I, Andreas Rizeq, declare that this work is my original author's work and that all the information resources are presented in the list of references.

Hradec Kralove
May 19, 2008 Andreas Rizeq

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INTRODUCTION

Physicians have observed the effects of diabetes for thousands of years. For much of this time, little was known about this fatal disease that caused wasting away of the body, extreme thirst, and frequent urination. It wasn't until 1922 that the first patient was successfully treated with insulin.
One of the effects of diabetes is the presence of glucose in the urine (glucosuria). Ancient Hindu writings, many thousands of years old, document how black ants and flies were attracted to the urine of diabetics. The Indian physician Sushruta in 400 B.C. described the sweet taste of urine from affected individuals, and for many centuries to come, the sweet taste of urine was key to diagnosis.[38]

Around 250 B.C., the name “diabetes” was first used. It is a Greek word that means “to syphon”, reflecting how diabetes seemed to rapidly drain fluid from the affected individual. The Greek physician Aretaeus noted that as affected individuals wasted away, they passed increasing amounts of urine as if there was “liquefaction of flesh and bones into urine”. The complete term “diabetes mellitus” was coined in 1674 by Thomas Willis, personal physician to King Charles II. Mellitus is Latin for honey, which is how Willis described the urine of diabetics (“as if imbued with honey and sugar”).[38]

Up until the mid-1800s, the treatments offered for diabetes varied tremendously. Various “fad” diets were prescribed, and the use of opium was suggested, as were bleeding and other therapies. The most successful treatments were starvation diets in which calorie intake was severely restricted. Naturally, this was intolerable for the patient and at best extended life expectancy for a few years.[38]

A breakthrough in the puzzle of diabetes came in 1889. German physicians Joseph von Mering and Oskar Minkowski surgically removed the pancreas from dogs. The dogs immediately developed diabetes. Now that a link was established between the pancreas gland and diabetes, research focused on isolating the pancreatic extract that could treat diabetes. When Dr. Frederick Banting took up the challenge of isolating a pancreatic extract, he was met with much skepticism. Many great physiologists had tried and failed to isolate an internal secretion from the pancreas. But Banting, a

surgeon, persisted and in May 1921, he began work in the laboratory of Professor John Macloed in Toronto, Canada. Charles Best, a medical student at the time, worked as his assistant.[37]

To concentrate what is known as insulin, Banting tied the pancreatic ducts of dogs. The pancreatic cells that released digestive enzymes (and could also destroy insulin) degenerated, but the cells that secreted insulin were spared. Over several weeks the pancreas degenerated into a residue from which insulin could be extracted. In July 1921, a dog that had had its pancreas surgically removed was injected with an extract collected from a duct-tied dog. In the two hours that followed the injection, the blood sugar level of the dog fell, and its condition improved. Another de-pancreatized (diabetic-like) dog was kept alive for eight days by regular injections until supplies of the extract, at that time called "isletin", were exhausted. Further experiments on dogs showed that extracts from the pancreas caused a drop in blood sugar, caused glucose in the urine to disappear, and produced a marked improvement in clinical condition. So long as the extract was being given, the dogs were kept alive. The supply of the extract was improved: the pancreas of different animals were used until that of the cow was settled upon. This extract kept a de-pancreatized dog alive for 70 days. Dr. J. Collip, a biochemist, was drafted to continue improving the purity of the pancreas extract, and later, Best carried on this work. A young boy, Leonard Thompson, was the first patient to receive insulin treatment. On January 11, 1922, aged 14 and weighing only 64 pounds, he was extremely ill. The first injections of insulin only produced a slight lowering of blood sugar level. [38]

The extract still was not pure enough, and abscesses developed at the injection site. Collip continued to refine the extract. Several weeks later, Leonard was treated again and showed a remarkable recovery. His blood sugar levels fell, he gained weight and lived for another 13 years. He died from pneumonia at the age of 27.[38]

During the spring of 1922, Best increased the production of insulin to enable the treatment of diabetic patients coming to the Toronto clinic. Over the next 60 years, insulin was further refined and purified, and long-acting and intermediate types were developed to provide more flexibility. A revolution came with the production of recombinant human DNA insulin in 1978. Instead of collecting insulin from animals, new human insulin could be synthesized.[38]

The impact of diabetes and of diabetes –related illnesses place an enormous burden on the health care systems of most of countries throughout the world. It has been estimated that by the year 2025, 300 million people

will have diabetes- a remarkable 5.4% of the world's projected population. [30]

Diabetes is an example of a disease with an unmet global medical need and conforms to the "commonality of interest" principle of the Priority Medicines Project. The increases in diabetes projected over the next several decades require a global strategy for prevention, treatment and medicine development. [30]

There are many oral agents that improve glucose control in diabetes by either improving insulin secretion or improving insulin action if diet and exercise are not working. The pharmaceutical industry considers development of effective diabetes medications as a major goal. For patients requiring insulin, current methods of insulin administration cannot reproduce the body's ability to precisely control blood glucose and other metabolic variables. [30]

AIM OF STUDY

The first goal is to describe diabetes mellitus as the disease, focusing mostly in the following information:

- Definition
- Classification
- Clinical manifestations
- Complications
- Diagnosis
- Non-pharmacological and pharmacological treatment

The second goal is divided in 3 parts:

- Firstly to give evidence-based guidelines and recommendations for the management, non-pharmacological and pharmacological treatment of type 1 and type 2 diabetes mellitus in children and adults, including the newer oral hypolipidemics.
- Secondly to give more impact to type 2 than type 1 diabetes mellitus, and to show the dangerous level that it has reached nowadays for children and adults.
- Thirdly to describe the general situation of diabetes mellitus in Cyprus, in European Union, and the global situation, giving more impact to European Union. After to make comparison between Cyprus and the European Union, and between Cyprus and the global situation.

METHODOLOGY

The methods used in this diploma thesis are mainly literature searches in electronic form found in websites and different databases, or in the form of books, journals and published articles.

The approach used in the first section of the theoretical part is:

- General description of diabetes mellitus using books and literature from several websites, including the World Health Organization (WHO) and the National Institute for Health and Clinical Excellence (NICE).
- Supplementary therapy using various journals from the Cyprus Diabetic Association (CDA), and websites about Diabetes Diet and Nutrition.

The approach used in the second section of the results is:

- NICE guidelines and recommendations for management and pharmacotherapy of type 1 and type 2 diabetes in children and adults, including the newer agents in the market, using the official website of NICE.
- Published articles using mostly PubMed and Medline databases (English language), concerning the epidemiology of diabetes in Cypriot population, using keywords as: Diabetes mellitus in Cyprus, Cypriot diabetics, Type 1 diabetes in Cyprus, Type 2 diabetes in Cyprus. General description of diabetes mellitus in Cyprus was found using various journals from the Cyprus Diabetic Association (CDA), and some websites concerning diabetes mellitus in EU were also considered.
- Situation about diabetes in Europe and the EU was found using literature in electronic form from several websites concerning the European Diabetes Foundation and the European Diabetes Epidemiology Study group.
- Global situation about diabetes mellitus was found searching databases in electronic form, mostly PubMed (English language), using keywords as: Global prevalence of diabetes, Diabetes in the

world, Global diabetes problem. Also search was made in the official website of the International Diabetes Foundation.

- Tables and figures were found after searching in the official website of the World Health Organization (WHO), and the National Centre for Health Statistics (NCHS).

I. THEORETICAL PART

1.1 Definition

Diabetes mellitus is a syndrome characterized by hyperglycemia resulting from absolute or relative impairment in insulin secretion and/or insulin action. [30]

Patients with type I diabetes mellitus, also known as insulin-dependent diabetes mellitus or juvenile-onset diabetes, may develop diabetic ketoacidosis. Patients with type II diabetes mellitus, also known as non-insulin-dependent diabetes mellitus, may develop non-ketotic hyperglycaemic-hyperosmolar coma. Common late microvascular complications include retinopathy, nephropathy and peripheral and autonomic neuropathies. Macrovascular complications include atherosclerotic coronary and peripheral arterial disease. [37]

1.2 Classification and Pathogenesis

1.2.1 Type I diabetes mellitus

Although it may occur at any age, type I diabetes mellitus most commonly develops in childhood or adolescence and is the predominant type of diabetes mellitus diagnosed before age 30. This type of diabetes accounts for 10 to 15% of all cases of diabetes mellitus and is characterized clinically by hyperglycemia and a propensity to diabetic ketoacidosis. The pancreas produces little or no insulin. [37]

About 80% of patients with type I diabetes mellitus have specific HLA phenotypes associated with detectable serum islet cell cytoplasmic antibodies and islet cell surface antibodies (antibodies to glutamic acid decarboxylase and to insulin are found in a similar proportion of cases). [33]

In these patients, type I diabetes mellitus results from a genetically susceptible, immune-mediated, selective destruction of > 90% of their insulin-secreting β cells. Their pancreatic islets exhibit insulitis, which is characterized by an infiltration of T lymphocytes accompanied by macrophages and B lymphocytes and by the loss of most of the β cells, without involvement of the glucagons-secreting α cells. Cell-mediated immune mechanisms are believed to play the major in the β-cell destruction. The antibodies present at diagnosis usually become undetectable after a few years. They may be primarily a response to β-cell destruction, but some are cytotoxic for β cells and may contribute to their loss. The clinical onset of type I diabetes mellitus may occur in some patients years after the insidious onset of the underlying autoimmune process. Screening for these antibodies is included in numerous ongoing preventive studies. [30]

In white populations, a strong association exists between type I diabetes mellitus diagnosed before age 30 and **specific HLA-D phenotypes** (HLA-DR3, HLA-DR4, and HLA-DR3/HLA-DR4). One or more genes that convey susceptibility to type I diabetes mellitus are believed to be located near or in the HLA-D locus on chromosome 6. Specific HLA-DQ alleles appear to be more intimately related to risks for or protection from type I diabetes mellitus than HLA-D antigens, and evidence suggests that genetic susceptibility to type I diabetes mellitus is probably polygenic. Only 10 to 12% of newly diagnosed children with type I diabetes mellitus have a first-degree relative with type I diabetes mellitus, and the concordance rate for type I diabetes mellitus in monozygotic twins is < or equal 50%. Thus, in addition to the genetic background, **environmental factors** affect the appearance of type I diabetes mellitus. Such environmental factors may be viruses(congenital rubella, mumps, and coxsackie B viruses may incite the development of autoimmune β-cell destruction) and exposure to cow's milk rather than maternal milk in infancy(a specific sequence of albumin from cow's milk may cross-react with islet protein). [37]

1.2.2 Type II diabetes mellitus

Type II diabetes mellitus is usually the type of diabetes diagnosed in patients > 30 years old, but it also occurs in children and adolescents. It is characterized clinically by hyperglycemia and insulin resistance. Diabetic ketoacidosis is rare. Although most patients are treated with diet, exercise, and oral drugs, some patients intermittently or persistently require insulin to control symptomatic hyperglycemia and prevent non-ketotic

hyperglycaemic-hyperosmolar coma. The concordance rate for type II diabetes mellitus in monozygotic twins is > 90%. Type II
diabetes mellitus is commonly associated with obesity, especially of the upper body (visceral/abdominal), and often presents after a period of weight gain. Impaired glucose tolerance associated with aging is closely correlated with the typical weight gain. Type II diabetes mellitus patients with visceral/abdominal obesity may have normal glucose levels after losing weight. [8]

Type II diabetes mellitus is a heterogeneous group of disorders in which hyperglycemia results from both an impaired insulin secretory response to glucose and decreased insulin effectiveness in stimulating glucose uptake by skeletal muscle and in restraining hepatic glucose production(**insulin resistance).** However, insulin resistance is common, and most patients with insulin resistance will not develop diabetes, because the body compensates by adequately increasing insulin secretion. Insulin resistance in the common variety of type II diabetes mellitus is not the result of genetic alterations in the insulin receptor or the glucose transporter.However,genetically determined postreceptor intracellular defects likely play a role. The resulting hyperinsulinemia may lead to other common conditions, such as obesity(abdominal),hypertension, hyperlipidemia and coronary artery disease(**the syndrome of insulin resistance). [37]**

Genetic factors appear to be the major determinants for the development of type II diabetes mellitus, yet no association between type II diabetes mellitus and specific HLA phenotypes or islet cell cytoplasmic antibodies has been demonstrated.(An exception is a subset of non-obese adults with detectable islet cell cytoplasmic antibodies who carry one of the HLA phenotypes and who may eventually develop type I diabetes mellitus. The pancreatic islets in type II diabetes mellitus retain β-cells in ratios to α-cells that are not consistently altered, and normal β-cell mass appears to be preserved in most patients. Pancreatic islet amyloid, resulting from a deposition of amylin, is found in a high percentage of type II diabetes mellitus patients at autopsy, but its relationship to the pathogenesis of type II diabetes mellitus is not well established. [29]

Before diabetes develops, patients generally lose the early insulin secretory response to glucose and may secrete relatively large amounts of proinsulin. In established diabetes, although fasting plasma insulin levels may be normal or even increased in type II diabetes mellitus patients, glucose-stimulated insulin secretion is clearly decreased. The decreased

insulin levels reduce insulin-mediated glucose uptake and fail to restrain hepatic glucose production. [37]

Hyperglycemia may not only be a consequence but also a cause of further impairment in glucose tolerance in the diabetic patient (**glucose toxicity)** because hyperglycemia decreases insulin sensitivity and increases hepatic glucose production. Once a patient's metabolic control improves, the insulin or hypoglycaemic drug dose is usually lowered. [3]

Some cases of type II diabetes mellitus occur in young, nonobese adolescents (**maturity-onset diabetes of the young)** with an autosomal dominant inheritance. Many families with maturity-onset diabetes of the young have a mutation in the glucokinase gene. Impairments in insulin secretion and in hepatic glucose regulation have been demonstrated in these patients. [37]

1.2.3 Children with type 2 diabetes mellitus

Can children get Type 2 diabetes?

Type 2 diabetes used to be practically unheard of in people under 30. That explains the other common name for the disease: adult-onset diabetes. Not long ago, almost all children with diabetes suffered from the Type 1 form of the disease, which means their bodies couldn't produce enough insulin. And Type 2 diabetes, in which the pancreas may produce normal insulin levels but cells become resistant to it, typically took decades to develop. [4]

But Type 2 diabetes isn't just for adults anymore. The number of children and adolescents with the condition (most of whom are diagnosed in their early teens) has skyrocketed within the last 20 years, prompting the journal Diabetes Care to call it an "emerging epidemic." While Type 1 diabetes is still more prevalent among children nationwide, experts estimate that Type 2 diabetes has grown from less than 5 percent in 1994 to 30 to 50 percent of all newly diagnosed cases of the disease in more recent years. [2]

Because young children who are obese are more likely to become diabetic when they're older, experts are paying particular attention to how

much -- or how little -- preadolescents eat and exercise. Disease researchers at the Centers for Disease Control and Prevention (CDC) recently made the stunning prediction that one in three children born in the United States in 2000 will likely develop Type 2 diabetes unless they get more exercise and improve their diets. The prediction was especially serious for Latino children. Without changes in diet and exercise, their odds of developing diabetes as they grow older was about 50-50. [23]

Type 2 is not usually as life-threatening or dramatic as Type 1 at the time of diagnosis, but it does increase the likelihood that children may develop serious long-term complications such as blindness, kidney disease, and heart disease. If untreated, the child may also eventually develop circulatory problems severe enough to require amputation of limbs. [35]

With proper medical treatment and a self-care program that incorporates exercise, glucose monitoring, and nutrition, however, your child can likely keep his or her blood sugar under control and avoid serious complications. [1]

Which children are at risk for Type 2 diabetes?

