clinical observation is not clear.

A randomized, controlled trial using cognitive behavior therapy (CBT) (25 CBT, 26 control, 10 weeks) demonstrated post treatment improvement of depression only, but statistically significant improvement of both depression and glucose control 6 months thereafter.25 However, as indicated by the investigators, the CBT group had patient education almost a full year longer than controls. The difference in education was not statistically significant, but the extra educational experience may have contributed to improved outcome in the CBT group.25

c) The final hypothesis- “Optimal management of diabetes in people with depression is possible and, without any additional intervention in depression management, will improve both comorbidities”. This counter-intuitive hypothesis has not been tested.

The previous studies do not provide clear guideline for the treatment of diabetes and depression to the practicing physician. The failure to demonstrate efficacy in diabetes outcomes with any given approach could be due to several reasons: The optimal experimental design has not been used; The pathogenic relationship between diabetes and depression speculated previously is incorrect; The complexity of the two comorbidities may require the treatment of a putative third component which is elusive at this time; A new hypothesis need to be formulated and novel treatment approaches may need to be tested.26,27

Given the serious and often unmet medical needs of people with co-morbid depression and diabetes, it is likely that work in this field will be highly productive and useful in improving the outcome of these patients.

6) Which should be the adequate treatment?

Since there are no studies that show effective therapeutic guidelines for diabetic patients with depression, we recommend a treatment focused to achieve a good control of the diabetes as well as accomplishing an improvement of the person’s state of feeling.

Treatment of diabetes mellitus should take the patient to control goals in glycated haemoglobin (A1c), fasting glucose and postprandial glycaemia as recommended by the diagnosis and treatment guidelines by the Latin-American Diabetes Association (ALAD).28,29

Even more, we should detect the patients on the impaired glucose tolerance phase seeking delay or prevent the development of type 2 diabetes mellitus. People with risk factors for diabetes, especially obesity and a sedentary lifestyle can be benefited with an adequate treatment.29 Correction of obesity and regular physical activity can also prevent a depressive state.

The patient that has had diabetes for over 5 years who has not had a good metabolic control will be exposed to develop micro and macrovascular complications. Retinopathy, nephropathy, amputations, etc. will be factors that complement in a meaningful way the development or aggravation of the depressive state. The secondary and tertiary prevention of diabetes mellitus is of capital importance.30

Treatment of depression using from behavioural techniques and/or drugs is justified.

The option that has proven to be most effective is the one that includes psychotherapy and antidepressant drugs, both in achieving a fast response as in maintaining the improvement.19 The first visits must be frequent, giving psychotherapy support, while the first clinic results are observed, which should be within 4 to 6 weeks.

The selection of the drug must be individualized and consider for its prescription the medication’s profile, possible side effects, drug interactions, price, dose per day and safety. There is no such thing as the ideal antidepressant, and two thirds of the patients respond well to first and second generation medications.

The premises will be: Solving depression, we will have a person with less risk for diabetes. A person with diabetes and not depressed, will be willing to undergo an optimal treatment of his/her disease and more easily achieve the control goals which will avoid complications and will not affect his/her life expectancy.
Referencias