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Diabetes mellitus

(Diploma Thesis)

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ABSTRAKT

Tato diplomová práce se zaměřila na popis diabetes mellitus z hlediska patogeneze, rizikových komplikací, farmakologické a nefarmakologické léčbě.

Kormě toho jsme se v této diplomové práci také zaměřili na vztah diabetes mellitus a Alzheimerova nemoc. U tohoto stavu dochází k poruchám metabolizmu cukru, čím dochází k poškození činnosti mozku což může přispívat také k rozvoji a progresi Alzheimerovy choroby.

ABSTRACT

This theses on Diabetes Mellitus aims at giving an insight at various aspects of this chronic disease and the risk factors that lead to it; the varius ways it develops in the human body; the old and new approaches to treatment, both from a pharmacological and a non-pharmacologiacal point of view; ways to prevent and to manage the diabetes complications; how to improve the live of the diabetic patients who are faced with not only physical but also psychological problems; statistical data from around the world wkich focuses on epidemiology and outlines the issue of the cost of diabetes.

Finally, this paper links diabetes mellitus with the Alzheimer's disease as a different expression of diabetes, since it is closely associated with several key neuronal factors implicated in dementia.

In many respects, Alzheimer's is a brain form of diabetes. Even in the earliest stages of the disease, the brain's ability to metabolize sugar is reduced. Normally, insulin plays a big role in helping the brain take up sugar from the blood. But, in Alzheimer's, insulin is not very effective in the brain. Consequently, the brain cells practically starve to death.

CONTENTS

1.1 Definition

Diabetes mellitus, or simply diabetes, is a group of diseases characterized by high blood glucose levels that result from defects in the body's ability to produce and/or use insulin.

It is a condition primarily defined by the level of hyperglycaemia giving rise to risk of microvascular damage (retinopathy, nephropathy and neuropathy). It is associated with reduced life expectancy, significant morbidity due to specific diabetes related microvascular complications, increased risk of macrovascular complications (ischaemic heart disease, stroke and peripheral vascular disease), and diminished quality of life (www.who.int/diabetes).

Several pathogenetic processes are involved in the development of diabetes. These include processes, which destroy the beta cells of the pancreas with consequent insulin deficiency,and others that result in resistance to insulin action. The abnormalities of carbohydrate, fat and protein metabolism are due to deficient action of insulin on target tissues resulting from insensitivity or lack of insulin (Report of a WHO Consultation, 1999).

Diabetes mellitus may present with characteristic symptoms such as thirst, polyuria, blurring of vision, and weight loss. Often symptoms are not severe, or may be absent.

1.2 History

For 2,000 years diabetes has been recognized as a devastating and deadly disease. In the first century A.D. a Greek physician, Aretaeus, described the destructive nature of the affliction, which he named "diabetes" from the Greek word for "siphon" (www.diabeteshealth.com). Physicians in ancient times, like Aretaeus, recognized the symptoms of diabetes but were powerless to treat it effectively.

In the 17thcentury a London physician, Dr. Thomas Willis, determined whether his patients had diabetes or not by sampling their urine. If it had a sweet taste he would

diagnose them with diabetes mellitus-"honeyed" diabetes. This method of monitoring blood sugars went largely unchanged until the 20th century.

Before the discovery of the insulin little could be done for patients suffering from diabetes. Low calorie diets prolonged their lives but left them weak and near starvation. But in 1921, doctors in Canada treated patients dying of diabetes with insulin and managed to drop high blood sugars to normal levels. Since then, medical breakthroughs have continued to prolong and ease the life of people with diabetes.

In the ’50s, it was discovered that there were two types of diabetes: "insulin sensitive" (type I) and "insulin insensitive" (type II).

Two thousand years have passed since Aretaeus spoke of diabetes as "the mysterious sickness". It has been a long and arduous process of discovery, as generations of physicians and scientists have added their collective knowledge to finding a cure. It was from this wealth of knowledge that the discovery of insulin emerged in a small laboratory in Canada. Since then, medical innovations have continued to make life easier for people with diabetes.

In the 21st century, diabetes researchers continue to pave the road toward a cure. Today, it is unclear what shape the road will take; perhaps another dramatic discovery like insulin waits around the corner, or possibly researchers will have to be content with the slow grind of progress (Satley, 2008).

1.3 Pathophysiology

An understanding of the pathophysiology of diabetes rests upon knowledge of the basics of carbohydrate metabolism and insulin action. Following the consumption of food, carbohydrates are broken down into glucose molecules in the gut. Glucose is absorbed into the bloodstream elevating blood glucose levels. This rise in glycemia stimulates the secretion of insulin from the beta cells of the pancreas. Insulin is needed by most cells to allow glucose entry. Insulin binds to specific cellular receptors and facilitates entry of glucose into the cell, which uses the glucose for energy. The increased insulin secretion from the pancreas and the subsequent cellular utilization of glucose results in lowering of blood glucose levels. Lower glucose levels then result in decreased insulin secretion.

If insulin production and secretion are altered by disease, blood glucose dynamics will also change. If insulin production is decreased, glucose entry into cells will be inhibited, resulting in hyperglycaemia. The same effect will be seen if insulin is secreted

from the pancreas but is not used properly by target cells. If insulin secretion is increased, blood glucose levels may become very low (hypoglycemia) as large amounts of glucose enter tissue cells and little remains in the bloodstream.

Multiple hormones may affect glycemia. Insulin is the only hormone that lowers blood glucose levels. The counter-regulatory hormones such as glucagon, catecholamines, growth hormone, thyroid hormone, and glucocorticoids all act to increase blood glucose levels, in addition to their other effects (Meley et al, 2006).

1.4 Complications

Complications due to diabetes are a major cause of disability, reduced quality of life, and death. Diabetes complications can affect various parts of the body manifesting in different ways for different people. Diabetes increases patients' risk for many serious health problems. In men, it is responsible for erectile dysfunction, low testosterone levels and emotional factors –such as depression, anxiety or stress–that can interfere with sexual feelings. In women, diabetes can be especially hard. Even those who do not have diabetes, pregnancy brings the risk of gestational diabetes. According to statistics from the American Diabetes Association, heart disease is the leading cause of death in women with diabetes(www.diabetes.org/living-with-diabetes). In addition, women with diabetes are afflicted by depression, their sexual health is at risk and eating disorders tend to occur more frequently.

Diabetes can affect every part of the body, including the feet, the eyes and the skin.In fact, such problems are sometimes the first sign that a person has diabetes. Foot complications can get worse and lead to serious complications, such as neuropathy, skin changes, calluses as well as foot ulcers, poor circulation and (Aalto, 1997).

1.5 Diagnosis

The diagnosis of diabetes mellitus is easily established when a patient presents the classic symptoms of hyperglycaemia and has a random blood glucose value of 200 mg/dL (11.1 mmol/L) or higher, and confirmed on another occasion.

The following tests are used for the basic diagnosis:

A fasting plasma glucose (FPG) test measures blood glucose in a person who has not eaten anything for at least 8 hours. This test is used to detect diabetes and prediabetes.

An oral glucose tolerance test (OGTT) measures blood glucose after a person fasts at least 8 hours and 2 hours after the person drinks a glucose-containing beverage. This test can be used to diagnose diabetes and prediabetes. The FPG test is the preferred test for diagnosing diabetes because of its convenience and low cost. However, it may miss some diabetes or prediabetes that can be found with the OGTT. The FPG test is most reliable when done in the morning. Research has shown that the OGTT is more sensitive than the FPG test for diagnosing prediabetes, but it is less convenient to administer.

A random plasma glucose test, also called a casual plasma glucose test, measures blood glucose without regard to when the person being tested last ate. This test, along with an assessment of symptoms, is used to diagnose diabetes but not prediabetes.

Test results indicating that a person has diabetes should be confirmed with a second test on a different day (Twillman, 2002).

The current WHO diagnostic criteria for diabetes should be maintained – fasting plasma glucose ≥ 7.0mmol/l (126mg/dl) or 2–h plasma glucose ≥ 11.1mmol/l (200mg/dl) (Report of a WHO Consultation, 1999).

1.6 Types of diabetes mellitus

The first widely accepted classification was published by the WHO in 1980 (Second Report, 1980). Two major classes of diabetes mellitus were proposed: IDDM (Type I) and NIDDM (Type II). Other types as well as gestational diabetes were also included. The modified form of 1985 (Diabetes Mellitus: Report of a WHO Study Group, 1985) was widely accepted and is used internationally.It was recommended that the terms "insulin-dependent diabetes mellitus" and "non-insulin-dependent diabetes mellitus" should no longer be used, because patients were classified according to treatment rather than pathogenesis. The terms Type I and Type II were introduced to describe the cases which are primarily due to pancreatic islet beta-cell destruction the former and the common major form of diabetes resulting from defects in insulin secretion the latter (Goodpaster, 2010).

1.6.1 Type I Diabetes

Type I accounts for only about 5—10% of all cases of diabetes; however, its incidence continues to increase worldwide and it has serious short-term and long-term implications. Type I indicates the process of beta-cell destruction in the pancreas that may

ultimately lead to diabetes mellitus in which “insulin is required for survival” to prevent the development of ketoacidosis, coma and death (Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications. Report of a WHO Consultation, 1999).