As many as 92 percent of all children and adolescents with Type 2 diabetes are significantly overweight, and about 40 percent are clinically obese. Indeed, researchers suspect that increases in obesity among young people is driving the new epidemic. [4]

There has long been a statistical link between obesity and Type 2 diabetes, but exactly why millions of overweight people develop Type 2 diabetes has long been a medical mystery. In January 2001, a study published in Nature suggested why millions of overweight people go on to develop the disease. The missing link, researchers argued, was a hormone they called resistin, which is produced by fat cells and incites tissues to resist insulin, the hormone our bodies need to turn blood sugar into energy. However in 2003, scientists scuttled this theory in a human study published in the Journal of Clinical Endocrinology and Metabolism. These scientists found no correlation between resistin levels and body mass index, lipid profile, or insulin resistance levels. [5]

Other studies have suggested that the type of obesity -- or where you store your fat -- may make a difference as well. Those who store it around the middle (the so-called apple shape) are at higher risk of developing diabetes. Some experts believe that high-carbohydrate, low-fiber diets are part of the problem. Finally, because exercise makes your body's muscle

cells more sensitive to insulin, a sedentary lifestyle is a risk factor. If your child rarely plays outside or exercises, then, he or she may be at greater risk of the disease. [6]

For unknown reasons, Native Americans, African-Americans, Asian-Americans, Pacific Islanders, and Latinos are also especially vulnerable to the disease. (One theory is that people whose hunter or gatherer ancestors led "feast or famine" lives developed a "thrifty gene," which allowed for very efficient fat storage.) Researchers at Children's Hospital in Cincinnati found that, compared with children of European descent, African-American boys and girls were 3.5 and 6.1 times more likely to develop Type 2 diabetes, respectively. Doctors at a Southern California diabetes clinic recently reported that 31 percent of young Mexican-American patients had the Type 2 variety, compared with 3 percent of the white children. [7]

Other factors can also put children at risk. If close family members have the disease or if a mother develops diabetes during pregnancy, for example, children are significantly more likely to develop the disease. [2]

What are the warning signs of Type 2 diabetes?

Many children go for years before they have symptoms that they recognize as a problem, but most children with Type 2 diabetes are diagnosed before they ever show symptoms. Still, it pays to be cautious, especially if your child is at high risk for the disease. Watch for these signs: increased urination, extreme thirst, increased appetite, and weight loss. One other potential sign of Type 2 diabetes is a skin condition called acanthosis nigricans. As many as 70 percent of children with Type 2 diabetes have this condition, which is characterized by a patch of extremely dark, velvety, and rippled skin, most often on an underarm or the back of the neck. [28]

Specific blood and urine tests are used to diagnose Type 2 diabetes, and these are not usually part of a routine physical exam. You should ask the doctor about these tests, especially if there's a history of the disease in the family and if your child is overweight. And again, Native Americans, Latinos, African-Americans, Asian-Americans, and Pacific Islanders are at increased risk. [3]

Are there everyday consequences for children with Type 2 diabetes?

Yes. Although Type 2 is usually not as serious in the shortrun as Type 1 -- and is generally easier to control -- there are several possible day-to-day effects of the disease. The American Diabetes Association (ADA) lists these common ones:

- Headache
- Blurred vision
- Thirst
- Frequent urination
- Dry, itchy skin

Long-term consequences are also a serious concern. If not controlled at an early age, Type 2 diabetes can lead to complications such as blindness, renal failure, hypertension, heart disease, and the need for amputations by the time children reach their 20s. [3]

How is childhood Type 2 diabetes treated?

Unlike children with Type 1 diabetes, those with Type 2 usually don't need insulin shots to control their blood sugar levels. In fact, most can manage their disease simply by eating fewer calories, cutting back on fats and sugars, and getting more exercise. Remember, kids get most of their lifestyle cues (not to mention their groceries) from their parents. By serving healthy foods, encouraging physical activity, and educating the family about diabetes, parents can make a huge contribution to their children's health. [22]

When lifestyle changes aren't enough -- or when they can't be made -- your child may need insulin shots. Some Sulfonylurea drugs and metformin can also help bring a child's blood sugar under control. [8]

And soon child may not have to stick themselves with insulin. In January 2006, the FDA approved inhaled insulin as a treatment option for Type 1 and Type 2 diabetes in adults. This new type of insulin, which goes by the name Exubera, comes in powder form and is the first new insulin delivery option since the discovery of the hormone in the 1920s. [10]

For Type 2 diabetics, inhaled insulin may be used alone, along with pills that control blood sugar, or with longer acting insulin. However the drug is not for smokers -- something to think about should it become available to children even if your child just lives with one -- and it is not recommended for people with asthma or bronchitis. [9]

While research on the effectiveness and safety of these drugs on children looks promising, they do have some side effects. [9]

Can childhood Type 2 diabetes be prevented?

The key to preventing Type 2 diabetes in children -- and adults for that matter -- is avoiding obesity. Give your child a balanced diet (including lots of fiber, whole-grain foods, and fruits and vegetables), avoid sugary junk foods and sodas, and encourage your child to get lots of exercise. By encouraging children to exercise and eat right from an early age, parents may be able to put a stop to this epidemic and set their children on the road to a long, healthy life. [1]

1.3 Symptoms and Signs

After many researches from physicians to diabetic patients, they have concluded that diabetes mellitus has diverse initial presentations. Type I diabetes mellitus usually presents with symptomatic hyperglycemia or diabetic ketoacidosis. Type II diabetes mellitus may present with symptomatic hyperglycemia or non-ketotic hyperglycaemic-hyperosmolar coma, but is frequently diagnosed in asymptomatic patients during a routine medical examination or when patients present with clinical manifestations of a late complication. [36]

Often following the acute onset of type I diabetes mellitus, there is substantial secretion of insulin. Type I diabetes mellitus patients may experience a honeymoon period characterized by a long phase of near-normal glucose levels without any treatment. [34]

Symptomatic hyperglycemia: Polyuria followed by polydipsia and weight loss occur when elevated plasma glucose levels cause marked glucosuria and an osmotic diuresis,resulting in dehydration. Hyperglycemia may also cause blurred vision, fatigue, and nausea and lead to various fungal and bacterial infections. In type II diabetes mellitus, symptomatic hyperglycemia may persist for days or weeks before medical attention is sought; in women, type II diabetes mellitus with symptomatic hyperglycemia is frequently associated with itching due to vaginal candidiasis. [18]

1.4 Complications

Late complications: Late complications occur after several years of poorly controlled hyperglycemia. Glucose levels are increased in all cells except where there is insulin-mediated glucose uptake (mainly muscle), resulting in an increase in glycolysation and in the activity of other metabolic pathways, which may be caused by complications. Most microvascular complications can be delayed, prevented, or even reversed by tight glycemic control, ie , achieving near-normal fasting and postprandial glucose levels, reflected by near-normal glycosylated haemoglobin (Hb A1c). Macrovascular disease such as atherosclerosis may lead to symptomatic coronary artery disease, claudication, skin breakdown, and infections. Although hyperglycemia may accelerate atherosclerosis, many years of hyperinsulinemia preceding the onset of diabetes (with insulin resistance) may play a major initiating role. Amputation of a lower limp for severe peripheral vascular disease, intermittent claudication, and gangrene remains common. Background **retinopathy** (the initial retinal changes seen on ophthalmoscopic examination or in retinal photographs) does not significantly alter vision, but it can progress to macular edema or proliferative retinopathy with retinal detachment or hemorrhage, which can cause blindness. About 85% of all diabetics eventually develop some degree of retinopathy. [17]

Diabetic **nephropathy** develops in about one third of type I diabetes mellitus patients and in a smaller percentage of type II diabetes mellitus patients. In type I diabetes mellitus patients, GFR may be increased initially with hyperglycemia. After about 5 years of type I diabetes mellitus, clinically detectable albuminuria (> or equal mg/L), which is unexplained by

other urinary tract disease, may develop. Albuminuria signals a progressive decrease in GFR with a high likelihood of development of end-stage renal disease within 3 to 20 years (median, 10 years). Albuminuria is almost 2.5 times higher in type I diabetes mellitus patients with diastolic BP>90mm Hg than in those with diastolic BP<70mm Hg. Thus, both hyperglycemia and hypertension accelerate the progression to end-stage renal disease. Diabetic nephropathy is usually asymptomatic until end-stage renal disease develops, but it can cause the nephrotic syndrome. Albuminuria and renal disease may be prevented or delayed with the ACE inhibitor captopril. While aggressive treatment of hypertension prevents the deterioration of renal function, ACE inhibitors have shown added benefits over other classes of antihypertensives. In fact, ACE inhibitors prevent proteinurea in hypertensive and nonhypertensive diabetics. Recent evidence suggests that ACE inhibitors also help prevent retinopathy. [35]

Diabetic neuropathy commonly occurs as a distal, symmetric, predominantly sensory **polyneuropathy** that causes sensory deficits, which begin with and are usually most marked by a stocking-glove distribution. Diabetic polyneuropathy may cause cause numbness, tingling, and paresthesias in the extremities and, less often, debilitating, severe, deep-seated pain and hyperesthesias. Ankle jerks are usually decreased or absent. Other causes of polyneuropathy must be excluded. Acute, painful **mononeuropathies** affecting the 3^{rd}, 4^{th}, or 6^{th} cranial nerve as well as other nerves, such as the femoral, may spontaneously improve over weeks to months, occur more frequently in older diabetics, and are attributed to nerve infarctions. **Autonomic neuropathy** occurs primarily in diabetics with polyneuropathy and can cause postural hypotension, disordered sweating, impotence and retrograde ejaculation in men, impaired bladder function, delayed gastric emptying (sometimes with dumping syndrome), esophageal dysfunction, constipation or diarrhea, and nocturnal diarrhea. A decrease in heart rate response to the Valsalva maneuver or on standing and unchanged heart rate variation during deep breathing are evidence of autonomic neuropathy in diabetics. [3]

Foot ulcers and joint problems are important causes of morbidity in diabetes mellitus. The major predisposing cause is diabetic polyneuropathy-the sensory denervation impairs the perception of trauma from such common causes as ill-fitting shoes or pebbles. Alterations in proprioception lead to an abnormal pattern of weight bearing and sometimes to the development of Charcot's joints. [30]

The risk of **infection** from fungi and bacteria is increased because of decreased cellular immunity caused by acute hyperglycemia and circulatory

deficits caused by chronic hyperglycemia. Peripheral skin infections and oral and vaginal thrush are most common. A mycotic infection may be the initial process, leading to wet interdigital lesions, cracks, fissures, and ulcerations that favour secondary bacterial invasion. Patients with infected foot ulcers frequently feel no pain because of neuropathy and have no systemic symptoms until late in a neglected course. Deep ulcers and particularly ulcers associated with any detectable cellulitis require immediate hospitilization, since systemic toxicity and permanent disability may develop. Osteomyelitis should be ruled out by bone scan. Early surgical debridement is an essential part of management, but amputation is sometimes necessary. [35]

1.5 Diagnosis

In asymptomatic patients, diabetes mellitus is established when the diagnostic criterion for fasting hyperglycemia recommended by the National Diabetes Data Group is met: a plasma (or serum) glucose level of > or equal with 140 mg/dL (> or equal with 7.77 mmol/L) after an overnight fast on two occasions in an adult or child. Recently, the American Diabetes Association recommended that fasting plasma glucose levels of > 126 mg/dL (>6.99 mmol/L) be considered diagnostic for diabetes mellitus. [3]

An **oral glucose tolerance test** may be helpful in diagnostic type II diabetes mellitus in patients whose fasting glucose is between 115 and 140 mg/dL (6.38 and 7.77 mmol/L) and in those with a clinical condition that might be related to undiagnosed diabetes mellitus(eg polyneuropathy, retinopathy). However, various conditions other than diabetes mellitus, such as effects of drugs, and normal aging can cause abnormalities in the oral glucose tolerance test. [3]

The National Diabetes Data Group also recommends criteria for the diagnosis of **impaired glucose tolerance** in patients who do not meet the oral glucose tolerance test diagnostic criteria for diabetes mellitus. Patients with impaired glucose tolerance may be at increased risk of developing fasting or symptomatic hyperglycemia, but in many patients the condition does not progress or it resolves. [33]

1.6 Diabetic diseases

1.6.1 Insulinopathies

Rare cases of diabetes mellitus, with the clinical characteristics of type II diabetes mellitus, result from the heterozygous inheritance of a defective gene, leading to secretion of insulin that does not bind normally to the insulin receptor. These patients have greatly elevated plasma immunoreactive insulin levels associated with normal plasma glucose responses to exogenous insulin. [26]

1.6.2 Diabetes attributed to pancreatic disease

Chronic pancreatitis, particularly in alcoholics, is frequently associated with diabetes. Such patients lose both insulin-secreting and glucagon-secreting islets. Therefore, they may be mildly hyperglycaemic and sensitive to low doses of insulin. Given the lack of effective counterregulation(exogenous insulin that is unopposed by glucagon), they frequently suffer from rapid onset of hypoglycaemia. In Cyprus,diabetes mellitus is commonly observed in young, severely malnourished patients with severe protein deficiency and pancreatic disease; these patients are not diabetic-ketoacidosis-prone but may require insulin. [27]

1.6.3 Diabetes associated with other endocrine diseases

Type II diabetes mellitus can be secondary to Cushing's syndrome, acromegaly, pheochromocytoma, glucagonoma, primary aldosteronism, or somatostatinoma. [14]
Most of these disorders are associated with peripheral or hepatic insulin resistance. Many patients will become diabetic once insulin secretion is also decreased. The prevalence of type I diabetes mellitus is increased in patients with certain autoimmune endocrine diseases, eg, Graves' disease Hashimoto's thyroiditis, and idiopathic Addison's disease. [28]

1.6.4 Insulin-resistant diabetes associated with acanthosis nigricans (type A and type B insulin resistance syndromes)

Two rare syndromes result from marked insulin resistance at the insulin receptor level associated with acanthosis nigricans. Acanthosis nigricans is a velvety hyperpigmentation on the neck, axillae, and groin and is probably the skin manifestation of severe and chronic hyperinsulinemia. Type A results from genetic alterations in the insulin receptor. Type B results from circulating antibodies to the insulin receptor and may be associated with other evidence of autoimmune disease. These cases are very rare in Cyprus. [24]

1.6.5 Lipoatrophic diabetes

This is a rare syndrome among Cypriot people in which insulin-resistant diabetes mellitus is associated with an extensive symmetric or virtually complete disappearance of subcutaneous adipose tissue. It has been linked to genetic alterations in the insulin receptor. [30]

1.6.6 Diabetes induced by β-cell toxins

Vacor, a rodenticide, is cytotoxic for human islets and can cause type I diabetes mellitus. Streptozocin can induce experimental diabetes in rats but rarely causes diabetes in humans. [37]

1.7 Non-pharmacological treatment

1.7.1 Diet management

Type 1 and type 2 diabetic patients should be carefull with their diet and the proportions of carbohydrates, fat and proteins that they consume and furthermore they should be carefull with the timing, size and the composition of meals to control their glucose levels.

