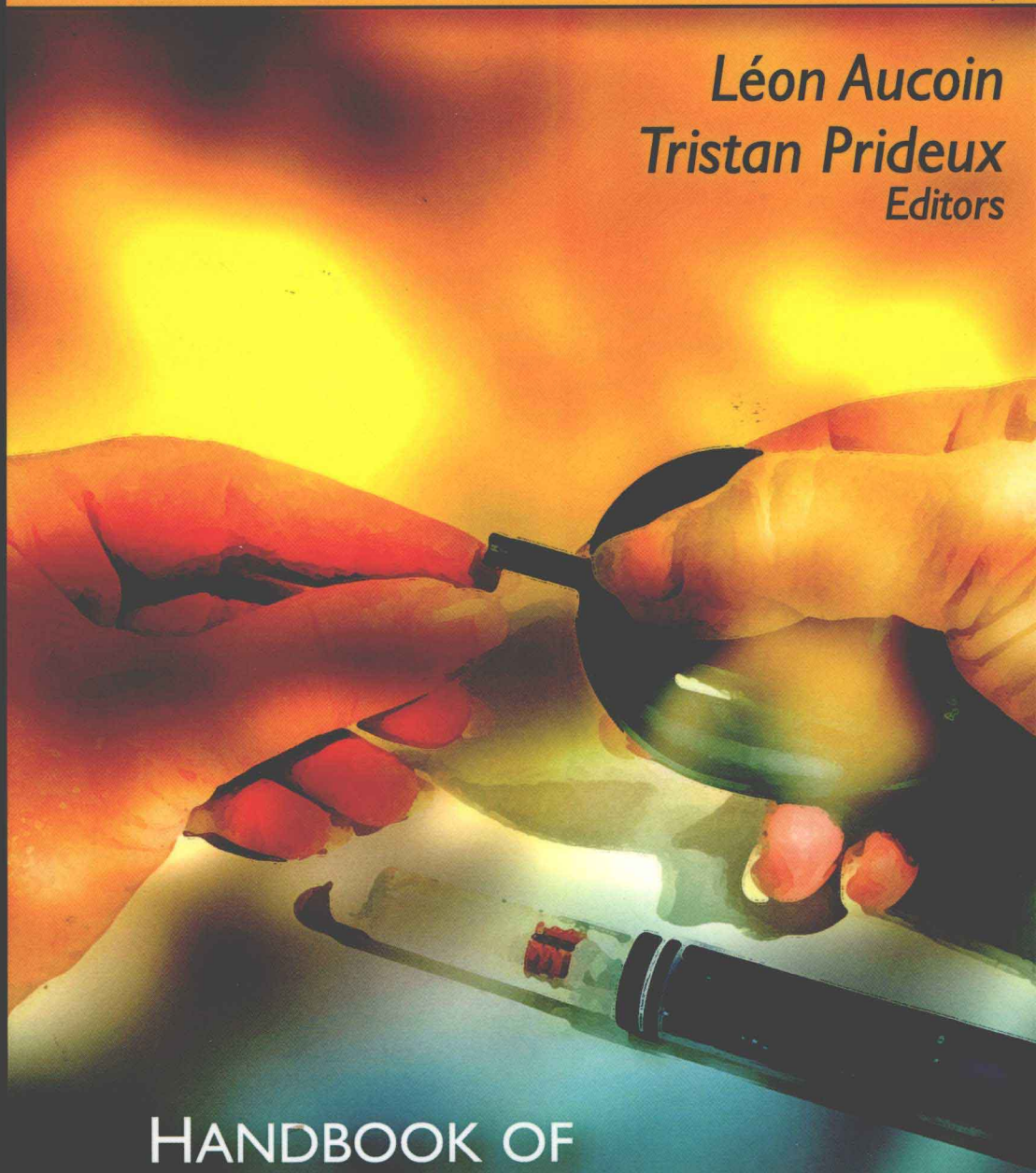
Metabolic Diseases - Laboratory and Clinical Research Series

Léon Aucoin
Tristan Prideux
Editors



HANDBOOK OF TYPE I DIABETES MELLITUS

Etiology, Diagnosis, and Treatment

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METABOLIC DISEASES – LABORATORY AND CLINICAL RESEARCH SERIES

HANDBOOK OF TYPE 1 DIABETES MELLITUS: ETIOLOGY, DIAGNOSIS, AND TREATMENT

LÉON AUCOIN
AND
TRISTAN PRIDEUX
EDITORS

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PREFACE

Type I diabetes (T1D) is an autoimmune, inflammatory disease, incurable up to date. This book reviews and discusses the progress on environmental triggers and endogenous alarmins linking innate immunity to the pathogenesis of type 1 diabetes. The potential anti-inflammatory treatments for T1D evaluated in several models of the disease are also examined. In addition, while many individual therapies provide partial protection against the development of autoimmune diabetes, recently developed multicomponent vaccine strategies hold promise for restoration of euglycemia and more durable maintenance of immunological homeostasis. This book discusses mechanisms underlying the onset and development of type I diabetes and assesses individual and multicomponent immunosuppression strategies. The T1D associated genes that have been replicated in different populations are also analyzed, and whether they could lead to the genetic diagnosis. Other chapters in this book examine the role of physical activity, insulin therapy and dietary management in the the treatment of type I diabetes. Aspects of type I diabetes management in children is also reviewed, including current treatment options available, insulin regiments and insulin delivery methods, and structures and mechanism of action of the new insulin analogues.