Management of Type I diabetes is best undertaken in the context of a multidisciplinary health team and requires continuing attention to many aspects, including insulin administration, blood glucose monitoring, meal planning, and screening for diabetes-related complications. These complications consist of microvascular and macrovascular disease, which account for the major morbidity and mortality associated with Type I diabetes (Daneman, 2006).

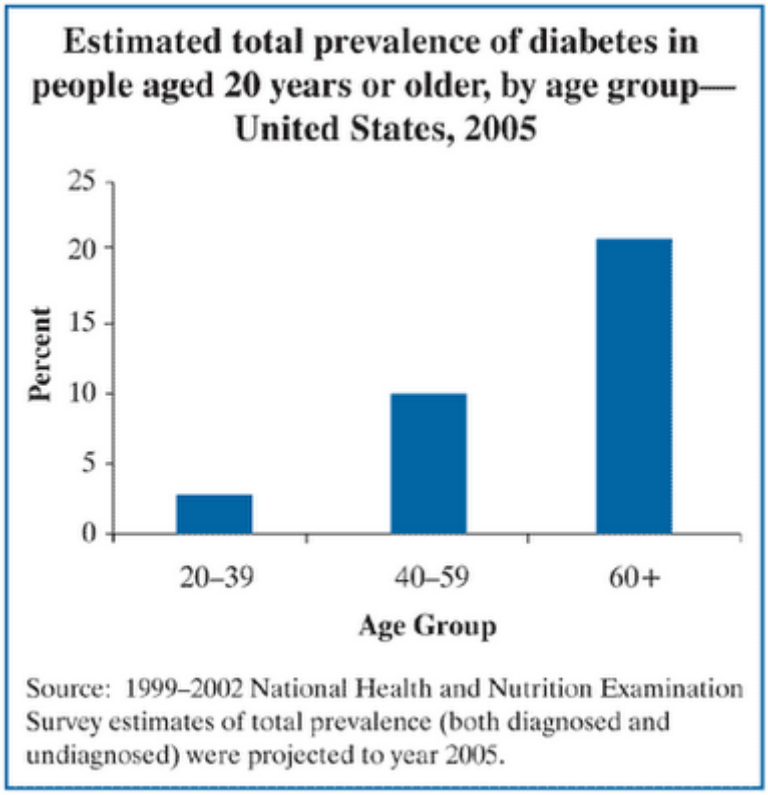
1.6.2. Type II Diabetes

Type II is the most common form of diabetes. Millions of people around the world have been diagnosed with Type II diabetes, and many more remain undiagnosed. People with diabetes are at a greater risk of developing cardiovascular diseases such as heart attack and stroke if the disease is left undiagnosed or poorly controlled. They also have elevated risks for sight loss, foot and leg amputation due to damage to the nerves and blood vessels, and renal failure requiring dialysis or transplantation (Pasinetti, 2011).

Before people develop Type II diabetes, they almost always have "prediabetes" – bloodglucose levels that are higher than normal but not yet high enough to be diagnosed as diabetes. Recent research has shown that some long-term damage to the body, especially the heart and circulatory system, may already be occurring during prediabetes(DePaula, 2008).

In Type II diabetes, either the body does not produce enough insulin or the cells ignore it. Insulin is necessary in order for the body to be able to use glucose for energy. After food consumption, the body breaks down all sugars and starches into glucose, which is the basic fuel for the cells. Insulin takes the sugar from the blood into the cells. When glucose builds up in the blood instead of going into the cells, it can lead to diabetes complications.

***Figure 1**: Estimated total prevalence of diabetes in people aged 20 years or older, by age group*
Source: National Health and Nutriton Examination, http://www.cdc.gov/diabetes/pubs/estimates05.htm, accessed at 12.2.2013



1.6.3 Prevention / Delay of Type II Diabetes

Before people develop Type II diabetes, they almost always have "prediabetes" – blood glucose levels that are higher than normal but not yet high enough to be diagnosed as diabetes. Prediabetes is a serious medical condition that can be treated. A recently completed study carried out by scientists in the United States conclusively showed that people with prediabetes can prevent the development of Type II diabetes by making changes in their diet and by increasing their level of physical activity. They may even be able to bring their blood glucose levels back to the normal range.

Lifestyle changes are of outmost importance. A balanced diet and an increase of the level of physical activity can help maintain a healthy weight, stay healthier for longer and reduce the risk of diabetes. The results of the Diabetes Prevention Program (DPP) proved that weight loss through moderate diet changes and physical activity can delay or prevent Type II diabetes (Haus, 2010). The Diabetes Prevention Program (DPP) was a major multicenter clinical research study aimed at discovering whether modest weight loss through dietary changes and increased physical activity or treatment with the oral diabetes drug metformin (Glucophage) could prevent or delay the onset of type II diabetes in study participants.

1.6.4 Diabetes in Pregnancy (Gestational Diabetes)

Gestational diabetes is diabetes found for the first time when a woman is pregnant. Women who are overweight, have had gestational diabetes before or have a strong family history of diabetes are at a higher risk of developing gestational diabetes. Untreated gestational diabetes may cause problems to the baby. Both the mother and the baby are at increased risk for Type II diabetes for the rest of their lives (Harris, 1991).

1.7 Risk factors

There are controllable risk factors associated with diabetes, including obesity and an inactive lifestyle. However, other uncontrollable risk factors, such as ethnicity and genetics, also play a dramatic role.

The primary risk factor for type I diabetes is a family history of this lifelong, chronic disease.Having family members with diabetes is a major risk factor. The American Diabetes Association (Standards of medical care in diabetes-2007)recommends that anyone with a first-degree relative with type I diabetes –a mother, father, sister, or brother– should get screened for diabetes. A simple blood test can diagnose Type I diabetes.

In addition, injury or diseases of the pancreas can inhibit its ability to produce insulin and lead to type I diabetes.A range of relatively rare infections and illnesses can damage the pancreas and cause Type I diabetes (Laakso, 1999).

The risk factors associated with type II diabetes include obesity, diet and physical inactivity, increasing age, insulin resistance, family history of diabetes, genetic factors, and race and ethnicity. As concerns genetic factors, research has shown that certain gene

variations raise the risk of developing diabetes. These genes can be associated with insulin sensitivity in the body's tissues, decreased insulin production and an increased risk of obesity. Race and ethnicity, on the other hand, are responsible for higher levels of diabetes in certain ethnic groups including African Americans, Mexican Americans, American Indians, native Hawaiians and some Asian Americans. The above mentioned groups have an increased risk of diabetes and heart disease. This is partly due to higher rates of high blood pressure, obesity and diabetes in these populations. African Americans are also more likely than other ethnic groups to develop Type IIDiabetes (Boulton et al, 2005).

Although genes and ethnicity are risk factors for diabetes, they are not the sole determinants of whether someone develops the disease. Changes in diet and decreased physical activity related to rapid technological development and urbanisation have led to sharp increases in the numbers of people developing diabetes.

A history of substance use has been reported as a significant factor associated with earlier age of onset of Type II diabetes. Illicit drug use has also been associated to it, according to research in the United States(Karlon et al, 2001).The most common drugs regularly used are marijuana and cocaine, while other illicit drugs (amphetamines, heroin, hallucinogens, and nonmedical inhalants) are regularly used by diabetic primary care patients (ibid).

2. Old and new approaches to treatment

Diabetes is now ranked as the sixth leading cause of death by disease in the U.S (National diabetes fact sheet,Atlanta2004). Its treatment as well as the management of diabetes-related complications remains a top priority for governments worldwide, since the economic burden in 2007 alone exceeded $174 billion (Dall et al, 2007).

2.1 Pharmacological treatment

Old approaches to the treatment of this chronic progressive disease include diet modification and oral hypoglycemic medications, which have proven inadequate, while insulin therapy only solves the problem temporarily. Even with the newest pharmaco-therapies, patients continue to develop macro- and microvascular complications. Diabetes is associated with increased cardiac- and stroke-related deaths, kidney failure, blindness,

and 60% of non-trauma lower-limb amputations (National diabetes fact sheet,Atlanta2004).

Alternative treatments targeting different models of this disease require careful and responsible examination. As shown below, apart from insulin treatment, it is possible to gain diabetes control after gastrointestinal bypass surgeries.

2.1.1 Insulin therapy

Diabetes, being one of the primary causes of increased cardiovascular morbidity and mortality in Western countries, constitutes a large burden to health care systems in terms of both direct and indirect costs. Therefore, efficient glucose control (attainment of normal HbA1C, prandial and postprandial glucose levels) is essential to the prevention of the life-threatening complications of this disease.

Insulin is a hormone that treats diabetes by controlling the amount of sugar (glucose) in the blood. When used as a medication, it is derived from either pork (porcine), beef (no longer available in the U.S.), or is genetically made to be identical to human insulin (Buysschaert, 2000).

Patients with type I diabetes mellitus depend on external insulin (most commonly injected subcutaneously) for their survival because the hormone is no longer produced internally. Patients with type II diabetes mellitus are insulin resistant, have relatively low insulin production, or both; certain patients with Type II diabetes may eventually require insulin if other medications fail to control blood glucose levels adequately.