In **insulin-treated diabetics,** diet management aims to restrict variations in the timing, size, or composition of meals, which could make the prescribed insulin regimen inappropriate and result in hypoglycaemia or marked postprandial hyperglycemia. All insulin-treated patients require detailed diet management, including a prescription for their total daily caloric intake; guidelines for proportions of carbohydrate, fat, and protein in their diets; and instruction on distributing calories among individual meals and snacks. A professional dietitian can tailor the diet plan and education to meet the patient's individual needs. Flexibility, however, helps maintain patient motivation. Publications are available from the American Diabetes Association and other sources for diet planning and patient education. Exchange list providing information on the carbohydrate, protein, fat, and caloric contents of individual servings are used to translate the dietary prescription into a diet plan, which should contain foods that the patient likes to eat, provided there is no specific reason to exclude a particular food. Foods with similar exchange values (ie, similar calories and contents of carbohydrate, protein, and fat) may have different effects on postprandial hyperglycemia in any individual diabetic. However, exchange lists are helpful in reducing the variation in the size and composition of the patient's usual breakfasts, lunches, dinners and snacks. [6]

In **obese type II diabetes mellitus patients,** the aims of diet management are losing weight and controlling hyperglycemia. The diet should meet the patient's minimum daily protein requirement (0.9 g/kg) and be designed to induce a gradual and sustained weight loss (about 2 lb/week) until ideal body weight is approached and maintained. A dietitian can assist in developing a diet that the patient will follow. Increased physical activity in sedentary obese type II diabetes mellitus patients is valuable and may decrease insulin resistance over time. Diabetics with hypertension should be treated with ACE inhibitors, which have been shown to be more protective against coronary artery disease than Ca channel blockers. [6]

1.7.2 Supplementary therapy to diabetes mellitus

1.7.2.1 Nutritional Therapy

Meal Planning

A non-diabetic produces the constantly varying amounts of insulin necessary for obtaining energy from glucose. A diabetic cannot achieve this balance. Beyond the basic requirements to provide adequate calories and necessary nutrients, there are marked differences in diet strategy for the two major groups of diabetic patients: Type 1 insulin-dependent non-obese patients and Type 2 obese patients who do not require insulin. Patients who are on insulin therapy must schedule their meals to provide regular caloric intake. In overweight patients, special attention must be given to total caloric consumption. [31]

There is no need to disproportionately restrict the intake of carbohydrates in the diet of most diabetic patients. In fact, Dr. H.P. Himsworth demonstrated in 1930 that if carbohydrates were taken out of the diet and replaced by either protein or fats, a person would quickly develop insulin resistance and diabetes. The key here is in the choice of high-fibre complex carbohydrates. [31]

One of the first dietary rules for all diabetics is to avoid all sugar and foods containing sugar, such as pastry, candy and soft drinks. While these refined sugars and other simple carbohydrates like white flour must be carefully watched, most diabetics are actually encouraged to eat more complex carbohydrates - the same bulky, fibre-rich unprocessed foods that are now recommended for everyone. Vegetables are ideal. For example, a diabetic can eat a large plate of spinach that contains as much carbohydrate as a tablespoonful of sugar, without suffering any ill effects. [7]

Spinach, asparagus, broccoli, cabbage, string beans and celery are among the so-called "Food Exchange Group A" vegetables that the American Diabetes Association (ADA) says can be generously included in the diabetic diet. What makes these complex carbohydrates special is their ability to slow down the body's absorption of carbohydrates by helping to delay the emptying of the stomach and thereby smoothing out the absorption of sugars into the blood. Whole grain cereals also have this ability. [7]

Fully one third of diabetic patients in clinical surveys have hyper-lipidemia, clearly indicating the need for dietary management. The most

sensible approach is to limit the amount of fat in their diet and to substitute polyunsaturated fats for the saturated type when possible. Fish and poultry are especially recommended instead of fatty cuts of meat. Greasy, fried foods are strongly discouraged. [6]

Obesity is much more likely in people who eat a high-fat diet, which is often a high calorie diet, since each gram of fat contains nine calories instead of the four calories in each gram of protein or carbohydrate. With obesity comes an increased risk of a variety of problems, not the least of which is adult-onset diabetes. [6]

Overweight diabetics, by carefully calculating the proper daily calorie intake for their body weight and activity level, and never exceeding it, can usually bring their weight down to an optimal level - a level which is actually 10% less than the standard height and weight charts recommend. [31]

The need to reduce fat is reflected in the standard diet and food exchange lists prepared by the ADA that restricts the intake of fat to 35% of calories. The reduction of saturated fats to one-third of the fat intake by substituting poultry, veal and fish for red meats, and the reduction of cholesterol to less than 300 mg/day are stressed. The carbohydrate content is 40-50 per cent of total calories, with unrefined carbohydrates recommended to the exclusion of refined and simple carbohydrates. [6]

Currently another diet, known as the 'HCF (high-carbohydrate high plant-fibre) diet' popularised by James Anderson has substantial support and validation in the scientific literature as the diet of choice in the treatment of diabetes. It is high in cereal grains, legumes and root vegetables and restricts simple sugar and fats. The calorie intake consists of 70-75 per cent complex carbohydrates, 15-20 per cent protein and only 5-10 per cent fat, and the total fibre content is almost 100 grams/day. The positive metabolic effects of the HCF diet are many: reduced after-mealtime hyperglycaemia and delayed hypoglycaemia; increased tissue sensitivity to insulin; reduced cholesterol and triglyceride levels with increased HDL-cholesterol levels; and progressive weight reduction. [7]

In general the HCF diet is adequate for the treatment of diabetes. However improvements can be made, primarily by substituting more natural (primitive) foods wherever possible. The Modified HCF or MHCF diet recommends a higher intake of legumes, along with restrictions of several foods allowed on the HCF diet, namely processed grains, and excludes fruit juices, low fibre fruits, skimmed milk and margarine. It is noteworthy that if patients resume a conventional ADA diet, their insulin requirements return to prior levels. [6]

Many diabetics have found it beneficial to eat smaller, more frequent meals, rather than the two or three big meals most people consume daily. Researchers have found that multiple frequent feedings tend to keep blood cholesterol levels lower, for the diabetic and non-diabetic alike. [4]

1.7.2.2 Vitamins and Minerals

Generally a well-balanced diet rich in vitamins and minerals is one of the most important factors in the control of diabetes and prevention of diabetic complications. One reason for stressing the need for proper levels of nutrients is the excessive urination experienced by the diabetic. [31]

Normally the body reabsorbs glucose and other water-soluble nutrients. When glucose rises to levels above 160-170mg/dl, as it does quite frequently in even well controlled diabetic patients, it acts as an osmotic diuretic. This process overwhelms the kidney's ability to reabsorb glucose and other water-soluble nutrients, thus the increased urination, and substantial losses of nutrients such as vitamins B-1, B-6 and B-12 and the minerals magnesium, zinc and chromium pass out along with the urine. Consequently diabetes and its complications are as much a result of nutritional wasting as of elevated blood sugar. [22]

In an article in the American Journal of Clinical Nutrition where 247 studies were reviewed, it was found that Type 1 (IDDM) diabetics generally had deficiencies in zinc, calcium, magnesium and the more active form of vitamin D. Those with Type 2 diabetes (NIDDM) generally were found to be low in zinc and magnesium and often low in vitamins B6 and C. [6]

The physical body needs all these water-soluble nutrients to maintain the integrity of its organ system. Perhaps one of the most important nutrients is magnesium. The medical literature is full of studies showing that diabetic patients invariably have lower blood levels of magnesium than normal, also with higher urinary losses. In a landmark study conducted in 1978 by Dr. P. McNair and titled Hypomagnesemia, a Risk Factor in Diabetic Retinopathy, it was demonstrated that diabetics with the lowest magnesium levels had the most severe retinopathy, and that low magnesium levels were linked significantly to retinopathy more than any other factor. The article argued that simply elevating the magnesium concentration with supplements would protect the eyes. [36]

Other nutrients are also attracting serious attention. Researchers in London recently reported that vitamin D is essential for the islet cells in the pancreas to be able to secrete insulin properly10. Their studies have shown that individuals with the lowest vitamin D levels experienced the worst blood sugar-handling problems and had a greater risk of developing diabetes. They found that those with greatest risk of developing vitamin D deficiency included the elderly who were either institutionalised or stayed indoors, those living in climates where sunlight is scarce several months a year, and those with indoor sedentary jobs. In an effort to eliminate the widespread vitamin D deficiencies in the institutionalised elderly, over 80% of those individuals are now being given 800 IU/day vitamin D3 supplements. [36]

Other researchers have found that the diabetic is unable to convert carotene into vitamin A. It is advisable therefore for the diabetic to ingest at least the recommended dietary allowance of vitamin A from a non-carotene source such as fish-liver oil. Diabetics and others on low-fat diets often need supplemental amounts of this fat-soluble nutrient. Also recommended is a vitamin E supplement, ranging from 400-1200 IU per day and a vitamin C supplement ranging from 1000-4000 mg per day to help prevent small-vessel disease of the extremities. [26]

Brewer's yeast is another food supplement that is recommended for the diabetic patient. The yeast is a rich source of chromium-containing GTF (glucose tolerance factor) which is able to potentiate the insulin in our bodies. GTF also contains amino acids such as glutamic acid, glycine, and cysteine. Both brewer's yeast (9 gm/day) and trivalent chromium (150-1000 mcg/day) have been shown to significantly improve blood sugar metabolism when taken for several weeks to months. As a side benefit it has also been found that brewer's yeast and chromium supplementation lower elevated total cholesterol and total lipids, and significantly raise the levels of HDL-cholesterol, the beneficial or protective fraction of cholesterol. [31]

Chromium is found in foods as both inorganic and organic salts. Brewer's yeast contains a form of chromium with high bioavailability, chromiumÇdinicotinic acidÇglutathione complex. The bioavailability of chromium in liver, American cheese and wheat germ is also relatively high. Chromium is also available from a variety of sources including whole grains, potatoes and apples with skins, spinach, oysters, carrots, and chicken breast. Recent research has identified certain varieties of barley grown in Mesopotamia to be some of the richest sources of chromium. [31]

A 1996 study of 180 Type 2 diabetics, carried out in China under the guidance of Dr. Richard A. Anderson11, found that 500 mcg of chromium

picolinate taken twice daily for four months lowered the fasting glucose level to an average of 129, compared to 160 in those taking a placebo. In addition, glycosylated haemoglobin (a test of longer-term glucose tolerance) averaged an almost normal level of 7.5% in those taking chromium - significantly lower than those on placebo. All of the effects of chromium appear to be due to increased insulin sensitivity. [19]

Another exceptionally useful trace mineral to combat diabetes is vanadium, which lowers blood sugar by mimicking insulin and improving the cells' sensitivity to insulin. A growing body of human research shows that vanadium compounds, most notably vanadyl sulfate, consistently improve fasting glucose and other measures of diabetes. These benefits were often extended for weeks after the mineral supplementation was discontinued. [31]

In addition to taking supplements, diabetics are encouraged to eat the widest possible variety of permitted foods to ensure getting the full range of trace elements and other nutrients. It is interesting to note that certain nutrients like vitamins B1, B2, B12, pantothenic acid, vitamin C, protein and potassium - along with small frequent meals containing some carbohydrate - can actually stimulate production of insulin within the body. [27]

Cautions

1. Fish oil capsules or supplements containing large amounts of para-aminobenzoic acid (PABA) can elevate blood sugar.
2. Supplements containing cysteine interfere with absorption of insulin by cells.
3. Extremely large dosages of vitamins B1 or C may inactivate insulin. Dosages listed above are within normal ranges. [6]

1.7.2.3 Botanical medicines

Since antiquity, diabetes has been treated with plant medicines. The following herbs appear to be the most effective, are relatively non-toxic and have substantial scientific documentation to attest to their efficacy. [31]

European Blueberry (Vaccinium myrtillus)

Traditional herbalism places great value on European Blueberry leaves, a.k.a. Bilberry, as a natural method of controlling or lowering blood sugar levels when they are slightly elevated. Results have shown the leaves have an active ingredient with a remarkable ability to reduce excess sugar in the blood. To use, steep two to three handfuls of leaves in 4 cups hot water for half an hour. Drink three cups a day. Modern research has demonstrated the berries or extract of the berries offer even greater benefit. The standard dose of the extract is 80-160 mg three times per day. [31]

Gymnema sylvestre

Native to the tropical forests of India. Used to lower blood sugar and help repair damage to pancreatic cells. Therapeutic dosage is 400 mg/day. A good source is a preparation by Natrol as a single herb 5:1 extract containing 300 mg. [6]

Bitter melon (Momordica Charantia)

Composed of several compounds with confirmed anti-diabetic properties. 50-60 ml (about 2 oz) of fresh juice per day has shown good results in clinical trials. Charantin, the key ingredient extracted by alcohol, is a hypoglycaemic agent composed of mixed steroids more potent than the drug Tolbutamide that is often used to treat diabetes. [6]

Onion and Garlic

The common bulbs, onion and garlic, have significant blood sugar-lowering action as well as lowering lipids, inhibiting platelet aggregation, and reducing blood pressure. [7]

Fenugreek

Fenugreek seeds have demonstrated anti-diabetic effects in experimental and clinical studies. Administration of the defatted seed (in daily doses of 1.5-2g/kg) reduces fasting and after-meal glucose, glucagon, somatostatin, insulin, total cholesterol and triglycerides, while increasing HDL-cholesterol levels. [31]

Salt Bush (Atriplex halimu)

Rich in fibre, protein, and numerous trace minerals, including chromium. Human studies in Israel have demonstrated improved blood glucose regulation and glucose tolerance in Type 2 diabetes. Dosage used in this study was 3g per day. [8]

Ginkgo biloba

Gingko biloba extract improves blood flow in the peripheral tissues of the arms, legs, fingers and toes and is therefore an important medicine in the treatment of peripheral vascular disease. It has also been shown to prevent diabetic retinopathy. Dosage of the extract standardised to contain 24% ginkgo flavoglycosides is 40-80 mg three times per day. [31]