Chapter I - Over the past decades, the knowledge of various immune abnormalities, including cellular and molecular mechanisms under the influence of predisposing genetic factors, has progressed in Type 1 insulin-dependent diabetes mellitus (IDDM) in humans and experimental animals. In addition, exogenous environmental factors such as diabetogenic viruses and cow's milk, diets, toxins and bacteria are likely candidates. Nevertheless, the incidence of Type 1 diabetes (T1D) is steadily increasing or remains unchanged in many developed countries, suggesting that unknown mechanisms and/or etiologies may underlie the pathogenesis of T1D. The aim of this chapter is to describe the current knowledge of environmental factors as potential etiologies; then, recent concepts/hypotheses including combined interactions between a series of environmental factors in the progression to clinical TID will be introduced.

Chapter II - Type 1 diabetes (T1D) is an autoimmune, inflammatory disease, incurable up to date. A number of versatile treatments aimed at neutralizing the cause of this disease were tested over the years. Primarily, the blockage of a deleterious immune response was attempted either through inhibition of autoimmune cells homing to pancreatic islets, inhibition of inflammatory mediators or apoptosis of β cells. More recent attempts have been

made in seeking the ways of β cell renewal either from residual β cells (by stimulating their replication) or other nearby cells with a potential to dedifferentiate. On the other hand, insulin administration as a supplement therapy commonly used now days could be replaced by transplantation of pancreatic islets which makes daily treatments unnecessary.

The focus of this review is the potential anti-inflammatory treatments for T1D evaluated in several models of the disease, such as diabetes induced by multiple low doses of streptozotozin (MLDS) in susceptible mouse and rat strains, and spontaneous and accelerated forms of diabetes in NOD mice. Preclinical studies are presented using complementary *in vivo* and *in vitro* approaches evaluated by clinical and pathohistological signs of the disease, lymphoproliferation, production of cytokines, reactive oxygen and nitrogen species, cell death and cell signaling pathways. First of all, benefits of modulation of pro-inflammatory cytokines including macrophage migration inhibitory factor (MIF), interleukin (IL-1), tumor necrosis factor (TNF)-α, interferon (IFN)-γ, and IL-17 are described. Then the application of several non-specific anti-inflammatory molecules, such as already existing drugs (mycophenolate mofetil - MMF, leflunomide, butylated hydroxyanisole - BHA, pentoxifylline, Vitamin A derivatives) or novel natural or chemical compounds (galectin-1, ISO-1, VGX-1027) and plant extracts (dry olive leaf extract) with potential beneficial effects in T1D are presented. The results may contribute to the design of specific screening protocols for testing immunomodulatory agents and evaluation of efficacy of therapeutics in different phases of the disease, which may allow technological improvement of drug production.

Chapter III - Early detection of subclinical autonomic dysfunction is of vital importance in patients with diabetes mellitus (DM) for the prevention of subsequent serious adverse consequences. Reduction in heart rate variability (HRV) is now regarded as the earliest indicator of cardiovascular dysregulation in DM. HRV has traditionally been quantified using linear (time and frequency domain) measures, which describe the magnitude of RR interval oscillations, but are insufficient to characterize complex heart rate dynamics. While HRV is mostly mediated by parasympathetic nervous system, beat-to-beat blood pressure recordings (blood pressure variability, BPV) may provide information regarding sympathetic activity. Assuming that heart and vessels are controlled by a nonlinear deterministic system, measures from nonlinear systems theory find increasingly more applications in cardiovascular signal analysis. A variety of novel measures has been developed to quantify nonlinear features of cardiovascular signals, providing information on the complexity of the dynamical system involved in the genesis of these short-term fluctuations. A loss of complexity is frequently observed in pathological states of the cardiovascular system suggesting that autonomic dysregulation represents a simplification of cardiovascular control since normal autonomic control results in complex system dynamics. Recent signal processing efforts aimed at quantifying the degree of synchronization between cardiovascular signals (e.g. cardio-respiratory coordination or cardiac baroreflex control). In our pilot study we demonstrated that novel nonlinear methods are often more sensitive to autonomic dysregulation than linear methods and therefore may improve the diagnostic power of cardiovascular variability analysis for cardiovascular autonomic neuropathy in DM. Our data indicate that cardiovascular dysregulation progresses in relatively short time frames, depending on the history of DM. Further, its progression appears to be associated with glycemic control. Different methods of cardiovascular variability analysis can provide mutually independent

information and, therefore, should be used simultaneously for a comprehensive analysis of autonomic dysfunction to identify patients at risk for autonomic neuropathy.