There are many types of insulin used to treat diabetes. They are classified by how fast they start to work, when they reach their "peak" level of action (i.e. when the concentration of insulin in the blood is highest), and how long their effects last.

The types of insulin include:

- ***Rapid-acting insulin***, which starts working within a few minutes and lasts for a couple of hours.
- ***Regular- or short-acting insulin***, which takes about 30 minutes to work and lasts for 3 to 6 hours.

- ***Intermediate-acting insulin***, which takes 2 to 4 hours to work and its effects can last for up to 18 hours.
- ***Long-acting insulin***, which takes 6 to 10 hours to reach the bloodstream, but it can keep working for an entire day (Tuomilehto, 2001).

Insulin for diabetes can be injected under the skin (subcutaneously) or into the vein (intravenously). Subcutaneous insulin injection continues to be the mainstay of therapy for all people with type I diabetes mellitus and the majority of individuals with type IIdiabetes mellitus. Insulin can be injected using a needle and syringe, a cartridge system, or prefilled pen systems. Insulin pumps are also available.

The initial dose is calculated based on the patient's weight and sensitivity to insulin, which varies from person to person. When given under the skin, insulin is typically taken so that two-thirds of the total daily dose is given in the morning and one-third of the total daily dose is given in the evening (Glasgow, 1999).

2.1.2 Complications of the insulin therapy

Diabetes mellitus is defined as a group of metabolic diseases characterized by hyperglycaemia, which when untreated can lead to long-term complications, including micro- and macrovascular complications. Tight glycaemic control with intensive insulin therapy has been suggested to reduce the risk of such complications in several diabetes populations; however, such an approach can also be associated with risks and challenges.

The major side effects of insulin taken for diabetes include low blood sugar (hypoglycemia), hypertrophy (enlargement of the area of the body that has received too many insulin injections), and rash at the site of injection or over the entire body (rare). The symptoms of the most common complication, i.e. low blood sugar, include extreme hunger, fatigue, irritability, cold sweats, trembling hands, intense anxiety and a general sense of confusion. They might be the signs of an insulin overdose, a potentially dangerous complication with diabetes, which happens to many diabetic patients (Gkaliagkousi, 2007). Thankfully, most episodes related to insulin are avoidable if patients stick with a few simple rules.

Diabetic ketoacidosis (DKA) is another insulin complication, which is the result of not taking enough insulin. In that case, excessive urination in response to high sugar

causes severe dehydration. At the same time, without enough insulin to allow sugar absorption, the body's cells act as if they are starving. Without insulin, patients with type I diabetes develop severely elevated blood sugar levels. This leads to increased urine glucose, which in turn leads to excessive loss of fluid and electrolytes in the urine. Lack of insulin also causes the inability to store fat and protein along with breakdown of existing fat and protein stores. This dysregulation results in the process of ketosis and the release of ketones into the blood. Ketones turn the blood acidic, a condition called diabetic ketoacidosis (DKA). Symptoms of diabetic ketoacidosis include nausea, vomiting, and abdominal pain. Without prompt medical treatment, patients with diabetic ketoacidosis can rapidly go into shock, coma, and even death (ibid).

Diabetic ketoacidosis (DKA) can be caused by infections, stress, or trauma, all of which may increase insulin requirements. In addition, missing doses of insulin is also an obvious risk factor for developing diabetic ketoacidosis. Urgent treatment of diabetic ketoacidosis involves the intravenous administration of fluid, electrolytes, and insulin, usually in a hospital intensive care unit. Dehydration can be very severe, and it is not unusual to need to replace 6-7 liters of fluid when a person presents in diabetic ketoacidosis. Antibiotics are given for infections. With treatment, abnormal blood sugar levels, ketone production, acidosis, and dehydration can be reversed rapidly, and patients can recover remarkably well (www.medicinenet.com/diabetes_mellitus).

Similar to DKA, hyperosmolar hyperglycemic nonketotic syndrome (HHNS)causes profound dehydration and can be life-threatening. It is an extremely serious complication that can lead to diabetic coma and even death in type II diabetes. Hyperosmolar hyperglycemic syndrome is much less common than DKA and tends to happen in older, obese patients with type II diabetes (Buysschaert, 2000).

Once they occur, these insulin complications require hospitalization for treatment. The mainstays of treatment for both HHNS and DKA are the same: correction of fluid deficits, electrolyte imbalances, and hyperglycaemia. In addition, it is particularly important in HHNS to identify and correct the underlying trigger condition.Hyperosmolar hyperglycemic nonketotic syndrome is often masked by the precipitating condition and comorbidities; it must be actively sought and the precipitating condition should be identified and treated.

In addition, HHNS has a high mortality rate. The fluid deficit is double than seen in diabetic ketoacidosis. The insulin therapy should be continued until the patient's mental status improves, hyperosmolality resolves, and the target glucose level is reached.

2.1.3 Non-Insulin Diabetes Treatment

There is a relatively new class of drugs called incretinmimetics, which mimic certain substances that can be found in the stomach and intestinal tract. These substances are normally released in response to food intake and signal the release of insulin from the pancreas. Since this reaction is reduced in people with type II diabetes, incretinmimetics work to stimulate insulin release and help lower blood sugar. The doctor may recommend incretinmimetics if a patient has not been able to adequately control their blood sugar with other types of treatment. These medications are taken by injection, either once or twice a day.

For people with type II diabetes, medications called DPP-4 inhibitors can be taken alone or in combination with other diabetes medications. DPP-4 inhibitors prevent the breakdown of incretin hormones. In turn, the incretins can help their body produce insulin to lower elevated blood sugar levels (Gkaliagkousi, 2007).

Oral Hypoglycemic Agents (oha)

The term "oral hypoglycemic agent" can refer to any anti-diabetic medication. The following five categories will be presented in brief: Sulphonylureasand similar (secretagogues), Biguanides (sensitizers), Thiazolidindiones, Alpha glucosidaseinhibitors, and Incretineanalogues/agonists (Boulton, 2005).

As concerns the mode of action of the secretagogues like sulphonylureas, they block the ATP-sensitive K+ channel and as a result they stimulate the insulin secretion. They are indicated to be the first choice once a patient is diagnosed with Type II Diabetes. The side effects include hypoglycaemia and disulfiram reaction, while its interaction is the competition for protein binding/metabolism/secretion. The first-generation agents include tolbutamide(Orinase), acetohexamide(Dymelor), tolazamide(Tolinase), and chlorpropamide(Diabinese); the second-generation agents include glipizide (Glucotrol), glyburide (Diabeta, Micronase, Glynase), and gliclazide(Diamicron); the third-generation agents include glimepiride(Amaryl). The Meglitinides are short acting secretagogues, similar to sulphonylureas. They also block the ATP-sensitive K+ and they open the Ca2 +

channels, thus stimulating insulin secretion. Their side effects include weight gain and hypoglycaemia.

i. As concerns the mode of action of the sensitisers such as the Biguanides, they reduce the hepatic synthesis and the output of glucose, while they increase the insulin uptake in the skeletal muscle. They are actually antihyperglycaemic and not hypoglycaemic. They are indicated for Type II Diabetes Mellitus and polycystic ovary syndrome. They help reduce LDL cholesterol and triglyceride levels and they may help with the weight loss. Their side effects include lactate acidosis, GIT discomfort, diarrhea, renal toxicity, but they do not cause hypoglycemia.
ii. As concerns the mode of action of the glitazones such as the Thiazolidinediones, they are selective agonists of PPARγ receptors, thus activating the insulin-sensitive genes regulating the glucose and fat metabolism. As a result, they increase the insulin sensitivity in the periphereal tissue. Their side effects include hepatotoxicity (troglitazone).
iii. As concerns the mode of action of the inhibitors of the alpha-glucosidase or the alpha amylace,they reduce the intestinal absorption of starch, dextrins, and disaccharides and as a result they reduce the postprandial plasma glucose. They are indicated both for Type I and Type II Diabetes, in combination with diet and insulin. Their side effects include malabsorption, flatulence, and diarrhea.
iv. As concerns the mode of action of the peptide analogues such as the GLP-1 agonists, they bind to a membrane GLP-1 receptor. They are metabolized by the dipeptidyl peptidase IV enzyme (DPP-IV). Their side effects include nausea, hypoglycemia (if given together with insulin secretagogue), and exenatide–acute pancreatitis. On the other hand, the mode of action of the GPP-4 inhibitors (gliptines) is that they increase the blood concentration of the incretin GLP-1 (glucagon-like peptide-1) by inhibiting its degradation by dipeptidylpeptidase-4 (DPP-4). It has fewer side effects than other OHA, but the fact they constitute a new class of drugs should be taken into account (Gkaliagkousi, 2007).

2.1.4 Metabolic surgery for type II diabetes

Metabolic surgery is now emerging as an area dedicated to the establishment of surgical procedures specifically aimed at treating diabetes. In the early 1980s, surgeons realized that many patients with type II diabetes who had undergone gastric bypass for the treatment of morbid obesity experienced a complete diabetes remission. This remission proved durable (Porries et al, 1995). Diabetes control and remission seems to be best obtained with procedures that include an intestinal bypass, as in gastric bypass or biliopancreatic diversion. With a 14-year follow-up, Pories et al. (1995) found an 83% resolution of Type II Diabetes in 608 patients after gastric bypass. Remission is typically not seen until several months postoperatively, only once weight loss has occurred.