Ginseng (Panax ginseng)

Ginseng, besides reducing fasting blood sugar levels and body weight, can elevate mood and improve psycho-physiological performance. Therapeutic dosage is 100-200 mg daily. [7]

Traditional Chinese medicine

According to Traditional Chinese Medicine, diabetes mellitus is a disorder characterized by Yin deficiency with dryness, heat and dampness. Yin deficiency is the underlying cause of the disease; dryness and heat represent the symptoms and signs; and dampness is reflected in increased blood glucose. Diabetes mellitus is most closely related to Wasting (Xiao Ke) syndrome, which can be categorized into Upper, Middle and Lower Wasting (Xiao Ke) syndrome, with the organs affected including the Lungs, Stomach and Kidneys, respectively. [31]

Upper Wasting (Xiao Ke) Syndrome is characterized by Lung heat drying up body fluids. Symptoms are fidgeting, polydipsia, dry red tongue (with or without cracks), with a thin, yellow coat, and a forceful, rapid pulse (especially at the cun position). Middle Wasting (Xiao Ke) Syndrome is characterized by Stomach fire damaging fluids, with such symptoms as polyphagia, constant hunger with good appetite, red tongue with a yellow coat, and a slippery, forceful, rapid pulse. Lower Wasting (Xiao Ke) Syndrome is sub-divided into Kidney Yin deficiency or Kidney Yin and Yang deficiencies. Kidney Yin deficiency is characterized by symptoms such as polyuria (especially at night), red tongue with little or no coat, and a

deep, thready, rapid pulse; Kidney Yin and Yang deficiency is characterized by polyuria (especially at night), teethmarks on both sides of the tongue, pale red tongue with a white coat, and a deep, thready, weak pulse. [31]

Despite the similarities between Diabetes and Wasting (Xiao Ke) Syndrome, it is important to keep in mind that they are not identical. Both Diabetes and Wasting (Xiao Ke) syndrome may be characterized by the presence of the three P's: polyuria, polydypsia and polyphagia. Diabetes, however, is defined as an increase in blood glucose levels, with or without the presence of the three P's. In addition, Diabetes may have many complications not present in Wasting (Xiao-Ke) syndrome, such as visual disturbances, impotence, amenorrhea, and frequent infections. Conversely, the presence of the three P's constitutes diagnosis of Wasting (Xiao-Ke) Syndrome. Polyuria, polydypsia and polyphagia may be caused by factors other than diabetes, such as fever, dehydration, or kidney disease. Understanding the similarities and differences between the two is essential for an accurate diagnosis and for optimal treatment of the patient. [31]

1.7.2.4 Chinese herbal treatments

Chinese herbs are very effective in treating patients with Type II, NIDDM. When prescribed correctly, Chinese herbs lower blood glucose levels, manage common signs and symptoms, and treat the complications of diabetes mellitus. Patients generally respond to herbal treatment within three-to-four weeks, with significant reduction in blood glucose levels and little fluctuation throughout the day. However, some patients may require up to six-to-eight weeks. For patients with Type I, IDDM, Chinese herbs are used in conjunction with insulin to manage symptoms and complications. Chinese herbs can also reduce the frequency and dosage of insulin injections. However, it is important to keep in mind that herbs cannot replace insulin, and patients with IDDM will still require insulin injections. [18]

Equilibrium

Equilibrium is the formula of choice for treating diabetes mellitus. From the perspective of Western medicine, Equilibrium contains herbs with excellent hypoglycemic effects, lowering blood glucose levels and reducing synthesis of fatty tissues. In addition, Equilibrium contains herbs that lower

blood cholesterol levels and improve blood circulation to the coronary arteries and peripheral parts of the body--thus managing common complications of diabetes, such as hyperlipidemia, atherosclerosis, coronary artery disease, peripheral neuropathy, etc. [31]

In terms of Chinese therapeutic actions, Equilibrium nourishes Lung, Stomach and Kidney Yin, clears heat, and dries dampness. It can be used for patients with Upper, Middle or Lower Wasting (Xiao Ke) syndromes. It effectively manages the three cardinal symptoms of Wasting (Xiao Ke) syndrome: polydipsia, polyphagia and polyuria. [28]

Equilibrium treats both the cause and the complications of diabetes mellitus. American ginseng (xi yang shen) greatly replenishes the vital essence of the body and promotes the secretion of body fluids, to treat polydipsia. Gypsum (shi gao) and anemarrhena (zhi mu) are a pair commonly used to treat heat in the Middle Burner (Jiao). They sedate Stomach fire and suppress appetite to relieve polyphagia. Scrophularia (xuan shen) enters the Lungs, Stomach and Kidneys to simultaneously replenish vital essence and clear heat. According to Oriental Medicine, an elevated glucose level is equivalent to excess retention of dampness in the body. Therefore, astragalus (huang qi) and dioscorea (shan yao) are used to tonify Qi and strengthen the Spleen to enhance its functions to dispel dampness. With their aromatic properties, white atractylodes (bai zhu) and atractylodes (cang zhu) strengthen the Spleen and directly dry dampness. Salvia root (dan shen) and carthamus (hong hua) invigorate blood circulation and enhance the overall effectiveness of the herbs by improving micro-circulation. Activation of blood circulation also reduces the risk of atherosclerosis by preventing buildup of cholesterol on the inner walls of blood vessels. Lastly, lotus embryo (lian zi xin) and lotus stamen (lian xu) tonify the Kidney and control frequent urination. [28]

Modification of Herbal Treatment Based on Wasting (Xiao-Ke) Syndrome

Equilibrium is the essential herbal formula used to lower blood glucose if the patient shows no other significant complications. If diabetic patients exhibit prominent signs and symptoms of Upper, Middle or Lower Wasting (Xiao Ke) syndromes, treatment must be modified by combining Equilibrium with the following formulas:

1. Upper Wasting (Xiao-Ke) Syndrome is characterized by Lung heat drying body fluids, resulting in symptoms such as fidgeting, polydipsia, a

dry red tongue (with or without cracks) with a thin, yellow coat, and a forceful, rapid, pulse (especially at the cun position). Patients with Upper Wasting (Xiao-Ke) Syndrome should combine Equilibrium with Ginseng & Gypsum Combination (Bai Hu Jia Ren Shen Tang). 2. Middle Wasting (Xiao-Ke) Syndrome is characterized by Stomach fire damaging the fluids, leading to such symptoms as polyphagia, constant hunger with good appetite, a red tongue with a yellow coat, and a slippery, forceful, rapid pulse. Patients with Middle Wasting (Xiao-Ke) Syndrome should combine Equilibrium with Rehmannia & Gypsum Combination (Yu Nu Jian). 3. Lower Wasting (Xiao Ke) Syndrome with Kidney Yin deficiency is characterized by such symptoms as polyuria (especially at night), a red tongue with little or no coat, and a deep, thready, rapid pulse. Patients with Lower Wasting (Xiao Ke) syndrome with Kidney Yin deficiency should combine Equilibrium with Rehmannia Six Formula (Liu Wei Di Huang Wan). 4. Lower Wasting (Xiao Ke) Syndrome with Kidney Yin and Yang deficiencies is characterized by polyuria (especially at night), teethmarks on both sides of the tongue, a pale red tongue with a white coat, and a deep, thready, weak pulse. Patients with Lower Wasting (Xiao Ke) Syndrome with Kidney Yin and Yang deficiencies should combine Equilibrium with Rehmannia Eight Formula (Ba Wei Di Huang Wan). [31]

Modification of Herbal Treatment Based on Complications

If diabetic patients exhibit prominent signs and symptoms of complications, treatment must be modified by combining Equilibrium with the following formulas:

1. For patients with high cholesterol, combine with Cholisma. 2. For patients with hypertension, combine with Gentiana Complex or Gastrodia Complex. 3. For patients with chronic buildup of cholesterol leading to coronary artery disease, combine with Circulation. 4. For patients with blurred vision or vision impairment, combine with Nourish. 5. For patients with impotence due to diabetic complications, combine with Vitality For Men. 6. For patients with recurrent urinary tract infections, combine with Gentiana Complex. [31]

Cautions

Patients should not stop using drug treatments abruptly as there is a risk of hyperglycemia or diabetic ketoacidosis. Herbal and drug treatments

should overlap for 1 to 2 weeks before patients are to begin tapering off drug treatments to ensure adequate control of blood glucose levels. [19]

Concurrent use of drugs and herbal treatment may have synergistic effects on lowering the blood glucose levels. During the transition period when the patients take both drugs and herbs, their blood glucose levels should be monitored at least twice daily to assess the effectiveness of the treatment and to avoid hypoglycemia. Dosage must be adjusted as needed to keep blood glucose within the normal range. Herbal treatment may reduce the dosage and frequency of insulin injections needed; however, it can never replace insulin, especially in insulin dependent diabetes mellitus (IDDM) patients. Patients with IDDM should always be treated with insulin, or a combination of insulin and herbs. [6]

1.7.3 Lifestyle instructions

Lifestyle adjustments are absolutely critical for short-term management and long-term recovery of diabetes. Patients should be encouraged to engage in regular daily exercise, sleep by 10 p.m. to enhance restoration of Yin elements in the body, and eliminate sugar, carbohydrates and caffeine from the diet. Additional dietary advice may be useful based on the primary organ systems affected. [30]

For patients with Type II, NIDDM, Equilibrium in combination with diet and exercise provides excellent clinical results. Most patients will get satisfactory clinical results within three-to-four weeks of beginning herbal treatment. Maximum effectiveness may require up to six-to-eight weeks of herbal treatment. Clinical effects include a significant reduction in blood glucose levels and less fluctuation throughout the day. [31]

Diabetes mellitus is defined simply as a rise in blood glucose levels. The clinical manifestations of the disease, however, are much more complicated than its definition. Patients with chronic diabetes mellitus are frequently plagued by various complications, such as visual disturbances, prolonged healing of wounds, frequent recurrences of infections, impotence, etc., which must be addressed within the overall treatment strategy. [35]

Diagnosis and treatment of the most common and complex endocrinologic disorder continues to pose a challenge for health care practitioners. Diabetes mellitus commonly may go undiagnosed as patients

with early stages of Type II, NIDDM are often asymptomatic. Also, as patients with chronic Type II, NIDDM often have a wide variety of complications, diabetes mellitus is frequently overlooked or mis-diagnosed. Once the correct diagnosis is made, diabetes and its complications can be effectively managed by both western drugs and herbal remedies. In conclusion, herbal medicine offers a safe and effective alternative for patients with diabetes mellitus. [7]

General considerations: The Diabetes Control and Complications Trial proved that hyperglycemia is responsible for most of the long-term microvascular complications of diabetes. It is demonstrated a linear relationship between the levels of Hb A1c and the rate at which complications developed. Other studies have suggested that Hb A1c <8% is a threshold below which most complications can be prevented. Thus, therapy for type I diabetes mellitus should try to intensify metabolic control to lower Hb A1c while avoiding hypoglycaemic episodes. However, treatment must be individualized and should be modified when circumstances make any risk of hypoglycaemia unacceptable (eg, in patients with a short life expectancy and in those with cerebrovascular or cardiac disease) or when the patient's risk of hypoglycaemia is increased (eg, in patients who are unreliable or who have autonomic neuropathy). [30]

Diet to achieve weight reduction is most important in overweight patients with type II diabetes mellitus. If improvement in hyperglycemia is not achieved by diet, trial with an oral drug should be started. [6]

Patient education, together with diet and exercise, is essential to ensure the effectiveness of the prescribed therapy, to recognise indications for seeking immediate medical attention, and to ensure appropriate foot care. **On each physician visit,** the patient should be assessed for symptoms or signs of complications, including a check of feet and pulses and sensation in the feet and legs, and a urine test for albumin. Periodic laboratory evaluation includes lipid profile, BUN and serum creatinine levels, ECG, and an annual complete ophthalmologic evaluation. [31]

Because diabetics are at increased risk of acute renal failure, x-ray studies that require IV injection of contrast dyes should be performed only when absolutely necessary and only when the patient is well hydrated. [30]

Hypercholesterolemia or hypertension increases the risks for specific late complications and requires special attention and appropriate treatment.

Although β-blockers(eg, propranolol) can be used safely in most diabetics, they can mask the β-adrenergic symptoms of insulin-induced hypoglycaemia and can impair the normal counterregulatory response. Thus, ACE inhibitors and calcium antagonists are often the drugs of choice. [35]

Plasma glucose monitoring: All patients should learn self-monitoring of glucose, and insulin-treated patients should be taught to adjust their insulin doses accordingly. Glucose levels can be tested with easy-to-use home analysers using a drop of fingertip blood. A spring-powered lancet is recommended to obtain the fingertip blood sample. The frequency of testing is determined individually. Insulin-treated diabetic patients ideally should test their plasma glucose daily before meals, 1 or 2 hours after meals, and at bedtime. However, in practice, two to four measurements may be obtained each day at different times, so that an overall assessment can be made after a week or so of treatment. [33]

Most physicians periodically determine **glycosylated haemoglobin (Hb A1c)** to estimate plasma glucose control during the preceding 1 to 3 mo. Hb A1c is the stable product of nonenzymatic glycosylation of the θ-chain of Hb by plasma glucose and is formed at rates that increase with increasing plasma glucose levels. In most laboratories, the normal Hb A1c level is about 6%; in poorly controlled diabetics, the level ranges from 9 to 12%. Hb A1c is not a specific test for diagnosing diabetes; however, elevated Hb A1c often indicates existing diabetes. [37]

Another test is of the **fructosamine** level. Fructosamine is formed by a chemical reaction of glucose with plasma protein and reflects glucose control in the previous 1 to 3 weeks. Therefore, this assay may show a change in control before Hb A1c and is often helpful when intensive treatment is applied and in short-term clinical trials. [37]

Patients with type I diabetes mellitus should be instructed to **test for urine ketones** with commercially available reagent strips and be advised to test for urine ketones whenever they develop symptoms of a cold, flu, or other intercurrent illness; nausea, vomiting, or abdominal pain; or polyuria; or if they find an unexpectedly high plasma glucose level on self-monitoring. Testing for ketones in all urine samples is recommended for type I diabetes mellitus patients who exhibit persistent, rapid, and marked fluctuations in their degree of hyperglycemia. [3]

1.8 Pharmacotherapy

The strategy of pharmacotherapy of diabetes mellitus is to control the disease either is type 1 or type 2. The current pharmacotherapy concering type 1 is with the use of insulin and mainly the insulin analogues. Pharmacotherapy concerning type 2 diabetes mellitus is with the use of oral hypoglycemic agents from which the most important are the sulphonylureas, metformin, thiazolidinediones and acarbose.