Chapter IV - Hepatic insulin resistance and altered insulin metabolism, as characterized by the desensitization of hepatic parenchymal cells to insulin, play a role in the pathogenesis of liver disease, particularly resulting in steatosis and steatohepatitis. By the same token, type II diabetic patients are at higher risk for developing liver diseases, including steatosis, hepatitis, cirrhosis, and hepatocellular carcinoma. On the other hand, established liver disease from any cause leads to glucose intolerance and peripheral insulin resistance systemically. The link between insulin resistance and liver pathology suggests that insulin resistance is closely related with a variety of liver diseases. Recent evidence indicates that the AMP activating protein kinase (AMPK) in conjunction with p70 ribosomal S6 kinase 1 (S6K1) serves as a key signaling pathway regulating insulin-dependent physiological functions; thus, this pathway serves as a target for the therapy of diseases associated with insulin resistance. In this chapter, the regulatory role of the AMPK-S6K1 pathway is discussed in terms of enhancing insulin receptor signaling with insulin receptor substrate-1/2 and phosphatidylinositol phosphate kinase activity, which may contribute to preventing and/or treating insulin resistance in the liver. Moreover, the clinical drugs and experimental therapeutic candidates that directly or indirectly target the AMPK-S6K1 pathway in unique manners are also reviewed with particular reference to their efficacy and beneficial effects for treating hepatic insulin resistance and liver disease.

Chapter V - Similar as other autoimmune diseases, a characteristic feature for type 1 diabetes (T1D) is the selective targeting of a specific type of cells, the insulin secreting β cells of the islets of Langerhans in the pancreas, by a certain population of autoreactive immune cells. Given the importance of innate immunity in triggering and/or tuning autoimmunity by modulating adaptive immune responses to self-antigens, its role in T1D pathogenesis has long been proposed. However, due to the challenge for identifying which cells, receptors and mediators associated with innate immunity are critical in T1D associated autoimmune settings, much research and attention have been focused on T cell mediated adaptive immune responses for the past few decades, while the implication of innate immunity in disease related etiology has almost been completely neglected. Recently, compelling evidence derived from the studies carried out in both animal models and T1D patients had consistently highlighted the importance of innate immunity in T1D etiology. In this chapter, we will review and discuss the progress on environmental triggers and endogenous alarmins linking innate immunity to the pathogenesis of type 1 diabetes. We will use HMGB1, an evolutionarily conserved endogenous danger signal, as an example to discuss the possible implications of innate immunity in autoimmune initiation and progression during T1D development, as well as islet allograft rejection in diabetic patients after islet transplantation, which may provide an insight into the development of novel therapeutic strategies for type 1 diabetes.

Chapter VI - Juvenile onset type 1 diabetes is a life-long, incurable, progressive autoimmune disease that is increasing throughout the world at an alarming rate. Insulin injection is the only known substantially effective therapy which has the risk of complications leading to a significant reduction in life expectancy. While many individual therapies provide partial protection against development of autoimmune diabetes, more

recently developed multicomponent vaccine strategies hold promise for halting diabetes progression restoring euglycemia and providing a more durable immunological homeostasis. In this chapter, we examine mechanisms underlying the onset and development of type 1 diabetes and assess individual and multicomponent immunosuppression strategies including edible plant and virus delivery of immunostimulated diabetes autoantigens and anti-inflammatory cytokines. Identification of mechanisms underlying interactions between combinatorial vaccine components and the host immune system will establish a basis for construction of safer, more effective and durable forms of immunotherapy for patients at risk or suffering from this life-long chronic inflammatory disease.

Chapter VII - Type 1 Diabetes (T1D) is a complex trait caused by autoimmune destruction of islet beta cells in the pancreas resulting of the interaction between genetic and environmental factors. Despite enormous advances in the study of T1D there is still no cure and both genetic and environmental factors remain undefined. To date the therapy was mainly aimed at controlling hyperglycemia; however, recent therapeutic approaches include both the immunosuppression and immunetolerance for prevention and treatment of T1D. Autoreactive T cells have been proposed as target of this strategy because they are responsible for the autoimmune beta cell destruction. It is well known that preventing or avoiding the secondary effects of these therapies require a precise diagnosis of the autoimmune diseases. Hence, a genetic diagnosis would be suitable in order to prevent T1D and to achieve a correct immunotherapy.

The major T1D susceptibility genes, the HLA class II loci (HLA-DRB1 and HLA-DQB1) on chromosome 6p21 act in combination with other non-HLA genes across the genome. Recently, genome-wide association studies have identified over 40 chromosome regions outside the HLA as being associated with T1D. Some of these non-HLA loci have been implicated in other autoimmune diseases like celiac disease, rheumatoid arthritis or multiple sclerosis. The fact that distinct genetic variants are shared by different autoimmune diseases suggests that common immunological mechanisms are involved in the etiology of these autoimmune diseases.

The aim of this chapter is to analyze the T1D associated genes that have been replicated in different populations and whether they could lead to the genetic diagnosis. For this purpose we performed an analysis of three main established susceptibility genes in a Spanish cohort. We found that the cumulative presence of predisposition variants of the mentioned genes increases significantly the risk to disease.