The mechanism of diabetes resolution after gastrointestinal bypass remains unclear but is apparently not related to weight loss alone. In most cases, remission is observed in the days to weeks after surgery before any substantial weight loss has occurred (Briatore et al 2008). Furthermore, emerging evidence now shows that these effects may be achievable in the non-obese population as well.Clinical studies also show that the effect on diabetes after gastric bypass procedures does not depend only on the amount of weight loss (DePaula et al 2008).

The surgical treatment of diabetes may be the answer to the global health crisis of the next generation. However, as with all other surgical procedures, the benefits of surgery must be weighed against the potential risks. In other words, one must consider the possible complications and mortality of surgery versus the probable remission of diabetes and decrease in lifelong diabetes-related morbidity and mortality. Contrary to commonly held misperceptions, bariatric surgery has a strikingly safe operative profile and associated low mortality (Rubino et al 2009). The benefits of diabetes resolution accomplished by surgery are significant. Diabetes-related mortality after Roux-en-Y gastric bypass has been followed over a period of 7 years and decreased 92% compared with controls (Adams et al 2007). Another benefit of the surgery is the general improvement in metabolic syndrome, which contributes to a decrease in cardiovascular risk factors. Studies have shown a significant improvement in all components of the metabolic syndrome (type II diabetes, hypertension, increased fasting glucose and triglycerides, decreased HDL, and abdominal obesity) and an overall resolution of 95.6% at 1 year (Rossi et al 2008).

Surgery seems to provide an additional weapon against diabetes. Despite the compelling outcome data, the decision to operate should be made based on a risk factor assessment for each patient. Surgery is by design an invasive treatment modality and carries risks related to both anesthesia and the procedure itself. The potential benefits of metabolic surgery are in fact enormous. However, its implementation requires a rethinking of diabetes treatments goals and strategies. In the meantime, investigation into the pathophysiological basis of diabetes continues, with the hope of discovering the optimal therapeutic targets and best-suited interventions.

2.2 Non-pharmacological treatment

When it comes to non-pharmacological treatment of diabetes mellitus –especially type II diabetes– lifestyle modification alone can prevent development of diabetes in impaired glucose tolerance patients. It can also be the sole therapeutic tool in early diabetes.

After being diagnosed with diabetes, a behavior and lifestyle modification is required. Health care providers should advice all diabetics not to initiate tobacco and emphasize stopping smoking in smokers as utmost priority for diabetic smokers (Diabetes care 1993), since it increases the risk of renal failure, visual impairment, foot ulcers, leg amputations and heart attacks in people with diabetes. The effects of stopping smoking in diabetes are substantial. The incidence of micro and macro vascular complications was significantly increased in smokers compared to non-smokers (Buysschaert, 2000).

As concerns alcohol, consumption of large amounts can cause hypoglycaemia and this can occur many hours after alcohol intake, particularly if no food has been consumed beforehand.

2.2.1 Diet and Diabetes Mellitus

The major environmental factors that lead to type II diabetes are sedentary lifestyle and over nutrition leading to obesity (Harris, 1991). Sedentary lifestyle is more common in urbanized societies.

Dietary advice is essential upon diagnosis of diabetes. Normal advice includes:

- reducing intake of fatty foods

- eating mainly vegetables, fruit, cereal, rice and pasta (using wholemeal products where
- possible)
- eating only small amounts of refined sugar (jam, sweets etc.)
- eating at regular intervals
- carrying glucose tablets, sweets or products in case of hypoglycaemia
- exercising regularly; not only does it help reduce hyperglycaemia, but it also reduces insulin resistance by reducing obesity.

Most cases are preventable with healthy lifestyle changes and some can even be reversed. Taking steps to prevent and control diabetes doesn't mean living in deprivation. While eating right is important, patients don't have to give up sweets entirely or resign themselves to a lifetime of "health food".

Carbohydrates have a big impact on your blood sugar levels –more so than fats and proteins. In general, patients should limit highly refined carbohydrates like white bread, pasta, and rice, as well as soda, candy, and snack foods. Focus instead on high-fiber complex carbohydrates—also known as slow-release carbs. Slow-release carbs help keep blood sugar levels even because they are digested more slowly, thus preventing the body from producing too much insulin. They also provide lasting energy and help people stay full longer (Gross, 2005).

2.2.2 Exercise and Diabetes Mellitus

Physical activity reduces the risk of developing type II diabetes by 30-50% and risk reductions are observed with as little as 30 minutes of moderate exercise per day (Gkaliagkousi 2007). Regular exercise improves glycaemic control in all forms of diabetes. Insulin resistance is the major cause of hypoglycemia in type II diabetes and physical exercise is the best way to reduce insulin resistance (Goodpaster et al 2010). Physical activity improves insulin sensitivity in many ways. Fat accumulation in the liver is the main cause of insulin resistance in obesity. Exercise can reduce the free fatty acid load to liver and thereby reduce hepatic insulin resistance (Haus et al 2010). Exercise recommended is moderate exercise for 30 minutes a day (Tuomilehto et al 2001) or moderate physical activity like brisk walking at least 150 minutes per week (Diabetes Prevention Programme research group in *NEJM* 2002). Putative protective mechanisms

include reduction of body weight; reduction of insulin resistance, and thereby the associated consequences of the metabolic syndrome, including hypertension, dyslipidaemia and inflammation; and enhancement of endothelial function (Gkliagkousi 2007).

There are further benefits from staying active apart from losing weight and keeping fit. According to the American Diabetes Association, physical activity improves glucose management, lowers blood pressure, improves blood fats, as well as reduce the amount of insulin or diabetic pills after losing weight. It also helps keep off the weight a person loses and lowers the risk for other health problems. Physically active people will soon discover that they gain more energy and get better sleep as a result of action, which also reduces stress, anxiety and depression. Physical activities build stronger bones and muscles and helps people of all ages stay more flexible (American Diabetes Association: Standards of medical care in diabetes-2007).

2.2.3 Biological drugs in the therapy of Diabetes Mellitus

Biological therapy is treatment designed to stimulate or restore the ability of the body's immune system to fight infection and disease. Biological therapy is also called biotherapy or immunotherapy. Biological drugs are defined as medicines the active substance of which comes from a biological source.

These drugs are very different from normal prescription drugs and are developed through advanced technology called "genetic modification". Most of the biological drugs today are monoclonal antibodies (mABs). They can fight disease in the same way normal antibodies do, but they have been specially changed to find the specific area that needs treatment and to treat a specific disease with fewer side effects (Hauset al, 2010).

In type I diabetes, insulin-producing pancreatic β-cells are attacked and destroyed by the immune system. Although man-made insulin is life-saving, it is not a cure and it cannot prevent long-term complications. In addition, most Type I Diabetes patients would do almost anything to achieve release from the burden of daily glucose monitoring and insulin injection. Despite the formation of very large and promising clinical trials, a means to prevent and cure the disease in humans remains elusive.

This has led to an increasing interest in the possibility of using T cells with regulatory properties (Treg cells) as a biological therapy to preserve and restore tolerance to self-antigens (ibid).

Type I Diabetes accounts for 5% of the diabetic cases. Patients can no longer produce their own insulin either as a result of the destruction of the patient's β-islet cells of the pancreas by autoreactive T-cells or due to the neutralizing effect of auto-antibodies directed against insulin. The only treatment option today is insulin replacement.

An ActoBiotic developed by ActoGeniX is capable of delivering pro-insulin and IL10 in the gut, showing a restoration of antigen-specific, long-term tolerance and reversal of diabetes in NOD mice, combined with low-dose anti-CD3. Mechanistically, this intervention approach increases local regulatory T-cell frequencies, which proliferate in the pancreatic islets and suppress the auto-immune reaction in an antigen-specific way (ibid). Monoclonal antibodies, like Otelixizumab and Rituximab, can be used in the treatment of Type I Diabetes.

Otelixizumab

Otelixizumab, also known as TRX4, is a humanised anti-CD3 monoclonal antibody, which has been developed by Tolerx, Inc. as a treatment for autoimmune disorders, including Type I Diabetes. Otelixizumab targets CD3, a T lymphocyte receptor involved in normal cell signaling. It blocks the function of effector T cells, which mistakenly attack and destroy insulin-producing beta cells, while stimulating regulatory T cells, which are understood to protect against effector T cell damage, thus preserving the beta cells' normal ability to make insulin.

In 2011, Otelixizumab failed in a pivotal Phase 3 study, leaving safety and efficacy issues of biological drugs open to speculation. Otelixizumab shows great promise but leaves room for improvement. Results of ongoing trials will help define its role in the prevention of T1DM (Goodpaster, 2010).

Rituximab is a monoclonal antibody against the protein CD20, which is primarily found on the surface of β-cells. It is used as a treatment to some autoimmune disorders, including Type I Diabetes.

Type I Diabetes is believed to be due to the autoimmune destruction of β-cells by T lymphocytes. It has been reported that a single course of Rituximab can attenuate C-peptide loss over the first year of disease (Daneman, 2006).