1.8.1 Insulin therapy

Human insulin is often preferred in initiating insulin treatment because it is less antigenic than animal-derived varieties. However, detectable insulin antibody levels, usually very low, develop in most insulin-treated patients, including those receiving human insulin preparations. [34]

Insulin is routinely provided in preparations containing 100 U/Ml (U-100 insulin) and is injected subcutaneously with disposal insulin syringes. The 1/2 –mL syringes are generally preferred by patients who routinely inject doses of < or equal with 50 U, because they can be read more easily and facilitate the accurate measurement of smaller doses. A multiple-dose insulin injection device(NovolinPen), commonly referred to as an insulin pen, is designed to use a cartridge containing several day's dosage. Insulin should be refrigerated *but never frozen*; however, most insulin preparations are stable at room temperature for months, which facilitates their use at work and when travelling. [35]

Insulin preparations are classified as short-acting(rapid-acting),intermediate-acting, or long-acting. The critical determinant of the onset and duration of action of an insulin preparation is the rate of insulin absorption from the injection site. [36]

Rapid-acting insulins include regular insulin, which is a preparation of zinc insulin crystals in a suspending solution; regular insulin is the only insulin preparation that can be given intravenously. Lispro, a form of regular insulin that is genetically engineered with a substitute of one amino acid, provides more rapid absorption of insulin and therefore may be administered with food. Semilente insulin is a slightly slower rapid-acting insulin, containing zinc insulin microcrystals in an acetate buffer. Intermediate-

acting insulin includes neutral protamine Hagedorn, which contains a stoichiometric mixture of regular and protamine zinc insulin, and Lente, which contains 30% Semilente insulin and 70% Ultralente insulin in an acetate buffer. Long-acting protamine zinc insulin contains insulin that is negatively charged, combined with an excess of positively charged fish sperm protamine. Ultralente contains large zinc insulin crystals in an acetate buffer. [35]

1.8.1.1 Insulin preparations

Mixtures of insulin preparations with different onsets and durations of action are frequently given in a single injection by drawing measured doses of two preparations into the same syringe immediately before use. The manufacturers recommend that Semilente be mixed only with Lente or Ultralente to maintain the same buffer solution. However, individual doses of regular insulin and neutral protamine Hagedorn or Lente insulin are commonly drawn up into the same syringe to combine rapid- and intermediate-acting insulin in a single injection. A preparation that contains a mixture of 70% neutral protamine Hagedorn and 30% regular human semisynthetic insulin(Novolin 70/30 or Humulin 70/30) is also available, but its fixed ratio of intermediate- to rapid-acting insulin may restrict its use. *Protamine zinc insulin must always be injected separately*, because it contains an excess of protamine. [34]

1.8.1.2 Insulin therapy in adults and children

Initiation of insulin therapy in adults: In Diabetes Control and Complications Trial, type I diabetes mellitus patients received an average total dose of about 40 U insulin a day. Because type II diabetes mellitus patients are insulin resistant, they require more insulin. Thus, those who are severely hyperglycaemic and obese may be started on about 40 U insulin a day. The initial total daily dose may be divided so that ½ will be administered before breakfast, ¼ before dinner, and ¼ at bedtime. Because

of severe insulin resistance, type II diabetes mellitus patients may need twice that much and often more. After the initial dose is selected, adjustments in the amounts, types, and timing are made based on plasma glucose determinations. The dose is adjusted to maintain preprandial plasma glucose between 80 and 150 mg/dL(4.44 and 8.33 mmol/L). Increments in insulin dose are generally restricted to 10% at a time, and the effects are assessed over about 3 days before any further increment is made. More rapid adjustments of regular insulin are indicated if hypoglycaemia threatens. [30]

Initiation of insulin therapy in children: Children who present at an early stage of type I diabetes mellitus with moderately hyperglycemia but without ketonuria or acidosis may be started with a single daily subcutaneous injection of 0.3 to 0.5 U/kg of intermediate-acting insulin alone. Children who present with both hyperglycemia and ketonuria but who are not acidotic or dehydrated may be started on 0.5 to 0.7 U/kg of intermediate-acting insulin and then supplemented by subcutaneous injections of 0.1 U/kg of regular insulin at 4- to 6- hours intervals. Insulin doses are usually adjusted to maintain preprandial plasma glucose levels between 80 and 150 mg/DL(4.44 and 8.33 mmol/L) or sometimes between 80 and 120 mg/DL(4.44 and 6.66 mmol/L). [28]

1.8.1.3 Insulin schedules

The goal of insulin therapy is to control hyperglycaemic surges after meals and to provide baseline levels that support normal glucose metabolism. Regimens must always be individualized, and some diabetics will achieve tight control with highly idiosyncratic schedules. However, the approach should include:

1. **Bedtime intermediate-acting insulin.** This helps control nocturnal hepatic glucose production. Starting the day with lower morning glucose levels will improve glucose tolerance throughout the day. Bedtime insulin is associated with less weight gain than is daytime insulin alone. Bedtime insulin is also a reasonable way to initiate insulin therapy in type II diabetes mellitus patients who are not controlled by oral drugs alone. [8]
2. **Before-breakfast mixed insulin.** This often is accomplished with a mixture of about 30% short-acting and 70% intermediate-acting insulin. Most diabetic patients will need about half the daily insulin dose before breakfast. [8]

3. **Before-lunch-and-dinner regular insulin.** For tight control, supplemental rapid-acting insulin should be taken before meals. The dose should be taken 15 to 30 min before a meal for regular or Semilente and with a meal for Lispro. [8]

1.8.1.4 Insulin administration

Multiple subcutaneous insulin injections: These are designed to maintain normal or near-normal plasma glucose levels throughout the day in patients with type I diabetes mellitus. Such treatment may increase the risks for frequent and severe episodes of hypoglycaemia. Patients should be highly motivated, well educated in diabetes mellitus, informed of the risks and uncertain benefits, competent in self-monitoring of glucose, and under the supervision of a physician experienced in its use. In a typical multiple subcutaneous insulin injection regimen, about 25% of the total daily dose is given as intermediate-acting insulin at bedtime, with additional doses of rapid-acting insulin given before each meal(a four-dose regimen). Type I diabetes mellitus patients may require intermediate- or long-acting insulin in the morning to give coverage throughout the day. The patient adjusts daily dosage on the basis of self-monitoring of glucose before each meal and at bedtime; the plasma glucose level between 2 and 4 AM is assessed at least once/week. [22]

Continuous subcutaneous insulin infusion: This mode of intensive insulin treatment in patients with type I diabetes mellitus involves a small battery-powered infusion pump that provides a continuous subcutaneous infusion of rapid-acting insulin through a small needle, usually inserted in the abdominal wall. The pump is programmed to infuse a selected basal rate of insulin, supplemented by manually triggered or programmed increased rates before each meal. The patient measures glucose levels several times a day to adjust the dosage. Control obtainable with this method is superior to that obtained with multiple injections. Hypoglycemic episodes are common with pump therapy, especially during the establishment of metabolic control. However, once metabolic control is established, pumps are not associated with more hypoglycaemia than are multiple injections. Experimental pump implants and intraperitoneal deliveries of insulin to the portal system may prove superior. However, the indwelling needle increases the risk of infections at needle sites. [22]

Insulin treatment of brittle diabetes: Brittle diabetics are type I diabetes mellitus patients who exhibit frequent, rapid swings in glucose levels without apparent cause. [22]

Brittle diabetes is most common in patients with no residual insulin secretory capacity. The metabolic processes through which insulin affects the plasma levels of glucose, albumin-bound free fatty acids, and ketones are normally regulated by shifts in the balance between the effects of insulin and the opposing effects of glucagon (in the liver) and the adrenergic autonomic nervous system. These counterregulatory mechanisms are independently regulated and normally increased during fasting, exercise, and other conditions that require protection against hypoglycaemia. Insulin doses must be adequate to deal with a sudden increase in counterregulatory mechanisms and to prevent rapidly developing symptomatic hyperglycemia and hyperketonemia, but this frequently produces transient plasma insulin excess. [30]

Many of these patients improve when switched to a modified multiple subcutaneous insulin regimen that provides most of the daily insulin as a rapid-acting insulin in daily adjusted dosages before each meal, with some intermediate-acting insulin in the morning, before the evening meal, or at bedtime. The aim is not to maintain the diurnal plasma glucose level in near-normal range but to stabilize the fluctuations in a range that prevents symptomatic hyper- and hypoglycaemia. [22]

1.8.1.5 Complications of insulin treatment

Hypoglycemia may occur because of an error in insulin dosage, a small or missed meal, or unplanned exercise (patients are usually instructed to reduce their insulin dose or to increase their carbohydrate intake before planned exercise) or without apparent cause. Patients are taught to recognize symptoms of hypoglycaemia, which usually respond rapidly to the ingestion of sugar. All diabetics should carry candy, lumps or sugar, or glucose tablets. An identification card, bracelet, or necklace indicating that the patient is an insulin-treated diabetic aids in recognizing hypoglycaemia in emergencies. Close family members should be instructed to administer glucagon with an easy-to-use injection device. Emergency medical personnel, after confirming the hypoglycaemia with a glucostick, should initiate therapy with a rapid bolus injection of 25 mL of 50% glucose solution followed by a continuous IV infusion of glucose. [8]

The **dawn phenomenon** refers to the normal tendency of the plasma glucose to rise in the early morning hours before breakfast, which is frequently exaggerated in patients with type I diabetes mellitus and in some patients with type II diabetes mellitus. Fasting glucose levels rise because of an increase in hepatic glucose production, which may be secondary to the midnight surge of growth hormone. In some patients with type I diabetes mellitus, nocturnal hypoglycaemia may be followed by a marked increase in fasting plasma glucose with an increase in plasma ketones (**Somogyi phenomenon).** Thus, both the dawn and Somogyi phenomena are characterized by morning hyperglycemia, but the latter is due to rebound (counterregulation) hyperglycemia. The frequency with which the latter phenomenon actually occurs is disputed. When it is suspected, the patient should wake between 2 and 4 AM to monitor blood glucose levels. If intermediate insulin is administered at bedtime, the dawn and Somogyi phenomena can often be prevented. [34]

Local allergic reactions at the site of insulin injections are less common with purified porcine and human insulins. These reactions can produse immediate pain and burning, followed after several hours by local erythema, pruritus, and induration, the latter sometimes persisting for days. Most reactions spontaneously disappear after weeks of continued insulin injection and require no specific treatment, although antihistamines are sometimes used. [35]

Generalized insulin allergy (usually to the insulin molecule) is rare but can occur when treatment is discontinued and restarted after a lapse of months or years. Such reactions may occur with any type of insulin, including human biosynthetic insulin. Symptoms usually develop shortly after an injection and may include urticaria, angioedema, pruritus, bronchospasm, and, in some cases, circulatory collapse. Treatment with antihistamines may suffice, but epinephrine and IV glucocorticoids may be required. If continued insulin treatment is required after the condition stabilizes, skin testing with a panel of purified insulin preparations and desensitization should be performed by an experienced physician. [34]

Insulin resistance is an increase in insulin requirement to > or equal with 200 U/day and is associated with marked increases in the plasma insulin-binding capacity. Most patients treated with insulin for > or equal with 6 mo develop antibodies to insulin. The relative antigenicity of purified insulin preparations is bovine >porcine>human, but genetic factors also affect individual response. Circulating insulin-binding antibodies can modify the pharmacokinetics of free insulin, but treatment usually is not adversely affected. In patients with insulin resistance, switching to purified porcine or

human insulin may lower the requirement. Remission may be spontaneous or may be induced in some type II diabetes mellitus patients who can stop insulin treatment for 1 to 3 mo. Prednisone may decrease insulin requirements within 2 weeks; treatment is usually initiated with about 30 mg bid and is tapered as the requirements decrease. [34]

Local fat atrophy or hypertrophy at injection sites is relatively rare and usually improves by switching to human insulin and injecting it directly into the affected area. No specific treatment of local fat hypertrophy is required, but injection sites should be rotated. [35]

1.8.2 Oral antidiabetic drugs

These drugs are used for type II diabetes mellitus but not for type I diabetes mellitus because they cannot prevent symptomatic hypeglycemia or diabetic ketoacidosis in such patients. Oral hypoglycaemic drugs are the biguanides, the α-glucosidase inhibitors, and the insulin sensitizers (thiazolidinediones[glitazones]). [8]

1.8.2.1 Sulfonylureas

The sulfonylureas lower plasma glucose primarily by stimulating insulin secretion. Secondary effects on improving peripheral and hepatic insulin sensitivity may be due to the decrease in both glucose toxicity and insulin clearance. Sulfonylureas differ in potency and duration of action. All of the sulfonylureas are metabolized in the liver, but only tolbutamide and tolazamide are inactivated exclusively by the liver. About 30% of chlorpropamide is normally excreted in the urine, and the principal hepatic metabolite of acetohexamide is highly active and excreted in urine; both drugs carry an increased risk of prolonged hypoglycaemia in patients with impaired renal function and in the elderly. The 2^{nd}-generation sulfonylureas (such as glipizide and glyburide) are about 100 times more potent than the 1^{st}-generation ones, are absorbed rapidly, and are metabolized mainly in the liver. Clinically, the 2^{nd}-generation sulfonylureas are similar in effectiveness. [35]

Allergic reactions and other side effects (eg, cholestatic jaundice) are relatively uncommon. Acetohexamide may be used in patients who are

allergic to other sulfonylureas. Chlorpropamide and acetohexamide should not be used in patients with impaired renal function. In addition, chlorpropamide should not be used in elderly patients, because it can potentiate the action of antidiuretic hormone, often leading to hyponatremia and a deterioration in mental status, which in an elderly patient may often not be recognized as a drug-induced effect. [35]

For the initial treatment, many authorities prefer the shorter-acting sulfonylureas, and most do not recommend using a combination of different sulfonylureas. Treatment is started with a low dose, which is adjusted after several days until a satisfactory response is obtained or the maximum recommended dosage is reached. About 10 to 20% of patients fail to respond to a trial of treatment (primary failures), and patients who fail to respond to one sulfonylurea often fail to respond to others. Of patients who initially respond, 5 to 10% per year experience secondary failures. In such cases, insulin may be added to sulfonylurea treatment. [8]

Hypoglycemia is the most important complication of sulfonylurea treatment. Hypoglycemia can occur in patients treated any of the sulfonylureas but occurs most frequently with long-acting ones (glyburide, chlorpropamide). Sulfonylurea-induced hypoglycaemia can be severe and may last or recur for days after treatment is stopped, even when it occurs in patients treated with tolbutamide, whose usual duration of action is 6 to 12 hours. A mortality rate of 4.3% in patients hospitalized with sulfonylurea-induced hypoglycaemia has been reported recently. Therefore, all sulfonylurea-treated patients who develop hypoglycaemia should be hospitalized, because even if they respond rapidly to initial treatment for hypoglycaemia, they must be closely monitored for 2 to 3 days. Most of these patients may not require further treatment with sulfonylureas. [35]