Chapter VIII - Long-chain polyunsaturated fatty acids (LCPUFAs) play an important role in the human body: they are incorporated into cell membranes and can influence the function of the membranes. N-3 LCPUFAs are precursors of anti-inflammatory eicosanoids, while the most important n-6 LCPUFA, arachidonic acid is precursor of proinflammatory prostaglandins, leucotriens and thromboxans. Diabetes mellitus is characterized by the disturbance of both carbohydrate and fatty acid homeostasis. In streptozotocin-induced diabetic rats, significantly higher plasma linoleic acid and significantly lower plasma arachidonic acid values were reported than in the non-diabetic control animals. Because insulin is the most potent activator of both delta-6- and delta-5-desaturase enzymes, these alterations in fatty acid metabolism can be explained by the relative lack of insulin in type-1 diabetes mellitus.

However, human studies are less unequivocal. Several authors found significantly higher linoleic acid values, while others did not find significant differences between type-1 diabetic patients and healthy controls. Nevertheless, in the majority of the human studies values of arachidonic acid and docosahexaenoic acid were found to be significantly lower in diabetic patients than in healthy controls. In a study utilizing continuous subcutaneous insulin therapy, improved fatty acid supply in diabetic patients compared to patients receiving conventional insulin therapy was seen: linoleic acid values decreased, while values of the two most important long-chain polyunsaturated metabolites, arachidonic acid and docosahexaenoic acid increased. This observation raises the possibility that better diabetic control improves the activity of the delta-5- and delta-6-desaturase enzymes. Diabetic ketoacidosis is an acute disturbance of the carbohydrate homeostasis. In an experimental study, arachidonic acid values decreased significantly from baseline during ketosis, and returned to baseline values after recovery. Our research group investigated diabetic children during and after diabetic ketoacidosis. Comparison of plasma fatty acid profiles at clinical admission for diabetic ketoacidosis with those following the successful treatment showed significant decrease of linoleic acid significant increase of arachidonic acid values during recovery from diabetic ketoacidosis.

Chronic hyperglycemia and hypoinsulinemia can cause several micro- and macrovascular complications in diabetic patients. Some of these complications may be related to disturbed fatty acid metabolism, the correction of which can contribute to the prevention of these complications. In fact, n-3 fatty acids may have a neuroprotective effect and they can have a positive impact on the composition of blood lipids: HDL-cholesterol levels increased, while triacylglycerol levels decreased in many studies investigating the effect of n-3 fatty acid supplementation.

Chapter IX - The liver is the first organ to receive nutrients that enter the body via the intestines after a meal, and this organ plays a pivotal role in energy metabolism. Nonalcoholic fatty liver disease (NAFLD) is among the most common causes of chronic liver disease in the world and is now considered to be a component of metabolic syndrome. A wide spectrum of histological changes has been observed in NAFLD, ranging from simple steatosis, which is generally non-progressive, to nonalcoholic steatohepatitis (NASH), liver cirrhosis, liver failure, and sometimes even hepatocellular carcinoma. Histologically, the condition is characterized by macrovesicular hepatic steatosis, and diagnoses are only made in patients who do not have a history of alcohol consumption in amounts sufficient to be considered harmful to the liver. Insulin resistance is nearly universal in patients with NAFLD and nonalcoholic steatohepatitis (NASH). Although the pivotal cause of the development of NAFLD/NASH is still unknown, insulin resistance is strongly suspected of playing an important role in the development of these lesions. Type 2 diabetes, glucose intolerance and insulin resistance occur at a high frequency in patients with NAFLD, and these conditions have been shown to be of prognostic significance. Regarding the molecular mechanisms underlying insulin resistance in patients with NAFLD/NASH, cytokine-adipokine interactions are believed to be intricately involved. Insulin resistance is thought to be regulated by proinflammatory cytokines, adipokines (TNF-α, adiponectin, leptin), and peroxisome proliferator-activator receptors (PPARs). Recent reports have described the involvement of genetic factors as well as environmental factors in the development of insulin

resistance. Genetic factors are also thought to be important in the development of NAFLD/NASH, and genetic polymorphisms of genes encoding TNF-α, adiponectin, and PPARs are reportedly associated with the development of NAFLD/NASH. Most therapeutic modalities that are already in use or under development target major pathways that are believed to be essential to the pathogenesis of NAFLD/NASH, and these therapies are often directed at improving insulin resistance via pharmacologic (thiazolidinediones, metformin), surgical, or dietary approaches. Here, we review recent evidence concerning insulin resistance and NAFLD/NASH as a step towards a comprehensive understanding of the pathophysiology and treatment of NAFLD/NASH.

Chapter X - Physical activity, along with insulin therapy and dietary management, constitutes an essential element in blood glucose regulation for individuals with type 1 diabetes (T1D). Regular exercise positively affects metabolic and cardiovascular functions, and its benefits include improvement of insulin sensitivity, decrease of fat mass, normalization of lipid profile, regulation of blood pressure and improvement of physical capacity. Additionally, all of these metabolic changes prevent the development of metabolic syndrome and other diabetic-related vascular complications. Children with T1D obtain health benefits similar to those of adults from physical exercise; however, due to the spontaneity of their physical activity, some changes observed in their adaptation to exercise should be considered. Type 1 diabetics should exercise on a daily basis at a low to moderate intensity for about 45 minutes. In addition to aerobic exercise, strength and flexibility exercises are recommended as well. Patients with T1D must be aware of possible complications such as hypoglycaemia, hyperglycaemia and ketosis which may occur due to metabolic changes caused by physical activity, both planned and recreational. Therefore, the role of a patient's education in the regulation of diet and insulin therapy before and after exercise seems to be of great importance in management of T1D. Parents, physical education teachers and physical therapists should motivate type 1 diabetic children to engage in physical activity and supervise them during exercise in order to reduce exercise-induced complications, thus creating a proper approach to physical exercise.