Biological drugs have been proven to help not only with the treatment of diabetes itself but also with the complications from which the patients suffer. In particular, they are used as a cure to diabetic foot ulcers and diabetic kidney disease. Therefore, patients can fight not only diabetes but other annoying issues as well. Prompt biological therapy has been proven to speed up diabetic foot ulcer healing.

3. Prevention and management of diabetes complications

Diabetes is a group of chronic diseases characterized by hyperglycaemia. Modern medical care uses a vast array of lifestyle and pharmaceutical interventions aimed at preventing and controlling hyperglycaemia. In addition to ensuring the adequate delivery of glucose to the tissues of the body, treatment of diabetes attempts to decrease the likelihood that the tissues of the body are harmed by hyperglycaemia.

The importance of protecting the body from hyperglycaemia cannot be overstated; the direct and indirect effects on the human vascular tree are the major source of morbidity and mortality in both type I and type II diabetes.

Diabetes complications are divided into two major categories:

a. Acute complications such as hypoglycaemia and comas resulting either form DKA or HHNS (as stated above) and
b. Chronic complications, either microvascular (diabetic retinopathy, nephropathy, neuropathy) or macrovascular (coronary artery disease, peripheral arterial disease, and stroke)

Microvascular

The most serious microvascular diabetes complications are the eye complications. Diabetic patients are strongly advised to have an annual ophthalmic exam. Diabetic retinopathy is the leading cause of blindness in the working population of the Western world. The risk of developing diabetic retinopathy or other microvascular complications

of diabetes depends on both the duration and the severity of hyperglycaemia (Almdal, 2006).

Diabetic retinopathy is generally classified as either background or proliferative. It is important to have a general understanding of the features of each to interpret eye examination reports and advise patients of disease progression and prognosis. Background retinopathy includes such features as small hemorrhages in the middle layers of the retina. They clinically appear as "dots" and therefore are frequently referred to as "dot hemorrhages." Proliferative retinopathy is characterized by the formation of new blood vessels on the surface of the retina and can lead to vitreous hemorrhage (Watkins 2003).

Diabetic nephropathy is the leading cause of renal failure in the United States. About 20% to 30% of the patients with diabetes develop evidence of nephropathy. Initial treatment of diabetic nephropathy, as of other complications of diabetes, is prevention. Like other microvascular complications of diabetes, there are strong associations between glucose control and the risk of developing diabetic nephropathy. Patients should be treated to the lowest safe glucose level that can be obtained to prevent or control diabetic nephropathy (Gross et al 2005). In addition to aggressive treatment of elevated blood glucose, patients with diabetic nephropathy benefit from treatment with antihypertensive drugs. Renin-angiotensin system blockade has additional benefits beyond the simple blood pressure-lowering effect in patients with diabetic nephropathy (Gross et al 2005).

Diabetic neuropathy is recognized by the American Diabetes Association (ADA) as "the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes" (Diabetes Care 2007). As with other microvascular complications, risk of developing diabetic neuropathy is proportional to both the magnitude and duration of hyperglycaemia, and some individuals may possess genetic attributes that affect their predisposition to developing such complications.

The precise nature of injury to the peripheral nerves from hyperglycaemia is not known but likely is related to mechanisms such as polyol accumulation, injury from AGEs, and oxidative stress. Peripheral neuropathy in diabetes may manifest in several different forms, including sensory, focal/multifocal, and autonomic neuropathies. More than 80% of amputations occur after foot ulceration or injury, which can result from diabetic neuropathy (Boulton et al 2005).

Diabetic autonomic neuropathy also causes significant morbidity and even mortality in patients with diabetes. Neurological dysfunction may occur in most organ systems and can by manifest by gastroparesis, constipation, diarrhea, anhidrosis, bladder dysfunction, erectile dysfunction, exercise intolerance, resting tachycardia, silent ischemia, and even sudden cardiac death ((Boulton et al 2005).Patientsmay be asymptomatic or complain of numbness, burning, tingling, and "electrical" pain. While the feet are mostly affected, the hands are seldom affected.

Macrovascular

The central pathological mechanism in macrovascular disease is the process of atherosclerosis, which leads to narrowing of arterial walls throughout the body. Atherosclerosis is thought to result from chronic inflammation and injury to the arterial wall in the peripheral or coronary vascular system (Lehto, 1996).

Diabetes increases the risk that an individual will develop cardiovascular disease (CVD). Although the precise mechanisms through which diabetes increases the likelihood of atherosclerotic plaque formation are not completely defined, the association between the two is profound (Laing et al 2003). Cardiovascular disease is a major complication and the leading cause of premature death among diabetic patients(Merz et al 2002). Diabetic patients have a 2 to 6 times higher risk for developing complications such as ischemic heart disease, cerebrovascular disease and peripheral vascular disease than the general population.

Among macrovascular diabetes complications, coronary heart disease has been associated with diabetes in numerous studies beginning with the Framingham study (Kannel et al 1979).

The major cardiovascular risk factors in the non-diabetic population (smoking, hypertension and hyperlipidemia) also operate in diabetes, but the risks are enhanced in the presence of diabetes. Overall life expectancy in diabetic patients is 7 to 10 years shorter than non-diabetic people.

Type II diabetes typically occurs in the setting of the metabolic syndrome, which also includes abdominal obesity, hypertension, hyperlipidemia, and increased coagulability. These other factors can also act to promote CVD. Even in this setting of multiple risk factors, type II diabetes acts as an independent risk factor for the

development of ischemic disease, stroke, and death (Almdal et al 2004), Diabetes is also a strong independent predictor of risk of stroke and cerebrovascular disease, as in coronary artery disease (Lehto et al 1996).

The increased risk of CVD has led to more aggressive treatment of these conditions to achieve primary or secondary prevention of coronary heart disease before it occurs. Studies in Type I Diabetes have shown that intensive diabetes control is associated with a lower resting heart rate and that patients with higher degrees of hyperglycaemia tend to have a higher heart rate, which is associated with higher risk of CVD (Paterson et al 2007).

Once clinical macro-vascular disease develops in diabetic patients they have a poorer prognosis for survival than normoglycaemic patients with macrovascular disease. The protective effects females have for the development of vascular disease are lost in diabetic females.

In addition, the combination of hypertension and diabetes is a serious situation, posing increased predisposition to cardiovascular morbidity and mortality. There is no doubt that hypertension occurs more commonly in diabetic patients, and confer a greater prospect of development of complications; it should therefore be taken as seriously as glycaemic control when planning treatment strategies.

Hyperlipidemia can occur as a result of poorly controlled diabetes, or may occur as an independent risk factor for macrovascular disease. About 25% of patients attending a diabetes clinic will have elevated lipid levels (Jacobson, 1985).

Infections

Diabetic patients are also in greater risk of infections than healthy individuals. The association between diabetes and increased susceptibility to infection in general is not supported by strong evidence. However, many specific infections are more common in diabetic patients and some occur almost exclusively in them. Other infections occur with increased severity and are associated with an increased risk of complications.

Several aspects of immunity are altered in patients with diabetes. There is evidence that improving glycaemic control improves immune function. Fungal cystitis,

rhino-cerebral mucormycosis and community-acquired pneumonia are among the most common infections the diabetic patients suffer from (Gu, 1998).

Recommendations for managing the complications of diabetes mellitus

- Blood pressure should be measured routinely. Goal blood pressure is < 130/80 mmHg. Patients with a blood pressure ≥ 140/90 mmHg should be treated with drug therapy in addition to diet and lifestyle modification.
- Patients with a blood pressure of 130-139/80-89 mmHg may attempt a trial of lifestyle and behavioral therapy for three months and then receive pharmacological therapy if their goal blood pressure is not achieved.
- Lipid testing should be performed in patients with diabetes at least annually. Lipid goals for adults with diabetes should be an LDL < 1000 mmol/l (or < 700mmol/l in patients with overt CVD), HDL > 500mmol/l, and fasting triglycerides < 1500mmol/l.
- All patients with diabetes should be encouraged to limit consumption of saturated fat, trans fat, and cholesterol.
- Patients with type I diabetes should receive a comprehensive eye examination and dilation within 3-5 years after the onset of diabetes. Patients with type II diabetes should undergo such screening at the time of diagnosis.
- Patients should strive for optimal glucose and blood pressure control to decrease the likelihood of developing diabetic retinopathy or experiencing progression of retinopathy (Paterson et al, 2007).
- All patients with diabetes should undergo screening for distal symmetric polyneuropathy at the time of diagnosis and yearly thereafter.
- Patients who experience peripheral neuropathy should begin appropriate foot self-care, including wearing special footwear to decrease their risk of ulceration.
- In addition to the above pharmacological recommendations, patients with diabetes should be encouraged to not begin smoking or to stop smoking to decrease their risk of CVD and benefit their health in other ways.

4. Life with Diabetes Mellitus

Diabetes affects over 24 million people in the United States today. It is a unique disease because people diagnosed with it must be responsible for the majority of their

own care. There are a lot of areas to cover. Insulin, medication, blood glucose monitoring, diet, and exercise are all important parts of diabetes management that must be incorporated into their lifestyle. There is not just one way of coping with the disease because it needs to be managed on a lot of different levels. Good diabetes management requires many different treatments and strategies in order to be effective.