1.8.2.2 Biguanides (Metformin)

Metformin has been used as primary therapy in type II diabetes mellitus patients for over 30 years in Cyprus. It has been recently approved for use in the USA. It acts by decreasing hepatic glucose production and may improve insulin sensitivity in those who lose weight. It is as effective as a sulfonylurea as monotherapy (when used alone it rarely causes hypoglycaemia) and is synergistic in combination with sulfonylurea therapy. Metformin also promotes weight loss and decreases lipid levels. Unlike phenformin, metformin rarely causes severe lactic acidosis. GI side effects are common, but often transient, and may be prevented if the drug is taken

with meals and if the dosage is gradually increased (by 500 mg/week up to 2.5 g). Metformin is contraindicated in patients with kidney and liver diseases or alcoholism. It is also contraindicated in patients with lactic acidosis and should be withheld during acute hospitalization in most patients. [34]

1.8.2.3 Acarbose

Acarbose is an **α-glucosidase inhibitor** that competitively inhibits hydrolysis of oligo- and monosaccharides. This delays carbohydrate digestion in the small intestine and subsequent absorption, resulting in less postprandial elevation of blood glucose levels. Because its mechanism of action differs from that of other oral hypoglycemics, it can be used in combination therapy with other oral agents. GI side effects are very common, but often transient. The drug must be taken with meals, and the dosage should be gradually increased from 25 mg up to 50 or 100 mg with each meal. [34]

1.8.2.4 Thiazolidinediones

Thiazolidinediones are the insulin-sensitizer drugs that improve insulin sensitivity in skeletal muscle and suppress hepatic glucose output. The only such drug available in the USA is troglitazone. It has been recently approved for use in the treatment of type II diabetes mellitus patients requiring insulin and has moderate effects on decreasing plasma glucose and triglyceride levels. This drug is administered once a day and has potentially idiosyncratic hepatotoxicity. Patients should be instructed to decrease their daily insulin dosage with the initiation of therapy. [34]

1.9 Body Weight and Diabetes

The link between excess body weight and Type 2 diabetes is indisputable. The incidence of diabetes is on the rise around the world and is directly linked to the rate of weight gain globally. [4]

Indeed, being obese and gaining weight increases the risk of developing Type 2 diabetes more than ninetyfold. For this reason, both the American Heart Association and the European diabetes associations recommend that people who have been diagnosed with diabetes lose weight to reach a healthy body weight (i.e., a Body Mass Index, BMI of 25 or less). [4]

Currently, about 8% of U.S. adults have been diagnosed with Type 2 diabetes and most are overweight. According to the Centres for Disease Control and Prevention (CDC), 85.2% of people diagnosed with diabetes are overweight with a BMI greater than 25 and 54.8% are obese with a BMI over 30. People with diabetes who are also obese are more likely to have poorer control over their blood sugars than those who are not overweight, and they are likely to have more problems with high blood pressure and elevated cholesterol levels. [5]

The combination of excess weight and diabetes is also associated with a greater risk for cardiovascular disease and developing complications from the diabetes, such as blindness and kidney disease. [17]

The impact of weight loss

While the statistics may seem grim, there is good news when it comes to both the prevention and treatment of Type 2 diabetes. [4]

Two hallmark trials, one done in Finland and the other in the U.S., conclusively found that modest weight losses can make a dramatic difference in preventing the development of diabetes among people who are at a high risk for developing the disease. [5]

In the Finnish trial, the risk was reduced by 58 percent, with the reduction being directly attributed to lifestyle change. The U.S. study also reduced the incidence by 58 percent with a 7% weight loss that was achieved with a lifestyle modification program that included diet and physical activity. [5]

For those who are overweight and already have diabetes, modest weight loss can also make a big difference. [4]

In one study, weight loss was associated with a 25% reduction in total mortality, a 28% reduction in deaths due to cardiovascular disease and complications from the diabetes. A weight loss of 20-29 pounds was linked with the greatest benefit. [4]

1.9.1 The Body Mass Index

Body mass index, BMI, is a measurement that evaluates the relationship between body weight and height. While BMI is not a direct measure of excess body fat, it is the recommended method to diagnose overweight and obesity. Because it expresses the weight-height relationship, BMI provides a more accurate measure than body weight alone. [6]

The formula for calculating BMI uses weight in kilograms and height in meters: BMI (kg/m2) = Weight (kg) ÷ Height (m) 2; or weight in pounds and height in inches: BMI (lb/in2) = Weight (lb) ÷ Height (in) 2*703 [6]

Definitions of overweight, obesity

Over 50 healthcare organizations around the world, including the National Institutes of Health, use the same BMI standards to define adult overweight and obesity. [4]

BMI is used as the standard to diagnose overweight and obesity because there are so many studies that show a link between BMI, the risk of several diseases and death.

Table 1. Body Mass Index

Definition	**BMI**
Overweight	25-29.9
Obese	30-39.9
Morbidly Obese	40+

Resource: Diabetes, Diet and Nutrition

http://www.healthnet.com/dandn.htm.

As BMI increases, so does the risk for several conditions, including

- Diabetes
- Cardiovascular disease
- Stroke
- Hypertension
- Gallbladder disease
- Osteoarthritis
- Sleep apnea
- Some cancers
- Premature death

While the links between BMI and disease risk is clear, it is important to remember that it is only one of several disease risk factors. In other words, BMI cannot tell an individual that he or she will get a disease, only that his or her risk of developing the disease is increased. [6]

BMI has some limitations. It tends to overestimate body fat in people who are very muscular and underestimate body fat in people who are highly sedentary. BMI also doesn't show where the body fat is located. Abdominal fat carries the greatest health risk. [5]

II. RESULTS

2.1 National Institute for Health And Clinical Excellence (NICE)

The following guidance is evidence-based. This guidance represents the view of the National Institute for Health and Clinical Excellence, which was arrived at after carefull consideration of the evidence available.

2.1.1 Type 1 Diabetes: diagnosis and management of type 1 diabetes in children, young people and adults according NICE guidelines.

2.1.1.1 Key priorities for implementation: children and young people Management from diagnosis:

Children and young people with type 1 diabetes should be offered an ongoing integrated package of care by a multidisciplinary paediatric diabetes care team. To optimise the effectiveness of care and reduce the risk of complications, the diabetes care team should include members with appropriate training in clinical, educational, dietetic, lifestyle, mental health and foot care aspects of diabetes for children and young people. [8]

At the time of diagnosis, children and young people with type 1 diabetes should be offered home-based or inpatient management according to clinical need, family circumstances and wishes, and residential proximity to inpatient services. Home-based care with support from the local paediatric

diabetes care team (including 24-hour telephone access to advice) is safe and as effective as inpatient initial management. [8]

Education

Children and young people with type 1 diabetes and their families should be offered timely and ongoing opportunities to access information about the development, management and effects of type 1 diabetes. The information provided should be accurate and consistent and it should support informed decision-making. [8]

Monitoring glycaemic control

Children and young people with type 1 diabetes and their families should be informed that the target for long-term glycaemic control is an HbA1c level of less than 7.5% without frequent disabling hypoglycaemia and that their care package should be designed to attempt to achieve this. [8]

Diabetic ketoacidosis

Children and young people with diabetic ketoacidosis should be treated according to the guidelines published by the British Society for Paediatric Endocrinology and Diabetes. [8]

Screening for complications and associated conditions

Children and young people with type 1 diabetes should be offered screening for:

- coeliac disease at diagnosis and at least every 3 years thereafter until transfer to adult services.
- thyroid disease at diagnosis and annually thereafter until transfer to adult services.
- retinopathy annually from the age of 12 years.
- microalbuminuria annually from the age of 12 years.
- blood pressure annually from the age of 12 years. [8]

Psychosocial support

Children and young people with type 1 diabetes and their families should be offered timely and ongoing access to mental health professionals

because they may experience psychological disturbances (such as anxiety, depression, behavioural and conduct disorders and family conflict) that can impact on the management of diabetes and well-being. [8]

2.1.1.2 Key messages: adults

The Guideline Development Group reviewed the recommendations and summarised these key messages for implementation. [8]

Patient-centred care

The views and preferences of individuals with type 1 diabetes should be integrated into their healthcare. Diabetes services should be organised, and staff trained, to allow and encourage this. [8]

Multidisciplinary team approach

The range of professional skills needed for delivery of optimal advice to adults with diabetes should be provided by a multidisciplinary team. Such a team should include members having specific training and interest to cover the following areas of care:

- education/information giving
- nutrition
- therapeutics
- identification and management of complications
- foot care
- counselling
- psychological care. [8]

Education for adults with diabetes

Culturally appropriate education should be offered after diagnosis to all adults with type 1 diabetes (and to those with significant input into the diabetes care of others). It should be repeated as requested and according to annual review of need. [8]

This should encompass the necessary understanding, motivation, and skills to manage appropriately:

- blood glucose control (insulin, self-monitoring, nutrition)

• arterial risk factors (blood lipids, blood pressure, smoking)
• late complications (feet, kidneys, eyes, heart). [8]

Blood glucose control

Blood glucose control should be optimised towards attaining DCCT-harmonised HbA1c targets for prevention of microvascular disease (less than 7.5%) and, in those at increased risk, arterial disease (less than or equal to 6.5%) as appropriate, while taking into account:
• the experiences and preferences of the insulin user, in order to avoid hypoglycaemia. [8]
• the necessity to seek advice from professionals knowledgeable about the range of available meal-time and basal insulins and about optimal combinations thereof, and their optimal use. [8]

Arterial risk-factor control

Adults with type 1 diabetes should be assessed for arterial risk at annual intervals. Those found to be at increased risk should be managed through appropriate interventions and regular review. [8]
Note should be taken of:
• microalbuminuria, in particular.
• the presence of features of the metabolic syndrome.
• conventional risk factors (family history, abnormal lipid profile, raised blood pressure, smoking). [8]

Late complications

Adults with type 1 diabetes should be assessed for early markers and features of eye, kidney, nerve, foot and arterial damage at annual intervals. According to assessed need, they should be offered appropriate interventions and/or referral in order to reduce the progression of such late complications into adverse health outcomes affecting quality of life. [8]

2.1.2 NICE Diet guidelines for Type 1 Diabetes

- Children and young people with type 1 diabetes should be offered appropriate dietetic support to help optimise body weight and glycaemic control.
- Children and young people with type 1 diabetes and their families should be informed that they have the same basic nutritional requirements as other children and young people. The food choices of children and young people should provide sufficient energy and nutrients for optimal growth and development, with total daily energy intake being distributed as follows:

• carbohydrates – more than 50%
• protein – 10–15%
• fat – 30–35%. [8]

The consumption of five portions of fruit and vegetables per day is also recommended. Neonates, infants and pre-school children require individualised dietary assessment to determine their energy needs. [8]

- Children and young people with type 1 diabetes should be encouraged to develop a good working knowledge of nutrition and how it affects their diabetes.
- Children and young people with type 1 diabetes and their families should be informed of the importance of healthy eating in reducing the risk of cardiovascular disease (including foods with a low glycaemic index, fruit and vegetables, and types and amounts of fats), and means of making appropriate nutritional changes in the period after diagnosis and according to need and interest at intervals thereafter.
- Children and young people with type 1 diabetes should be encouraged to consider eating a bedtime snack. The nutritional composition and timing of all snacks should be discussed with the diabetes care team.
- Children and young people using multiple daily injection regimens should be offered education about insulin and dietary management as part of their diabetes care package, to enable them to adjust their insulin dose to reflect their carbohydrate intake.

- Children and young people with type 1 diabetes should be offered education about the practical problems associated with fasting and feasting. [8]

2.1.3 Treatment of type 1 diabetes

2.1.3.1 NICE recommendations for treatment of Type 1 Diabetes in children

Insulin regimens

While the insulin regimen should be individualised for each patient, three basic types of insulin regimen can be considered. [8]

One, two or three insulin injections per day: these are usually injections of short-acting insulin or rapid-acting insulin analogue mixed with intermediate-acting insulin. The insulin preparations may be mixed by the patient at the time of injection. [8]

Multiple daily injection regimen: the person has injections of short acting insulin or rapid-acting insulin analogue before meals, together with one or more separate daily injections of intermediate-acting insulin or long-acting insulin analogue. [8]

Continuous subcutaneous insulin infusion (insulin pump therapy):

A programmable pump and insulin storage reservoir that gives a regular or continuous amount of insulin (usually in the form of a rapid-acting insulin analogue or short-acting insulin) by a subcutaneous needle or cannula. [8]

- Pre-school and primary school children with type 1 diabetes should be offered the most appropriate individualised regimens to optimise their glycaemic control.
- Young people with type 1 diabetes should be offered multiple daily injection regimens to help optimise their glycaemic control.
- Multiple daily injection regimens should be offered only as part of a package of care that involves continuing education, dietary management, instruction on the use of insulin delivery systems and

blood glucose monitoring, emotional and behavioural support, and medical, nursing and dietetic expertise in paediatric diabetes, because this improves glycaemic control.

- Children and young people using multiple daily injection regimens should be informed that they may experience an initial increase in the risk of hypoglycaemia and short-term weight gain.
- Children and young people with type 1 diabetes and their families should be informed about strategies for the avoidance and management of hypoglycaemia.
- Young people who do not achieve satisfactory glycaemic control with multiple daily injection regimens should be offered additional support and, if appropriate, alternative insulin therapy (once-, twice- or three-times daily mixed insulin regimens or continuous subcutaneous insulin infusion using an insulin pump).
- Young people with type 1 diabetes who have difficulty adhering to multiple daily injection regimens should be offered twice-daily injection regimens.
- Continuous subcutaneous insulin infusion (or insulin pump therapy) is recommended as an option for people with type 1 diabetes provided that: multiple-dose insulin therapy (including, where appropriate, the use of insulin glargine) has failed; and those receiving the treatment have the commitment and competence to use the therapy effectively.
- Continuous subcutaneous insulin infusion therapy should be initiated only by a trained specialist team, which should normally comprise a physician with a specialist interest in insulin pump therapy, a diabetes specialist nurse and a dietitian.
- All individuals beginning continuous subcutaneous insulin infusion therapy should be provided with specific training in its use. Ongoing support from a specialist team should be available, particularly in the period immediately following the initiation of continuous subcutaneous insulin infusion. It is recommended that specialist teams should agree a common core of advice appropriate for continuous subcutaneous insulin infusion users.
- Established users of continuous subcutaneous insulin infusion therapy should have their insulin management reviewed by their specialist team so that a decision can be made about whether a trial or a switch to multiple-dose insulin incorporating insulin glargine would be appropriate. [8]

Insulin preparations

Different types of insulin are available for use in the insulin regimens for type 1 diabetes. They work for different lengths of time when injected subcutaneously. The appropriate insulin with its particular absorption profile should be matched to the person's needs in an attempt to obtain normal to near-normal blood glucose control. [8]

The main categories of insulin are:

• **rapid-acting insulin analogues**: these aim to work like the insulin normally produced to cope with a meal; they have an onset of action of approximately 15 minutes and a duration of action of 2–5 hours.