Chapter XI - Type 1 diabetes mellitus (T1DM) is an autoimmune disease that results in destruction of the beta cells in the islet of Langerhans, leading to severe insulin deficiency.

Diabetic control depend on both pharmacological treatment and lifestyle: behavioural science research in diabetes promotes lifestyle changes related to physical activity and nutrition. Medical nutrition therapy is very important in the primary prevention of diabetes, in the secondary prevention of diabetes complications, and in the tertiary prevention of associated morbidity and mortality.

Persons with T1DM are subjected to widely varying dietary advice based in part on the putative effects of different foods on glycemic control. The American Diabetes Association (ADA) nutrition recommendations suggest that people with T1DM adjust insulin doses to meal content, meal size, and activity levels to achieve near-normal glycemic control. Day-to-day carbohydrate consistency has been suggested to be especially important for individuals using fixed daily insulin doses.

Healthy dietary behaviour in T1DM is essential to have good nutritional status, which makes it possible to get good metabolic control (glycosylated haemoglobin [HbAlc] < 6%). It is important to recognize that there is no single measurement method to estimate body

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composition, however clinical, humoral and instrumental evaluations can show nutritional status pretty well.

Clinical evaluations include Body Mass Index (BMI, kg/m^2), skinfold thickness measuring at the subscapular (SSF), biceps (BCF), triceps (TCF), suprailiac (SIF) areas, circumference measuring at waist, hip, midarm (MAC), upper thigh (UTC). The ratios waist/hip (WHR), waist/thigh (WTR), and trunk/total skinfolds are calculated. The traditional total upper arm area, $TUA = MAC^2/4\Pi$, upper arm muscle area, $UMA = [MAC - (TCF \times \Pi)]^2/4\Pi$, and upper arm fat area, UFA = TUA - UFA, as well as the new upper arm fat area estimate, UFE = MAC × (TCF/2), and upper arm muscle area estimate, UME = TUA - UFE, are also calculated.

The plasma concentrations of some proteins, like albumin, retinol-binding protein, insulin-like growth factor I, etc, are used as visceral proteins metabolism expression.

Bioelectrical Impedance Analyzer (BIA) doesn't measure body composition directly, but it gives two bioelectric parameters: resistance (R, Ω) and reactance (Xc, Ω) offered by the body to the flow of 50 kHz alternating electrical current.

People with diabetes have the same nutritional needs as anyone else: considerable evidence supports the importance of maintaining a $20 < BMI < 25$ kg/m^2, eating a nutritionally balanced diet. The recommended daily caloric intake (National Institute of Nutrition, LARN) is 25-30 kcal/kg/die, the caloric division between macronutrients is: 25-30% fat (satured < 7%, polyunsatured ≈10%), 55-60% carbohydrate, rich in fiber (25–30 g/day), and 15-20% protein. Cholesterol from the food may increase the blood cholesterol, so it is better to eat less than 200 mg per day (ADA). American Heart Association (AHA) dietary guidelines advice limiting salt (< 6g/day) and alcohol intake, and engaging in a regular physical activity (30–60 min on most if not all days of the week).

Chapter XII - Children with type 1 diabetes (DM1) are treated with subcutaneous insulin, either using injections or a continuous insulin infusion pump, to maintain normal blood glucose levels. Poor or inadequate control of blood glucose is associated with complications of diabetes such as retinopathy, nephropathy, neuropathy, and an increased risk of cardiovascular disease. Many different insulin regimens are used in order to achieve a balance of adequate glycemic control and an acceptable routine for the child and their family.

The current standard of care is to give insulin in a minimum of three times daily (TID) insulin injections. More frequent multiple daily injections (basal-bolus regimen) or an insulin pump offers the advantage of increasing flexibility and the ability to more finely adjust insulin dosing. These insulin regimens have been used with rapid acting insulin analogues. Recently, long acting insulin analogues have been introduced that have been shown to have less variability and to decrease the risk for hypoglycemia.

Aspects of type 1 diabetes management in children will be reviewed including: current treatment options available, insulin regimens and insulin delivery methods, structures and mechanism of action of the new insulin analogues. The use of new insulin analogues will be discussed in children with type 1 diabetes and specifically the impact on metabolic control, frequency of hypoglycemia and weight.