People experience a variety of feelings when they are first diagnosed with diabetes. Denial to accept that something is wrong, guilt of having caused the diabetes themselves or even anger are some of the most common reactions to the bad news.

Diabetes is a common disease, yet every individual needs unique care (www.diabets.org/living-with-diabetes/treatment-and-care). The health care team is the point to start from. However, patients should always keep in mind that they themselves are the most important member of the health care team, which in turn depends on them to talk to them honestly and tell them how they feel or if they have noticed any problems.

In general, treatment of diabetes aims to do what the body of a diabetic patient would normally do –maintain a proper balance of insulin and glucose. Living well with diabetes means keeping the level of glucose in the blood as close to normal as possible.

The three elements for controlling type I diabetes are food, exercise and insulin. In many people with type II diabetes, diet and exercise alone can control blood glucose levels. A health care team will be able to suggest a specific lifestyle or exercise plan depending on age, lifestyle and overall health (Glasgow, 1999).

The health care team

The Primary Care Provider, who may be a primary care or family practice physician, is who the patients see for general checkups and when they get sick. Other health care providers who provide primary care include nurse practitioners and physician assistants, who typically work in collaboration with a physician (Diabetes Prevention Programme research group. Reduction in the incidence of type2 diabetes with life style intervensions or metformin. *NEJM* 2002)

A nurse educator or ***diabetes nurse practitioner*** is a registered nurse (RN) with special training and background in caring for and teaching people with diabetes. Many are

certified in the field of diabetes. Nurse educators often help the patients learn the day-to-day aspects of diabetes self-care (ibid).

A ***registered dietitian (RD)*** is trained in nutrition but patients should make sure that the RD also has training and experience with diabetes. The RD helps patients figure out their food needs based on their desired weight, lifestyle, medication, and other health goals (such as lowering blood fat levels or blood pressure). Dietitians can also help patients learn how the foods they eat affect their blood sugar and blood fat levels (Laakso, 1999).

An ***endocrinologist*** is a doctor who specializes in treating diabetes and other diseases of the "endocrine system" –the body's system of glands that produce hormones that control the way the body works. The pancreas is part of the endocrine system, and insulin is one of the key hormones the body needs to function properly.

The ***eyedoctor*** is another key member of a patient's health care team, because diabetes can affect the blood vessels in the eyes. When eye problems are caught early, there are very good treatments. The eye doctor will be either an ophthalmologist or an optometrist. The American Diabetes Association guidelines say you should see your eye doctor at least once a year. These checkups are the best way to detect diabetic eye disease (Rubin, 2000).

Mental health professionals help with the personal and emotional side of living with diabetes. A few sessions with a psychologist might help during a time of special stress. On a long-term basis, a psychologist might help work on more lasting problems. A psychiatrist is a medical doctor who can prescribe medication to treat physical causes for emotional problems. Psychiatrists also provide counseling.

A ***podiatrist*** is trained to treat feet and problems of the lower legs. Diabetes makes patients prone to poor blood flow and nerve damage in the lower legs. They may get infections more often. Sores, even small ones, can quickly turn into serious problems. Any foot sore or callus needs to be checked by a primary care doctor or a podiatrist.

A ***pharmacist*** has a wealth of information on medicines: what's in them and how they interact with each other. Pharmacists are highly trained professionals who must know about the chemistry of the products they dispense and what effects, both good and bad, medications have on the body. Therefore, they can also give advice on whether and how

any medication patients take for their diabetes or other conditions could or will affect their blood glucose levels. Pharmacists do more for diabetic patients than fill their prescriptions. They alert them to the potential common or severe side effects of any drug they are going to take. With each new prescription, they can review their medication profile to see if any of their current medications might interact with their new prescription. So, in addition to asking their diabetes care provider, diabetic patients can ask their pharmacist to recommend over-the-counter medicines for colds or other minor illnesses. For example, if a pharmacist knows that a diabetic patient takes a sulfonylurea, he or she may recommend a cold medicine with little or no alcohol to avoid any possible interaction between the two medications.

Diabetic patients should visit a ***dentist*** every six months. People with diabetes are at somewhat greater risk for gum disease. The excess blood sugar in their mouths makes it a good home for bacteria, which leads to infection.

An ***exercise physiologist*** is an indispensable part of a health care team when it comes to treat people with diabetes. Exercise plays a major role in diabetes care, either type I or type II diabetes, since it can help lower blood sugar, help the body better use insulin, and help control weight. It can also improve blood fat levels, reduce stress, and improve the overall fitness level. Diabetic patients should always get their doctor's approval for any exercise programme.

4.1 Quality of life

Quality of life is also increasingly recognized as an important health outcome in its own right, representing the ultimate goal of all health interventions. More than 70 years ago, the World Health Organization stated that health was defined not only by the absence of disease and infirmity, but also by the presence of physical, mental, and social well-being (World Health Organozation: Handbook of Basic Documents 1952). Though health care providers sometimes focus on medical outcomes alone when assessing the efficacy of their interventions, any person with diabetes will confess that these outcomes are truly meaningful only to the extent that they affect physical, emotional, and social well-being –thatis, quality of life.

Diabetes is a demanding disease. Almost every diabetic person feels that diabetes powerfully affects their lives, and most feel burdened by the manifold demands of their

disease, an experience that could be called "diabetes *overwhelmus*," since so many people feel overwhelmed by the continuous burden of their disease and its management. These emotional and social burdens may be compounded by the acute physical distress of hypoglycaemia or hyperglycaemia and by the chronic physical distress of diabetes-related complications.

It seems clear that diabetes can affect a person's quality of life. But what is quality of life? In the most general terms, quality of life may be thought of as a multidimensional construct incorporating an individual's subjective perception of physical, emotional, and social well-being, including both a cognitive component (satisfaction) and an emotional component (happiness) (Richard 2000).

Quality of life has importance for people with diabetes and their health care providers for several reasons. Diabetes *overwhelmus* leads to diminished self-care, which in turn leads to worsened glycaemic control, increased risks for complications, and exacerbation of diabetes *overwhelmus* in both the short run and the long run.

Some demographic variables are associated with quality of life in people with diabetes, just as they are in the general population:

- Men generally report better quality of life than women.
- Younger people generally report better quality of life than older people.
- Those with more education or income generally report better quality of life than those with less of either.

When it comes to quality of life for men with diabetes, sexual problems can be all too common. While both men and women can develop sexual problems because of damage to nerves and small blood vessels, men are much more affected. The National Diabetes Information Clearing House (NDIC) states that erectile dysfunction can range from 20% to as high as 75% of men with diabetes (www.diabetes.about.com). Men can also experience problems with ejaculation.

All people encounter change in sexual function as they age. However, men with diabetes may start to experience problems at a younger age and with more severity due to small blood vessel and nerve damage caused by poor control of diabetes. Problems can appear as much as 10-15 years earlier than can be expected for men without diabetes. In

fact, erectile dysfunction in men younger than 45 years old can be a sign of diabetes or indicate a high risk for developing diabetes in the future.

In order to lower the risk of sexual problems, men with diabetes should manage it very well, keep a healthy diet, exercise regularly as well as keep abdominal fat within normal limits. A health care provider may also suggest a treatment for erectile dysfunction but the first step is counseling and seeking out emotional and psychological support (Quality of Life -A population study, Diabetes Care 2004).

4.2 Psychological factors and Diabetes Mellitus

Any potentially life-threatening condition has some psychological impact, and that of diabetes is profound. In type I diabetes cases, family members often experience the classic stages of grief, progressing from anger and denial to bargaining, depression, and finally resolution or acceptance.

The growing interest in health-related quality of life in general and diabetes-related quality of life in particular is a positive trend, which reflects a deeper understanding and appreciation of the crucial role of behavioral and psychosocial factors in the lives of diabetic patients (Glasgow et al 1999). It is widely accepted that diabetes can affect a patient's quality of life, and that perceived quality of life can powerfully affect a person's commitment to active diabetes self-management. The growing awareness of the importance of quality of life in diabetes has led researchers to ask a broad range of questions concerning their interrelationships.

Some psychosocial factors, including health-related beliefs, social support, coping style, and personality type might have a potent effect on quality of life. These effects may be direct, or they may be indirect, buffering the negative impact of diabetes or its demands. In fact, these psychosocial factors may be the most powerful predictors of quality of life, often outweighing the effects of important disease-related factors, such as complications (Peyrot et al 1999).

Among adults, recent studies have shown that better Diabetes Related Quality of Life (DRQoL) is associated with higher levels of social support, self-efficacy, physical activity, education, income, and with the absence of health complications and co-morbid psychiatric disorders (Aalto et al 1997).

4.3 Depression and Diabetes Mellitus

Depression

The emotional well being of people with diabetes is important and is integral to the overall health of an individual, particularly for people with long-term conditions such as diabetes. People with diabetes may have emotional or psychological support needs resulting from living with diabetes or due to causes external to the condition.