• **short-acting insulins**: these work more slowly than rapid-acting insulin analogues; they have an onset of action of 30–60 minutes and a duration of action of up to 8 hours.

• **intermediate-acting insulins**: these have an onset of action of approximately 1–2 hours, maximal effects between 4 and 12 hours and a duration of action of 16–35 hours.

• **long-acting insulin analogues**: these can last for a longer period than intermediate-acting insulins; they are normally used once a day and achieve a steady-state level after 2–4 days to produce a constant level of insulin. [8]

A biphasic insulin is a mixture of rapid-acting insulin analogue or short-acting insulin together with intermediate-acting insulin. [8]

- Children and young people with type 1 diabetes should be offered the most appropriate insulin preparations (rapid-acting insulin analogues, short-acting insulins, intermediate-acting insulins, long-acting insulin analogues or biphasic insulins) according to their individual needs and the instructions in the patient information leaflet supplied with the product, with the aim of obtaining an HbA1c level of less than 7.5% without frequent disabling hypoglycaemia and maximising quality of life.
- Children and young people with type 1 diabetes using multiple daily insulin regimens should be informed that injection of rapid-acting insulin analogues before eating (rather than after eating) reduces post-prandial blood glucose levels and thus helps to optimise blood glucose control.
- For pre-school children with type 1 diabetes it may be appropriate to use rapid-acting insulin analogues shortly after eating (rather than before eating) because food intake can be unpredictable.

- Children and young people with type 1 diabetes who use insulin preparations containing intermediate-acting insulin should be informed that these preparations should be mixed before use according to the instructions in the patient information leaflet supplied with the product. [8]

Methods of delivering insulin

- Children and young people with type 1 diabetes should be offered a choice of insulin delivery systems that takes account of their insulin requirements and personal preferences.
- Children and young people with type 1 diabetes using insulin injection regimens should be offered needles that are of an appropriate length for their body fat (short needles are appropriate for children and young people with less body fat; longer needles are appropriate for children and young people with more body fat). [8]

Non-insulin agents(oral antidiabetic drugs)

- Children and young people with type 1 diabetes should not be offered acarbose or sulphonylureas (glibenclamide, gliclazide, glipizide, tolazamide or glyburide) in combination with insulin because they may increase the risk of hypoglycaemia without improving glycaemic control.
- Metformin in combination with insulin is suitable for use only within research studies because the effectiveness of this combined treatment in improving glycaemic control is uncertain. [8]

2.1.3.2 NICE Recommendations for treatment of Type 1 Diabetes in adults

Insulin regimens

- Adults with type 1 diabetes should have access to the types (preparation and species) of insulin they find allow them optimal well-being.
- Cultural preferences need to be discussed and respected in agreeing the insulin regimen for a person with type 1 diabetes.
- Multiple insulin injection regimens, in adults who prefer them, should be used as part of an integrated package of which education, food and skills training should be integral parts.
- Appropriate self-monitoring and education should be used as part of an integrated package to help achieve optimal diabetes outcomes.
- Meal-time insulin injections should be provided by injection of unmodified ('soluble') insulin or rapid-acting insulin analogues before main meals.
- Rapid-acting insulin analogues should be used as an alternative to meal-time unmodified insulin:

• where nocturnal or late inter-prandial hypoglycaemia is a problem.
• in those in whom they allow equivalent blood glucose control without use of snacks between meals and this is needed or desired.

- Basal insulin supply (including nocturnal insulin supply) should be provided by the use of isophane (NPH) insulin or long-acting insulin analogues (insulin glargine). Isophane (NPH) insulin should be given at bedtime. If rapid-acting insulin analogues are given at meal times or the midday insulin dose is small or lacking, the need to give isophane (NPH) insulin twice daily (or more often) should be considered.
- Long-acting insulin analogues (insulin glargine) should be used when:

• nocturnal hypoglycaemia is a problem on isophane (NPH) insulin.
• morning hyperglycaemia on isophane (NPH) insulin results in difficult daytime blood glucose control.
• rapid-acting insulin analogues are used for meal-time blood glucose control.

- Twice-daily insulin regimens should be used by those adults who consider number of daily injections an important issue in quality of life.

• Biphasic insulin preparations (pre-mixes) are often the preparations of choice in this circumstance.
• Biphasic rapid-acting insulin analogue pre-mixes may give an advantage to those prone to hypoglycaemia at night.
Such twice daily regimens may also help:
• those who find adherence to their agreed lunch-time. insulin injection difficult.
• adults with learning difficulties who may require assistance from others.

- Adults whose nutritional and physical activity patterns vary considerably from day to day, for vocational or recreational reasons, may need careful and detailed review of their self-monitoring and insulin injection regimen(s). This should include all the appropriate preparations, and consideration of unusual patterns and combinations.
- For adults undergoing periods of fasting or sleep following eating (such as during religious feasts and fasts or after night-shift work), a rapid-acting insulin analogue before the meal (provided the meal is not prolonged) should be considered.
- For adults with erratic and unpredictable blood glucose control (hyper- and hypoglycaemia at no consistent times), rather than a change in a previously optimised insulin regimen, the following should be considered:

• resuspension of insulin and injection technique.
• injection sites.
• self-monitoring skills.
• knowledge and self-management skills.
• nature of lifestyle.
• psychological and psychosocial difficulties.
• possible organic causes such as gastroparesis.

- Continuous subcutaneous insulin infusion (or insulin pump therapy) is recommended as an option for people with type 1 diabetes provided that: multiple-dose insulin therapy (including, where appropriate, the use of insulin glargine) has failed; and those receiving the treatment have the commitment and competence to use the therapy effectively.
- Partial insulin replacement to achieve blood glucose control targets (basal insulin only, or just some meal-time insulin) should be

considered for adults starting insulin therapy, until such time as islet B-cell deficiency progresses further.

- Clear guidelines and protocols ('sick-day rules') should be given to all adults with type 1 diabetes to assist them in adjusting insulin doses appropriately during intercurrent illness.
- Oral glucose-lowering drugs should generally not be used in the management of adults with type 1 diabetes. [8]

Insulin delivery

- Adults with diabetes who inject insulin should have access to the insulin injection delivery device they find allows them optimal well-being, often using one or more types of insulin injection pen.
- Adults with type 1 diabetes who have special visual or psychological needs should be provided with injection devices or needle-free systems that they can use independently for accurate dosing.
- Insulin injection should be made into the deep subcutaneous fat. To achieve this, needles of a length appropriate to the individual should be made available.
- Adults with type 1 diabetes should be informed that the abdominal wall is the therapeutic choice for meal-time insulin injections.
- Adults with type 1 diabetes should be informed that extended-acting suspension insulin, for example isophane (NPH) insulin, may give a longer profile of action when injected into the subcutaneous tissue of the thigh rather than the arm or abdominal wall.
- Adults with diabetes should be recommended to use one anatomical area for the injections given at the same time of day, but to move the precise injection site around in the whole of the available skin within that area.
- Adults with diabetes should be provided with suitable containers for the collection of used needles. Arrangements should be available for the suitable disposal of these containers.
- The injection-site condition should be checked annually and if new problems with blood glucose control occur. [8]

2.1.4 NICE guidance for non-pharmacological management of Type 2 Diabetes

The following guidance is based on the best available evidence. It describes in details the methods and the evidence used to develop the guidance.

Dietary advice

- Provide all people with diabetes with individualised nutritional advice as part of ongoing management from someone with specific expertise in nutrition.

- Provide that advice in a form sensitive to the individual's needs, culture, and beliefs, being sensitive to their willingness to change, and the effects on their quality of life.

- Place particular emphasis on general population dietetic measures (include carbohydrate from fruits, vegetables, whole-grains, and pulses [and thus high fibre and low glycaemic index], the inclusion of low fat dairy products and oily fish, and control of saturated and trans fatty acid intake) when providing advice to people with diabetes.

- Integrate the advice given into the individual's overall diabetes management plan, including other aspects of lifestyle modification such as increasing physical activity.

- Target, for the overweight, an initial body weight loss of 5-10%, while remembering that any weight loss may be of benefit, and larger degrees of weight loss in the longer term will have advantageous metabolic impact.

- Individualise carbohydrate and alcohol recommendations, and meal pattern, in particular for people using insulin or insulin secretagogues aiming to reduce the risk of hypoglycaemia.

- Advise that limited use of sucrose-containing foods is allowable when substituted for other carbohydrate in the meal plan but with care to avoid excess energy intake.

- Discourage the use of foods marketed specifically for people with diabetes.

- When patients are admitted to hospital as in-patients or to any other institutions, implement a meal planning system that provides consistency in the carbohydrate content of meals. [8]

2.1.5 NICE guidance for the pharmacotherapy of Type 2 Diabetes

2.1.5.1 Oral glucose control therapies (1): metformin, insulin secretagogues, and acarbose

1. Metformin

- Begin metformin in people who are overweight or obese for their ethnic group and whose blood glucose control is inadequate when using lifestyle interventions (nutrition and exercise) alone.

- Consider metformin as an option for first-line glucose-lowering therapy in people who are not overweight.

- Continue metformin when blood glucose control remains or becomes inadequate and other oral glucose-lowering medication (usually a sulfonylurea) is added.

- Step up metformin therapy gradually over weeks to minimise risk of gastro-intestinal (GI) side effects. Consider a trial of extended-

absorption metformin tablets, where GI tolerability prevents continuation of metformin therapy.

- Review metformin dose when serum creatinine >130 micromol/litre or estimated glomerular filtration rate (eGFR) <45 ml/min/1.73 m^2.

    • Stop metformin if serum creatinine >150 micromol/litre or eGFR <30 ml/min/1.73 m^2.
    • Prescribe metformin with caution in those at risk of sudden deterioration of kidney function, or at risk of a decline of eGFR to <45 ml/min/1.73 m^2.
- The benefits of metformin therapy should be discussed with people who have type 2 diabetes and mild to moderate liver dysfunction or cardiac impairment so that:

- due consideration is given to the cardiovascular protective effects of the drug
- an informed patient decision is made regarding whether to continue or stop the metformin therapy. [8]

2. Insulin secretagogues

- Consider a sulfonylurea as an option for first-line glucose-lowering therapy in people who are not overweight:

    • where metformin is not tolerated or is contraindicated
    • where a rapid response to therapy is required because of hyperglycaemic symptoms.
- Use a sulfonylurea as second-line therapy when blood glucose control remains or becomes inadequate on metformin.

- Continue a sulfonylurea when blood glucose control remains or becomes inadequate and other oral glucose-lowering medication is added.

- Prescribe a sulfonylurea with low acquisition cost (but not glibenclamide) where an insulin secretagogue is indicated as above.

- In people where drug concordance is problematic a once daily long-acting sulfonylurea should be offered.

- Educate people being treated with an insulin secretagogue about the risk of hypoglycaemia, in particular those with renal impairment. [8]

3. Rapid-acting insulin secretagogues

- Consider offering rapid-acting insulin secretagogues to people with non-routine daily lifestyle patterns to assist in attaining glucose control to their individual target. [8]

4. Acarbose

- Consider acarbose as an alternative glucose-lowering therapy in people unable to use other oral glucose-lowering medications. [8]

2.1.5.2 Oral glucose control therapies (2): other oral agents and exenatide

1. PPAR-γ agonists

- Consider, after discussion with the person with diabetes, a PPAR-γ agonist (thiazolidinedione) when glucose concentrations are not adequately controlled (to HbA_{1c} of <7.5% or other higher level individually agreed), adding it to:

  • the combination of metformin and a sulfonylurea where insulin is contraindicated or is likely to be poorly tolerated, for example because of the nature of employment (for example, HGV licence holders), needle phobia, or other personal issues, or:
  • a sulfonylurea where metformin is not tolerated, or
  • metformin as an alternative to a sulfonylurea where occupation or other issues make the hypoglycaemia risk with sulfonylureas of particular significance.†

- Warn people prescribed a thiazolidinedione about the possibility of development of significant oedema, and the action to take should that occur.

- PPAR-γ agonists should not be commenced or continued in people who have evidence of heart failure.

- Prescribe the thiazolidinedione which has the lower acquisition cost, where such a medication is indicated as above. [8]

2. GLP-1 mimetics - exenatide

- Exenatide is not recommended for routine use for people with type 2 diabetes.

- Exenatide should only be considered for people with type 2 diabetes who have all of the following:

  • a body mass index over 35.0 kg/m2
  • specific problems of a psychological, biochemical, or physical nature arising from high body weight
  • inadequate blood glucose control (HbA_{1c} >7.5 %) on conventional oral agent therapy after trial of metformin and sulfonylurea, and
  • where other high cost medications such as thiazolidinediones or insulin injection therapy would otherwise be started.

- Continue exenatide therapy only if a useful metabolic response (at least 1.0 % HbA1c reduction in 6 months and a weight loss of at least 5 % at 1 year) is obtained and maintained. [8]

2.1.5.3 Type 2 Diabetes: newer agents for blood glucose control in type 2 diabetes

Incretin enhancers (DPP-4 inhibitors)

- Sitagliptin. Sitagliptin has UK marketing authorisation for use in patients with type 2 diabetes mellitus as oral therapy to improve glycaemic control in combination with:

1. metformin if diet and exercise plus metformin do not provide adequate glycaemic control.

2.a sulphonylurea, in patients with insufficient glycaemic control despite the maximum tolerated dose of a sulphonylurea and for whom metformin is inappropriate because of contraindications or intolerance.

3.a sulphonylurea and metformin, in patients with insufficient glycaemic control

4.a thiazolidinedione, in patients with insufficient glycaemic control and for whom the use of a thiazolidinedione is appropriate.

- Vildagliptin. Vildagliptin has UK marketing authorisation for use in the treatment of type 2 diabetes mellitus as dual oral therapy in combination with:

1.metformin, in patients with insufficient glycaemic control despite the maximum tolerated dose of monotherapy with metformin.

2.sulphonylurea, in patients with insufficient glycaemic control despite the maximum tolerated dose of a sulphonylurea and for whom metformin is inappropriate because of contraindications or intolerance.