Chapter XIII - Type 1 diabetes is an autoimmune disorder typically presenting in the pediatric population. Individuals with type 1 diabetes have increased prevalence of other autoimmune diseases including autoimmune thyroid disease, celiac disease, and primary

adrenal failure. In some patients, a shared genetic susceptibility for these diseases has been demonstrated. Current recommendations are to screen patients with Type 1 diabetes for autoimmune thyroid disease and celiac disease in a proactive manner, while screening for adrenal failure should be done when there is a high index of suspicion. Clinical signs and symptoms, particularly unexplained hypoglycemia, can point to the presence of an associated autoimmune disease. Failure to recognize and treat these disorders can lead to worsening diabetes control. When an individual has multiple autoimmune endocrinopathies, the treating physician should consider the diagnosis of an autoimmune polyglandular syndrome. This review will discuss genetic associations, screening, and treatment strategies in individuals with Type 1 diabetes who are at higher risk for other autoimmune diseases.

Chapter XIV - Diabetes mellitus (DM) affects people of all ages and races. Who develops DM still remains a mystery. Exhaustion of the beta cells in relationship to elevated 2h postprandial glucose level has been demonstrated. Much emphasis is placed and a great part of the resources is spent to determine the cause and find a cure for DM. While this approach is far-fetched, DM has imposed an economic burden on the society due to the treatment of its complications. Our focus should be on the ways and means to prevent these complications by maintaining postprandial blood sugar under 200 mg/dL (<11.1 mmol/L).

Sustained uncontrolled hyperglycemia above 200 mg/dL (>11.1 mmol/L) is likely to give rise to: peripheral neuropathy; foot ulcer; gangrene of feet resulting in amputation; deteriorating vision; heart attack and stroke; kidney failure; and sexual dysfunction.

Because of the vast gamut of complications, which are mostly due to mismanagement and confused nomenclature (Type 1 and Type 2), DM patients have become a target for business enterprise. Involvement of the kidneys (diabetic nephropathy) and sex organs (erectile dysfunction) are the focus for the industry. Fifty articles on diabetic nephropathy were reviewed to reach a general consensus on the appropriateness of the management of diabetes. In all the articles, the consensus is on treatment of minimal proteinuria (called microalbuminuria) with angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blocker (ARB) to prevent progression of diabetic nephropathy to end-stage renal disease (ESRD). In no articles were any data presented about glucose levels and the means of control of hyperglycemia (occasional articles showed HbA1c). No articles presented data on 2h postprandial glucose level, which relates to renal outcome.

No attention to glucose control, coupled with indiscriminate use of ACEI/ARB, has increased the incidence of ESRD and preponderance of dialysis clinics with consequential effect of lucrative businesses for the nephrologists, pharmaceutical companies, and dialysis corporations.

Renal complications and all other complications of DM are highly preventable by adequate and continuous glucose control, blood pressure control, diet control, and regular office visits to ensure maintenance of the controls. To these effects, patients must be motivated to check sugar and take injections of insulin as a routine. No therapy is more appropriate than insulin to keep sugar under control and to avert most or all the complications of DM. Oral antidiabetic agents may be additive to insulin but not be used as a substitute for insulin. They work not like insulin and are not effective in preventing the complications of DM.

Chapter XV - Islet transplantation is a promising treatment option for type 1 diabetes. Two major obstacles, shortage of islet donors and deleterious side effects of immunosuppression, challenge both scientists and clinicians. The limited supply of donor islets can be improved by alternative sources, regeneration therapy, and reducing islet cell death during islet isolation, culture, and transplantation. Toxicities associated with lifelong use of the current immunosuppressive drugs may limit the widespread application of this therapy. Recent research data reveal that blockade of co-stimulatory molecules which activate T-cells is highly effective in promoting islet graft survival in animal models. Biomarkers for predicting transplant rejection and combinations of immune modulation to reduce or prevent adverse effects of current immunosuppressive protocols are required to further improve success of islet transplantation. Despite challenges, tremendous progress has been observed in islet isolation and preservation. Innovations in clinical islet transplantation have led to evidence of reduced complications, including retinopathy and hypoglycemia. This review will address both progress and limitations in islet transplantation. In order to accomplish better long-term insulin independence and improved protection from complications, novel strategies and approaches are suggested.

Chapter XVI - Insulin resistance is commonly defined as decreased sensitivity or responsiveness to metabolic actions of insulin affecting between 10 and 25 % of the general population. Insulin resistance is associated with a clustering of metabolic disorders including hyperlipidemia, cardiovascular disease, diabetes mellitus, obesity and hypertension. Polycystic ovary syndrome (PCOS) is the most common hormonal disorder of reproductive aged women, affecting 5-10% of this population. Approximately 50- 70% of women with PCOS are insulin resistant. Insulin resistance is a cardinal finding in the pathophysiology of PCOS. Quantifying insulin senstivity/resistance is of great importance for studies and eventual use in clinical practice. Early detection of insulin resistance is crucial in the management of PCOS. An improvement of insulin resistance in PCOS ameliorates endocrine and reproductive functions. Though obesity increases insulin resistance by itself, both lean and obese women have significant insulin resistance that is independent of obesity. Insulin sensitivity has been shown to be increased by vitamin D supplementation. Serum vitamin D is significantly lower in obese than in non obese individuals. Obesity and insulin resistance aggravate hyperandrogenism. In addition to life style interventions (weight loss, diet and exercise) and treatment with insulin sensitizers vitamin D supplementation should be kept in mind. The relationship between insulin resistance and depression has been investigated. Treatment of depression might be a strategy in the prevention of type 2 diabetes mellitus. Psychological symptoms should be evaluated as well as clinical symptoms in the treatment of PCOS.