Coming to terms with diagnosis, the development of a complication, the side effects of medication, or dealing with the daily responsibility of self-managing diabetes can take their toll on emotional well-being. In some cases this can lead to depression, anxiety, eating disorders, or phobias. The prevalence of depression is approximately twice as high in people with diabetes as it is in the general population (Katon et al 2004).

Diabetes self-management, especially type I, can be difficult and frustrating for both patients and practitioners. Thus, it is important to discuss psychosocial barriers to diabetes self-management and quality of life. Defining the meaning of psychological barriers is not easy. Webster's dictionary defines a barrier as "*something immaterial that impedes or separates*" (Webster's Encyclopedic Unabridged Dictionary of the English Language 1994). In the case of diabetes, researchers are concerned with psychological and interpersonal factors that impede diabetes management or diabetes-related quality of life. In this conceptualization, depression would be a barrier, due to its demonstrated inverse relationship to self-management and quality of life.

People who are diagnosed with a chronic physical health problem such as diabetes are three times more likely to be diagnosed with depression than people without it (www.diabetes.co.uk/diabetes-and-depression). Depression can have a serious impact on a person's well being and their ability and motivation to self-manage their condition. Depression is the most common psychiatric disorder witnessed in the diabetes community. It may develop because of stress but also may result from the metabolic effects of diabetes on the brain (Kovacs et al 1995). Some studies have suggested that women with diabetes may be more likely to suffer from depression compared with their male counterparts (Wilkinson et al 1988).

For people with diabetes, dealing with a lifelong condition and managing the risk of complications can seem like an overwhelming task, particularly for newly diagnosed patients. Many diabetics struggle to cope with the requirements, feeling overwhelmed and unmotivated. If diabetes is not faced with an attitude of perseverance and defiance, often depression will prevail.

Depression is associated with hyperglycaemia and an increased risk for diabetic complications; relief of depression is associated with improved glycaemic control. Depression has also been associated with an increased risk for complications of diabetes, particularly cardiovascular disease and retinopathy (Jacobson et al 1985). The mechanisms of these associations are not fully understood, but it is plausible that alleviation of depression improves glycaemic control and thereby decreases the risk for complications. Pharmacotherapy for depression may be poorly tolerated or may be insufficient to produce full remission in as many as 50% of diabetic patients with major depression (Popkin et al 1985).

Depression for those with diabetes is an important comorbidity that requires careful management because of its severe impact on quality of life (Goldney et al 2004). Depression can affect a patient's capacity to deal with their diabetes, including managing blood glucose levels appropriately. Research has found that people who suffer from both diabetes and depression have poorer metabolic and glycaemic control which has, in turn, been found to intensify symptoms of depression (Lustman et al 2005). Treating depression with psychotherapy, medication or a combination of these treatments can improve a patient’s well-being and ability to manage diabetes (Ciechonowski et al 2000).

Additionally, anti-depressants have been found to have hypoglycaemic effects causing serious problems for self-management. It has previously been reported that depressed people with diabetes are less likely to adherence to medication and diet regimens and subsequently have a reduction in quality of life and increased health care expenditure.Research has shown that by addressing depression, glycaemic control is enhanced, and mood and quality of life are significantly improved (Lustman et al 2005).

Apart from depression, there are other mental health issues that can arise as a result of being diagnosed with a chronic physical condition such as diabetes. Conditions including bipolar disorder and anxiety disorders are also common in people who have diabetes.

Managing the two conditions together

Coping with the two conditions effectively can be a hard task. Patients are advised to adopt diabetes programmes that focus on behavior and they have been successful in helping people improve their metabolic control, increase fitness levels, and manage weight loss and other cardiovascular disease risk factors. They can also help improve the patients' sense of well-being and quality of life.

Furthermore, participants in psychotherapy, particularly cognitive behavioral therapy, have reported improvements in depression, which has resulted in better diabetes management. Psychotherapy is the principal non-pharmacologic method for the management of depression. Cognitive behavioral therapy identifies the indivindual's thoughts (rather than external influences) as the cause of their feelings and actions. Therapists focus on altering the way patients think, in order to help them feel better (Wilkinson, 1988).

5. Statistics

Statistical data from around the world shows the prevalence of this disease. There is an emerging global epidemic of diabetes that can be traced back to rapid increases in overweight, obesity and physical inactivity. According to statistical data from the World Health Organisation, n developed countries most people with diabetes are above the age of retirement, whereas in developing countries those most frequently affected are aged between 35 and 64 (www.who.int).

Prevalence of diabetes is increasing in the European Region, already reaching rates of 10-12% of the population in some Member States. This increase is strongly associated with increasing trends towards overweight and obesity, unhealthy diets, physical inactivity and socioeconomic disadvantage. These risk factors also contribute to the development of the other three noncommunicable diseases (NCDs) that have become international public health priorities (cardiovascular disease, chronic respiratory diseases and cancer), making it imperative that the prevention of diabetes be integrated into population approaches to prevent NCDs as a group (World Health Organization, Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications. Report of a WHO Consultation,1999).

The associated burden on a global level is increasing globally, particularly in developing countries. Noncommunicable diseases (NCDs), such as heart disease, stroke, cancer, chronic respiratory diseases and diabetes, are the leading cause of mortality in the world. This invisible epidemic is an under-appreciated cause of poverty and hinders the economic development of many countries.

6. Type III Diabetes Mellitus

New evidence has come to light concerning the different expressions of diabetes, as well as its connection to other diseases. It used to be thought that there were two types of diabetes: the type people are born with (Type I) and Type II, which was called 'adult onset' until it started ravaging chidren. Type II is brought about by a combination of factors, including diet. However, the idea that Alzheimer's might be Type III diabetes has been around since 2006 (Martins, 2006).

Over a century ago, aneuropathologist named Alois Alzheimer noticed that an odd form of protein was taking the place of normal brain cells. How those beta amyloid plaques (as they are called) get there has remained a mystery. What is becoming clear, however, is that a lack of insulin —or insulin resistance —not only impairs cognition but it also seems to be implicated in the formation of those plaques.

Ever since this condition of clinical dementia was first described by Alois Alzheimer in1907, the incidence of Alzheimer's Disease has increased exponentially. It is actually a progressive neurodegenerative disorder characterized by a progressive decline in memory functions. There are presently 5 million Americans affected with it, and the estimated annual health care cost is almost 100 billion dollars, which explains why it has become a growing public health concern. Furthermore, due to the expected increase in the number of individuals 65 years or older, it has been estimated that the total incidence of Alzheimer's Disease will quadruple by the year 2050 (Brookmeyer et al 1998).

It has recently been suggested that there is a linkbetween Alzheimer's Disease and Type II Diabetes Mellitus (Pasinetti, 2011). Dr. Suzanne de la Monte from RIH is the one responsible for making this fascinating connection, having found in her research that diabetes is closely associated with several key neuronal factors implicated in dementia. It turns out that Alzheimer's progresses as a result of the brain developing resistance to insulin, which in turn prevents proper lipid (fat) metabolism. Over time, these lipids build

up in the brain rather than properly absorb, which results in increased stress and inflammation, as well as the symptoms commonly associated with dementia (Monte et al, 2011).

Suzanne de la Monte (ibid)has been working on these phenomena in humans and rats. When she blocked the path of insulin to rats' brains, their neurons deteriorated, they became physically disoriented and their brains showed all the signs of Alzheimer's. The fact that Alzheimer's can be associated with low levels of insulin in the brain is the reason why increasing numbers of researchers have taken to calling it Type III diabetes, or diabetes of the (ibid).

Emerging research on the widespread degenerative brain disease known as Alzheimer's suggests that this prevalent form of dementia is actually a type of diabetes. Published in the Journal of Alzheimer's Disease, a recent study out of Rhode Island Hospital (RIH) confirms that Alzheimer's is marked by brain insulin resistance and corresponding inflammation, a condition that some researchers are now referring to as Type III Diabetes (ibid).

In many respects, Alzheimer's is a brain form of diabetes. Even in the earliest stages of the disease, the brain's ability to metabolize sugar is reduced. Normally, insulin plays a big role in helping the brain take up sugar from the blood. But, in Alzheimer's, insulin is not very effective in the brain. Consequently, the brain cells practically starve to death (Sun, 2011).

These days, type II Diabetes Mellitus is the prevalent type of diabetes. Basically, cells throughout the body become resistant to insulin signals. In an effort to encourage cells to take up more sugar from the blood, the pancreas increases the output of insulin. The high levels of insulin could damage small blood vessels in the brain, and eventually lead to poor brain circulation. This problem could partly explain why Type II diabetes harms the brain. In Alzheimer's, the brain, especially parts that deal with memory and personality, become resistant to insulin (ibid).

As in most organs, insulin stimulates brain cells to take up glucose or sugar, and metabolize it to produce energy. In addition, insulin is very important for the chemicals known as neurotransmitters, which are needed for neurons to communicate with each

other. Insulin also stimulates many functions that are needed to form new memories and conquer tasks that require learning and memory (Pasinetti, 2011).

People with diabetes are more likely to be diagnosed with Alzheimer'sDisease as well. In fact, their risk is doubled, at least. Obesity also increases the risk of cognitive impairment, or mental decline. This doesnot mean that everyone who has diabetes will develop Alzheimer's in the long run or that all people with Alzheimer's have diabetes. It isimportant to recognise that there is considerable overlap between Alzheimer's and diabetes.

6.1 Shared pathophysiology between Type II Diabetes Mellitus and Alzheimer's disease

Diabetes and Alzheimer's disease have traditionally been thought to be independent disorders. However, the results of recent epidemiological and basic science investigation have suggested possible associations and some common pathophysiological mechanisms. If true, common pharmacotherapy should be effective.

Type II Diabetes Mellitus and Alzheimer's disease are both more prevalent with ageing, but it has generally been assumed that this is coincidental, not a reflection of co-morbidity. However, evidence suggests that patients with Type II Diabetes Mellitus are at an increased risk of getting Alzheimer's Disease and that hyperinsulinaemia and insulin resistance –hallmarks of Type II Diabetes Mellitus– can lead to memory impairment (Akter et al 2011).

Alzheimer's disease currently accounts for 60–80% of cases of dementia. Onset of symptoms progresses to cognitive decline and eventually leads to death. The exact pathological defects in Alzheimer's Diseaseare unknown, but prevailing theories implicate build-up of soluble β-amyloid oligomers or insoluble plaques or neurofibrillary tangles (ibid).

As concerns the role of insulin in Alzheimer's Disease, insulin and insulin signaling have been suggested to play a role to its pathophysiology. In population-based studies, individuals with Type II Diabetes Mellitus are at an increased risk for cognitive impairment, dementia, and neurodegeneration. Mechanisms through which diabetes presents a risk factor include glycaemia, insulin resistance, oxidative stress, advanced glycationend-products, inflammatory cytokines, and microvascular and macrovascular

disease. The principal defect in Type II Diabetes Mellitus is insulin resistance, leading to insulin deficiency. The islet of Langerhans (in the pancreas) in Type II Diabetes is characterized by β-cell loss and islet amyloid derived from islet amyloid polypeptide (IAPP), a protein co-expressed and secreted with insulin by β-cells. As with Aβ peptides, IAPP spontaneously forms into amyloid aggregates in an aqueous environment. Additionally, as with Alzheimer's Disease, the incidence of Type II Diabetes strongly increases with age. Borderline diabetes is also associated with increased risks of dementia and Alzheimer's Disease, independent of whether one develops diabetes in later life, and may interact with severe systolic hypertension to multiply one's risk for Alzheimer's disease. These findings implicate a close biological relationship between Type II Diabetes and AD (Pasinetti et al 2011).

6.2 The link between Alzheimer's Disease and Type II Diabetes Mellitus

Alzheimer's disease is a devastating neurodegenerative condition. There is much evidence suggesting that certain dietary lifestyles can help to prevent and possibly treat Alzheimer's disease.

High-fat diets and sedentary lifestyles have become major concerns throughout the world. They have led to a growing incidence of obesity, dyslipidemia, high blood pressure, and hyperglycemic conditions, known collectively to be components of metabolic syndrome. These health conditions are well known to develop along with, or be precursors of, atherosclerosis, cardiovascular disease, and diabetes. Recent studies have found that most of these disorders can also be linked to an increased risk of the Alzheimer's Disease. Of note, accumulating evidence suggests a mechanistic link between the cholesterol metabolism in the brain and the formation of amyloid plaques in AD development (Martins et al 2006).

The risk for developing both Type II Diabetes Mellitus and sporadic Alzheimer's Disease increases exponentially with age, and having Type II Diabetes Mellitus doubles the risk of developing Alzheimer's Disease. The postmortem brains of Alzheimer's Disease patients show altered activities of insulin receptors and downstream molecules, as well as reduced protein and mRNA levels of insulin (Monte et al, 2011).

Morerecent laboratory research using animal models has identified mechanisms that are shared by diabetes and Alzheimer's Disease. Exogenous application of

streptozotocin, which disrupts systemic insulin secretion, results in insulin deficiency, increased tau phosphorylation, and cognitive impairments that can be reversed by exogenous insulin supplementation ((Sun 2011).

However, Alzheimer's Disease pathology is more severe in Type II Diabetes Mellitus. The symptoms of this Alzheimer'sDisease pathology included increased tau phosphorylation at multiple sites, increased tau cleavage, and greater neuronal and synaptic damage, even with increased amyloid β protein production. Therefore, it has been suggested that hyperinsulinemia and insulin resistance represent major factors underlying Alzheimer's Disease in Type II Diabetes Mellitus (Monte 2011).

A recent study involving cross-mating ob/ob and amyloid precursor protein transgenic mice provided evidence that Type II Diabetes Mellitus and Alzheimer's Diseaseaggravate each other, and suggested that cerebral vessels constitute an important substrate that is commonly damaged by the two major disorders. Given the evidence provided by animal models, further investigation of the mechanisms underlying Type II Diabetes Mellitus in Alzheimer's Diseaseshould help to identify potential treatment targets in Alzheimer's Disease (Sun 2011).

Conclusions

According to the World Health Organization, diabetes is a chronic disease, which occurs when the pancreas does not produce enough insulin, or when the body cannot effectively use the insulin it produces. This leads to an increased concentration of glucose in the blood (hyperglycaemia).Type I diabetes (previously known as insulin-dependent or childhood-onset diabetes) is characterized by a lack of insulin production.Type II diabetes (formerly called non-insulin-dependent or adult-onset diabetes) is caused by the body's ineffective use of insulin. It often results from excess body weight and physical inactivity.Gestational diabetes is hyperglycaemia that is first recognized during pregnancy.

It is essential to raise awareness about diabetes and its escalating rates around the world. That is the reason why the International Diabetes Federation and the World Health Organization started the International Diabetes Day. It is celebrated on 14th November to mark the birthday of Frederick Banting who, along with Charles Best, was instrumental in

the discovery of insulin in 1922, a life-saving treatment for diabetes patients. (The information is provided at theofficial website of WHO).

It is not easy for anyone to hear that they have diabetes. But for millions of people around the world, learning about their diabetes is the first step toward feeling better and living a longer, healthier life.However, the situation is not always irreversible. Lifestyle interventions including modified diet, increased physical activity, and weight loss are critical for all diabetes patients. For highly motivated patients, whose diabetes is at a relatively early stage, it is even possible to pursue lifestyle interventions for three to six months before starting medication.

There are old and new approaches to the treatment of diabetes mellitus. Old approaches include diet modification and oral hypoglycemic medication. Insulin is a temporary solution to the problem. In addition, insulin therapy has serious complications, such as diabetic ketoacidosis etc. Non-insulin diabetes treatment engages incretin mimetics, which the substances found in the stomach and the intestinal tract as a response to food intake. Then, they signal the release of insulin from the pancreas. There are the oral hypoglycemic agents, such as sulphonylureas and similar (secretagogues), biguanides (sensitizers), thiazolidindiones, alpha glucosidaseinhibitors, and incretineanalogues/agonists. It is possible to undergo metabolic surgery, gastric bypass in particular. Biological drugs can also help fight diabetes mellitus.

The complications of diabetes often lead to the death of most diabetic patients, since the risk for stroke and heart disease is much higher when compared to adults without diabetes. Diabetes can also lead to blindness, kidney disease, nervous system damage, infections, dental disease, and complications of pregnancy. It can also be a cause for amputations. There is also greater possibility for diabetic patients to have depression. Cosequently, it is important for them to invlve themselves in psychotherapy, which will not only help them with depression but it will also help with the management of diabetes. Apart from the diabetist and the psychotherapist, the health care team of diabetic patients should consist of

The population of the developed world is aging, and the incidence of age-related metabolic and neurodegenerative diseases are increasing. Diabetes and Alzheimer disease —two age-related diseases— are both increasing in prevalence, and numerous studies have demonstrated that patients with diabetes have an increased risk of developing

Alzheimer's Diseasecompared with healthy individuals. Both diseases are associated with enormous and increasing socio-economic effects. The co-existence of these two diseases in a society with an increasing mean age is a significant issue. However, it has generally been assumed that this co-existence is coincidental and not a reflection of co-morbidity.

The underlying biological mechanisms that link the development of diabetes with Alzheimer's Disease are not fully understood. Abnormal protein processing, abnormalities in insulin signaling, dysregulated glucose metabolism, oxidative stress, the formation of advanced glycation end products, and the activation of inflammatory pathways are features common to both diseases. Hypercholesterolemia is another factor that has received attention, owing to its potential association with diabetes and Alzheimer's Disease.

Much research has been conducted to reveal the mechanisms potentially linking Type II Diabetes Mellitus with cognitive impairment on the one hand and its link to Alzheimer's Disease on the other. Alzheimer's disease is one of the most common degenerative dementias, and more than 115 million new cases are projected worldwide in the next 40 years. There is clinical and experimental evidence that treatment with insulin or insulin sensitizer agents can enhance cognitive function and in some circumstances help slow the rate of cognitive decline in Alzheimer's Disease. Alzheimer's and other neurodegenerative diseases destroy the brain until the patients finally succumb. In order to effectively halt the process of neurodegeneration, the forces that advance and perpetuate the disease, particularly with regard to the progressive worsening of brain insulin/IGF resistance, must be understood.

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