PCOS is charactherized by chronic anovulation, hyperandrogenism, insulin resistance, obesity, infertility and increased risk of spontaneous abortion. Doppler analysis of uterine perfusion and ovarian stromal blood flow in PCOS may improve understanding failure of implantation and spontaneous abortion. Increased ovarian stromal blood flow and decreased uterine perfusion may be related to insulin resistance and increased androgens. Women with PCOS should undergo a comprehensive evaluation and must be closely monitored for deteriotion in glucose tolerence. Lifestyle modification is the first line therapy; combined oral

contraceptives are the most often used treatment modality and insulin sensitizing agents are recent therapeutic strategy in women with PCOS.

Chapter XVII - Diabetes mellitus arises from defects in insulin secretion, or action, or both. In pancreatic islets, insulin production is tightly regulated with Zn^{2+}, whose transport into β-cells is mediated by Zn^{2+}-transporter-8 (ZnT-8), a product of the SLC30A8 gene. Therefore, altered activity of ZnT-8 is expected to be associated with impaired glucose-induced insulin response and promote progression from glucose intolerance to diabetes. Recent findings do emerged a role of SLC30A8 in diabetes. Genome-wide association scans for type 2 diabetes (T2D) susceptibility loci revealed and then replicated a highly significant association between the R325W variant of SLC30A8 (marker rs13266634) and T2D in Caucasians. A role of ZnT-8 as a new major self-antigenic determinant in type 1 diabetes (T1D) was found. Marker rs13266634 was also shown to modulate anti-ZnT-8 self-antibody specificity in islet autoimmunity. Hence, these findings suggest for a dual role of SLC30A8 in diabetes, which is consisted in conferring genetic susceptibility to T2D and being a major islet self-antigen in T1D as well. Here we characterize an emerging role of ZnT-8 in diabetes and discuss potential mechanisms of its involvement in the etiology of both forms of diabetes.

Chapter XVIII - *Introduction*: In the year 1994 the authors realized a transversal study about the prevalence of diabetic retinopathy and renal lesion determining the microalbuminuria and overt nephropathy.

With the introduction of new diagnostic criteria for diabetes performed in 2000, by the WHO that recognizes the 2 hour glucose level are a good standard for diagnosis of diabetes, but indicate that a fasting plasma glucose of > 7.0 mmol/l (126 mg/dl) can be accepted as a satisfactory alternative in epidemiological studies; and the application of the results of DCCT and UKPDS in the control of the patients with diabetes mellitus, the prevalence and characteristics of diabetes complications may changed. The aim of the present study is to observe the changes succeeded in the prevalence of diabetic retinopathy and renal lesion after 15 years in a type 1 DM population.

Methods: Setting of the study. The Hospital St Joan is the only surgical ophthalmic centre in Reus (Catalonia/Spain), with a dependent population of 218,740 inhabitants, and all diabetic patients are examined one time a year by the Service of Ophthalmology, derived by the general practitioners and endocrinologists to the Hospital.

Since 1987 a register has been kept of any new cases of type I diabetes mellitus in Catalonia (Spain), the incidence of new cases has changed of 11.4 cases per 100.000 inhabitants in 1987 to 13 cases per 100.000 inhabitants in 2008. The registration of all type 1DM patients at Hospital St Joan was of 569 in 1994 and 819 patients in 2008 year.

The sample was obtained by randomized hazard selection of 275 type 1 DM patients in the 2008 study, and 106 type 1 diabetic patients in 1994 study. We evaluate the prevalence of diabetic retinopathy, microalbuminuria, overt nephropathy, and its risk factors.

Results: In type 1 DM patients the prevalence of diabetic retinopathy was 33.96% in 1994 and 34.90% in 2008. The diabetic macular edema prevalence was 12.26% in 1994 study and 13.50% in 2008 study; microalbuminuria not decreased between the two samples patients (from 28.00% to 27.35% in 1994 in front 2008), overt nephropathy decreased from 7.27% to

7.54%,. We may observe a decrease in the number of patients with blindness, from 9.43% to 6.90% in type 1DM patients.

Conclusions: we may observe a decrease in the prevalence of diabetic retinopathy, overt nephropathy and blindness in type 1 DM without a decrease in the prevalence of microalbuminuria.

Chapter XIX - The diagnostic criteria needed to differentiate between type 1 and type 2 diabetes seemed clear not so long ago. It was believed that just as the insulin deficit connected with β-cell destruction was typical of type 1 diabetes, the insulin resistance was a specific feature of type 2 diabetes. At present it is known that hyperglycaemia originates from these both disorders. The differences are quantitative, rather than qualitative. Moreover, the background mechanism and the increase rate of each these phenomena can also be different which gives specific clinical picture. The growing availability of excellent diagnostic measures have led to a notion that this old classification is not enough. The increasing number of cases which cannot be unambiguously classified according to the still valid WHO criteria from 1998 creates strong necessity to revise and set up a new division. These difficulties concern mainly children, adolescents and young adults. Is there a type 1.5 diabetes then? A constant progress in the field of genetics and immunology allows us to broaden the studies of diabetes pathogenesis and patophysiology. In the light of new evidence formerly described characteristics of types of diabetes loose their specificity and tend to permeate through one another. One should also keep in mind some other certain types of diabetes that can be encountered. The whole group of monogenic types of diabetes, which are more and more frequently diagnosed, form a good example. The growing body of evidence contributes to a great need to revise and verify the old diagnostic criteria for diabetes.

Chapter XX - As the world population has aged, dementia has become a common diagnosis in aging populations and the numbers will increase in the forthcoming years. Epidemiological evidence has suggested that diabetes mellitus significantly increases the risk for Alzheimer Disease, independent from vascular risk factors.

Exogenous insulin improves memory performance indicating a positive effect on cognition in humans and animals. Likely memory-related mechanisms include modulation of synaptic structure and function, long-term potentiation, and CNS levels of neurotransmitters, and insulin receptors are highly concentrated in the cognitive active areas of the brain. However, impaired insulin or IGF-1 signaling, as in insulin resistance, causes Tau phosphorylation and neurofibrillary tangle formation and increased beta amyloid aggregation in late onset Alzheimer Disease. Furthermore, insulin-degrading enzyme may have an important effect on Aβ aggregation.

Current data supported that insulin resistance may play main role in the pathogenesis of the Alzheimer Disease, and insulin sensitizer agents may have therapeutic benefit for patients with Alzheimer type dementia and also for prevention of the disease. Therefore, we think that the insulin resistance should be taken into account in both explaining the pathophysiological mechanisms and the managing of the Alzheimer Disease.

Chapter XXI - *Introduction:* Oxidative stress plays an important role in the development of type 1 diabetes mellitus and its complications. We consider antioxidant treatment a promising approach for complementary therapy in diabetes mellitus. Several

phyytotherapeutical products contain a complexity of free radical scavenger substances and present no side effects on long term treatment.

Material and methods: Our research team focused on two dietary supplements, Eridiarom® and Diavit®. Eridiarom® is a blueberry fruit concentrate, and Diavit® contains blueberry (*Vaccinum myrtillus*) and sea buckthorn fruits (*Hippophae rhamnoides*). These products present a powerful hypoglycemic effect due to myrtillene (so called "vegetal insulin"), and they are effective in reducing oxidative stress containing several antioxidant substances. Diavit® and Eridiarom® have a regenerative effect on pancreatic beta cells, fact demonstrated histologically in rats by our research team, and this was demonstrated afterwards in human subjects suffering from type 1 diabetes mellitus. Our subjects were patients of the II. Clinical Hospital of Pediatrics in Târgu Mureş, Romania.

We evaluated oxidative stress in diabetic patients by measuring malondialdehyde concentration (a final product of lipid peroxidation) and we also followed the dinamics of antioxidant enzyme concentration (superoxide dismutase, glutation peroxidase) under Diavit® treatment. Carbohydrate metabolic balance was evaluated by measuring glycated hemoglobin levels and making glycaemic profiles. Endogenous insulin production capacity was evaluated based on C peptide concentration measurement, and we also determined the dinamics of required insulin doses before and after treatment with these dietary supplements.

Results: We used three methods for measuring lipid peroxidation products in type 1 diabetic patients compared to non-diabetic subjects of the same age-group. We used the LPO 586 kit and two methods based on the reaction between malondialdehyde and thiobarbituric acid. We revealed that oxidative stress was more intense in diabetic children compared to healthy subjects, and we obtained good correlation of the results provided by the three methods. Malondialdehyde concentration was significantly lower after treatment with the dietary supplements formerely mentioned ($p<0.05$) and carbohydrate metabolic balance improved significantly.

After two months of administering Diavit® to type 1 diabetic children, the erythrocyte superoxide dismutase activity was significantly higher ($p<0.05$), levels of glycated hemoglobin were significantly lower ($p<0.05$). The activity of whole blood glutathione peroxidase was moderately increased, but the difference was not statistically significant. C peptide concentration was significantly higher after treatment with this dietary supplement ($p<0.05$), and insulin doses could be reduced. Treatment with Eridiarom® resulted in lower HbA1c levels, reduced lipid peroxidation products ($p<0.05$) and patients required lower insulin doses. The regenerative effect of Diavit® and Eridiarom® on pancreatic beta cells was demonstrated histologically in Streptozotocin-induced diabetic rats by our research team.

Conclusions: The results obtained suggest that these dietary supplements have a beneficial effect in the treatment of type 1 diabetic children and they should be used together with insulin as powerful phytotherapeutic products in the fight against diabetes mellitus.

Chapter XXII - Type 1 diabetes is a T-cell mediated autoimmune disease with progressive loss of self-tolerance to β-cell antigens. A variety of therapeutic strategies, mostly designed to target the immune system, have been tested to modulate the disease process, either in patients predisposed to developing type 1 diabetes or in patients recently diagnosed with type 1 diabetes. These strategies have achieved variable success, and a likely underlying contributor to treatment failure is the severely diminished residual β-cell mass

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