3. thiazolidinedione, in patients with insufficient glycaemic control and for whom the use of a thiazolidinedione is appropriate. [8]

Incretin mimetics (GLP-1 analogues)

- Exenatide. Exenatide currently has UK marketing authorisation for the treatment of type 2 diabetes mellitus in combination with metformin and/or sulphonylureas in people who have insufficient glycaemic control on the maximum tolerated doses of these oral therapies. It is administered as a subcutaneous injection.
- Liraglutide. Liraglutide does not yet have UK marketing authorisation. It has been studied in phase III trials in patients with type 2 diabetes who have been treated with oral glucose-lowering medications (metformin and a sulphonylurea). These studies have examined the use of liraglutide as monotherapy and as combination with metformin, sulphonylureas, metformin and a sulphonylurea, and metformin and a thiazolidinedione. Liraglutide has also been studied

in combination with a sulphonylurea, and in combination with a thiazolidinedione. [8]

Thiazolidinediones

- Pioglitazone. Pioglitazone is administered orally and has UK marketing authorisation for use:
    1.as monotherapy in people (particularly those who are overweight) who have insufficient glycaemic control from diet and exercise, and for whom metformin is inappropriate because of contraindications of intolerance.
    2.as dual oral therapy in combination with metformin in people (particularly those who are overweight) with insufficient glycaemic control despite the maximum tolerated dose of monotherapy with metformin.
    3.as dual oral therapy in combination with a sulphonylurea, only in people who show intolerance to metformin or for whom metformin is contraindicated, and who have insufficient glycaemic control despite the maximum tolerated dose of monotherapy with a sulphonylurea.
    4.as triple therapy in combination with metformin and a sulphonylurea, in people (particularly those who are overweight) with insufficient glycaemic control despite dual oral therapy.
    5.in combination with insulin in people with type 2 diabetes with insufficient glycaemic control on insulin for whom metformin is inappropriate because of contraindications or intolerance.
- Pioglitazone/metformin combination. This combination product is administered orally and is indicated for the treatment of type 2 diabetes, particularly in people who are overweight, and who are unable to achieve sufficient glycaemic control at the maximum tolerated dose of oral metformin alone.
- Rosiglitazone. Rosiglitazone is indicated for the treatment of type 2 diabetes and has UK marketing authorisation for use:
    1.as oral monotherapy in people (particularly those who are overweight) who have insufficient glycaemic control from diet and exercise for whom metformin is inappropriate because of contraindications or intolerance.

2.as dual oral therapy in combination with metformin in people (particularly those who are overweight) with insufficient glycaemic control despite the maximum tolerated dose of monotherapy with metformin.

3.as dual oral therapy in combination with a sulphonylurea, only in people who show intolerance to metformin or for whom metformin is contraindicated, and who have insufficient glycaemic control despite the maximum tolerated dose of monotherapy with a sulphonylurea.

4.as triple therapy in combination with metformin and a sulphonylurea, in people (particularly those who are overweight) with insufficient glycaemic control despite dual oral therapy.

- Rosiglitazone/metformin combination. This combination has UK marketing authorisation for oral use in people for whom the maximum tolerated dose of oral metformin alone does not provide sufficient glycaemic control. It also has UK marketing authorisation for use as triple oral therapy with a sulphonylurea in people with insufficient glycaemic control despite dual oral therapy with the maximum tolerated dose of metformin and a sulphonylurea. [8]

Long-acting recombinant human insulin analogues

- Insulin detemir. Insulin detemir is indicated for the treatment of diabetes mellitus, including use with oral hypoglycaemia agents. It is administered via subcutaneous injection.
- Insulin glargine. Insulin glargine is indicated for the treatment of diabetes mellitus, including use with oral hypoglycaemia agents. It is administered via subcutaneous injection. [8]

2.1.5.4 Glucose control: insulin therapy

1. Oral agent combination therapy with insulin

- When commencing basal insulin therapy in a person with type 2 diabetes:

• continue metformin and sulfonylureas (α-glucosidase inhibitors if used may also be continued)
• review use of the sulfonylurea if hypoglycaemia occurs.

- When commencing pre-mix insulin therapy (or meal-time+basal insulin regimens) in a person with type 2 diabetes:

  • continue metformin
  • continue sulfonylureas initially but review and discontinue if hypoglycaemia occurs.
- Combined pioglitazone-insulin therapy should be considered:

  • in people who have previously shown a marked glucose-lowering response to thiazolidinedione therapy
  • in those on high dose insulin therapy with inadequate blood glucose control.

  Warn to discontinue the thiazolidinedione if significant fluid retention develops. [8]

2. Insulin therapy

- In people with type 2 diabetes when other measures have failed to achieve blood glucose control the benefits and risks of insulin therapy should be discussed. Insulin therapy should be commenced if agreed.

- Insulin therapy should be commenced using a structured programme employing active insulin dose titration founded on:

  • structured education
  • continuing telephone support
  • frequent self-monitoring
  • dose titration to target
  • dietary understanding
  • management of hypoglycaemia
  • management of acute changes in plasma glucose control
  • with support from an appropriately trained and experienced health-care professional.
- Insulin therapy should be initiated from a choice of a number of insulin types and regimens.

• Begin with human NPH insulin, given at bed-time or twice daily according to need.
• Insulin glargine is not recommended for routine use for people with type 2 diabetes who require insulin therapy. Insulin glargine treatment should be considered only for those people with type 2 diabetes who require insulin therapy and who fall into one of the following categories:
  − Those who require assistance from a carer or healthcare professional to administer their insulin injections.
  − Those whose lifestyle is significantly restricted by recurrent symptomatic hypoglycaemic episodes.
  − Those who would otherwise need twice-daily basal insulin injections in combination with oral antidiabetic drugs.
• Consider starting with biphasic insulin (pre-mix) regimens once or twice daily, the latter in particular where HbA_{1c} is elevated above 9.0%.
• Consider insulin analogue-based pre-mixes instead of human insulin pre-mixes where:
  − immediate injection before a meal is preferred,
  − if hypoglycaemia is a problem, or where
  − post-prandial blood glucose excursions are marked.

A trial of a long-acting insulin analogue (insulin glargine) should be offered where people starting NPH insulin suffer significant nocturnal hypoglycaemia.

- Monitor people using basal insulin regimens (NPH or a long-acting insulin analogue [insulin glargine] for the need for addition of meal-time insulin (or use of pre-mix insulins). Where blood glucose control remains inadequate (not to agreed target levels without problematic hypoglycaemia) move to a more intensive meal-time plus basal insulin regimen, including an analogue-based regimen.

- Monitor people using pre-mixed insulin once or twice a day for the need of a further pre-prandial injection or eventually changing to a meal-time plus basal insulin regimen, including an analogue-based regimen where blood glucose control remains inadequate. [8]

2.2 Diabetes mellitus in Cyprus

The main goal of the following description is to give the general situation concerning diabetes mellitus in Cyprus, including: epidemiological facts, general management of diabetes in clinics, the role of the Cyprus Diabetic Association, the role of the state, measures taken for prevention of the disease, reimbursement of insulin and other antidiabetics.

The present situation regarding Diabetes Care in Cyprus is that all Government General Hospitals have a diabetes clinic. All the doctors are internists with special interest in diabetes or endocrinology. There are four diabetes clinics for children with diabetes. In March 2000, the Ministry of Health organised a seminar about the care of diabetic patients. About 26 nurses were trained in diabetes issues. There are four dieticians working in the Government Sector but no Chiropodists. There are laboratory and ophthalmology services and services for pregnant women, children and elderly people with diabetes. A National Diabetic Retinopathy Screening Programme, using digital imaging and grading will be initiated by the Department of Health and Public Health Services with a target population of all people with diabetes over the age of 12 years. [26]

It is the policy of the Ministry of Health to develop a National Plan for Diabetes Mellitus in Cyprus. The National Committee will include the Ministry of Health, the Ministry of Social Affairs, non-governmental organisations, the Diabetes, Medical and Dietetic Associations, Pharmaceutical Services and Friends. Objectives for activities will include Public and Professional awareness and primary and secondary prevention. [27]

Primary prevention includes the education of the Cypriot population through health promotion (lectures, leaflets), school services and targeted activities. Programmes to prevent type 2 diabetes and other risk factors for cardiovascular disease in the population are planned with School Health Services and the Ministry of Agriculture. Other initiatives include lectures to women from rural areas, leaflets, healthy eating days, promoting the Mediterranean diet in co-operation with local municipalities and non-governmental organisations. The key non-governmental organisation is the

Cyprus Diabetes Organisation, which is involved in the National Co-ordinating Committee for Diabetes, as well as the Medical Scientific Associations. Education for General Practitioners (Government and Private) is provided in a short course about diabetes issues. The course includes prevention and treatment of diabetes and the prevention and treatment of complications. [29]

Secondary prevention is addressed through four clinics for diabetes in the Government Hospitals in Nicosia, Limassol, Larnaka and Archbishop Makarios III for children with diabetes. The Ministry of Health and the National Co-ordinating Committee for Diabetes are committed to establishing a **Centre of Excellence for Diabetes, a Programme of seminars and lectures to all General Practitioners and four doctors to work for a year or more in University Diabetes Clinics.** [19]

2.2.1 General facts

The objective of the following table is to show the total prevalence of diabetes among Greek Cypriots in 2003 and the actions taken from the state against the disease. The cost was not estimated precisely. The data were taken from the Cyprus Diabetic Association which collected the data from the Ministry of Health.

Table2. Prevalence, cost and national plans for diabetes in Cyprus

FACTS	
Estimated prevalence (% of total population above 20 years old)	5.1-10.3%
Total diabetes prevalent cases	27,700-170,000
Cost of diabetes (% of total healthcare budget)	Not estimated
POLICY FRAMEWORK	
National Plan	-
Guidelines	In progress
Planned Actions	Healthcare reforms Diabetes National Plan

Resource: Cyprus Diabetic Association (CDA). www.diabetes.org.cy.

2.2.1.1 Incidence/Prevalence of diabetes

In 2001, the (growing) number of people in Cyprus living with diabetes was estimated at more than 60,000 with a further 60,000 undiagnosed. Comprehensive data is scant for the Republic of Cyprus as, until the diabetes register is completed, there are no records. [26]

The estimated diabetes prevalence was 5.1% in 2003 according to the IDF Atlas. According to the Cyprus Diabetes Association, diabetes prevalence today is estimated at 10.3%, with more than 70,000 people living with diabetes. Furthermore, the WHO predicts that the prevalence of diabetes in Cyprus will increase by 74% between 2000 and 2030. [28]

Diabetes is thought to represent about 2.1% of the disease burden in Cyprus and approximately 2.3% of total deaths. These numbers underestimate the importance of diabetes because they do not take account of diabetes as a secondary cause of death. For example, cardiovascular disease, one of the many serious complications associated with diabetes, represents 17% of the disease burden in Cyprus, and is estimated to account for around 41% of deaths in the country. [2]

Obesity is one of the high risk factors for the onset of diabetes and up to 23% of 13-17-year olds in Cyprus are obese or overweight. With respect to obesity, Cyprus shares second place in the EU with Greece, Italy, and Ireland. [26]

2.2.1.2 Cost of diabetes care

Expenditure on health (excluding capital spending) has increased during the last ten years, reaching 5.8% of GDP in 2002 against 2.8% in 1980. It is estimated by the Cyprus Diabetic Association that the annual cost of treatment of a person with diabetes in Cyprus is £3,000 per year. The growth rate for the last five years is estimated at 2.3%. [27]

2.2.1.3 Government priorities

Reform of the healthcare sector is currently a high priority for the Government of the Republic of Cyprus. The present system has been criticised for the fragmentation of services and lack of coordination between the public and private health sectors. The Strategic Plan 1999-2003 aimed to improve the level of coordination of the two sectors, improve public health and preventative activities, create a medical school, encourage medical research and create a district level authority for decentralization. [21]

On 20 April 2001, the House of Representatives enacted a law for the introduction of a National Health Insurance System (NHIS), which is currently being implemented and is intended to provide free healthcare at the point of delivery. It will be universal as regards population coverage and will be financed by contributions from the state, employers, employees, the self-employed, pensioners and all those who have non-employment incomes. [24]

As part of these reforms, the Government is also considering the development of a national plan for diabetes that is intended to evolve in line with the new national healthcare system. [21]

2.2.1.4 Policy Framework

In 2003, the "National Coordinating Committee for Diabetes" Committee proposed a "Plan of Action for Diabetes" to the Ministry of Health: this is still under discussion. The programme would include the creation of a "Diabetes Register", including an immediate epidemiological survey on diabetes prevalence. [27]

The Government is developing specialised diabetes clinics in hospitals throughout Cyprus to be staffed by specialised healthcare professionals. [21]

2.2.1.5 Guidelines

The Health Ministry is currently finalising guidelines for health professionals, particularly in the newly-created diabetes clinics. [21]

2.2.1.6 Reimbursement

People with type I or type II diabetes are eligible for free medication from the Government Hospitals, ie. Insulin (human, all types with pen injector), tablets for monitoring diabetes and any other drugs for complications caused by diabetes, as well as strips for blood glucose analyses. [26]

In March 2005 the Ministry of Health introduced a new policy designed to reduce the costs of pharmaceuticals in Cyprus. Patients suffering from diabetes should benefit by a reduction of up to 53% in the price of treatment. [29]

2.2.2 Incidence of type 1 diabetes

2.2.2.1 Incidence of insulin dependent diabetes mellitus in Greek Cypriot children and adolescents, 1990-1994.

The objective of this study was to estimate the incidence of type 1 diabetes mellitus (IDDM) in the Greek population of Cyprus based on epidemiological data collected during the period 1990-1994.

Insulin dependent diabetes mellitus (IDDM) is one of the most common chronic diseases among children and adolescents worldwide. It has been well established that there are marked geographic differences in the incidence of IDDM, which may provide important clues concerning its as yet unknown etiology. The results of this survey showed that the incidence of IDDM in the Greek population of Cyprus is 10.5/100,000 population under the age of 15 years, which is in agreement with other European countries. There was a slight increase in the number of newly diagnosed patients in 1994. The mean age of onset is 8 years whereas the peak age of onset occurs at 11-12 years. There is a slight overall female predominance but not among children who manifest IDDM before the age of five years in whom males significantly predominate. Distribution by month of onset of IDDM revealed an increased number of cases during autumn and winter as expected. [12]

2.2.2.2 The incidence of type 1 diabetes mellitus in Greek-Cypriot children and adolescents in 1990-2000.

The oblective of this study was to ascertain the exact incidence of type 1 diabetes mellitus (DM1) in Greek-Cypriots under the age of 15 yr, to analyze possible gender differences in the age of onset and to observe any seasonal variation in the manifestation of the disease. All cases of newly diagnosed DM1 patients under the age of 15 yr from 1990 to 2000 were collected and relevant information was obtained. The data were statistically processed in relation to the population data provided by the Department of Statistics and Research of the Ministry of Finance.

The mean annual incidence of DM1 in the Greek population of Cyprus under the age of 15 yr for the period 1990-2000 is 11.32/100,000. There is a trend towards increasing incidence during this period. There is a gender influence on the age of onset: more males develop DM1 before the age of 6 yr and after 13 yr. Moreover, there is a gender difference in the group who manifest DM1 in the age range 5-9 yr, with females having a mean age of onset of 8.1 yr, compared with 7.3 yr for males. There is a statistically significant seasonal variation, but not among preschool subjects who manifest DM1 before the age of 4 yr. DM1 is a common condition in Greek-Cypriots under the age of 15 yr. The gender difference in the age of onset probably reflects the peripubertal period of each gender. The seasonal variation cannot be solely attributed to weather and temperature changes. This survey covers a 10-yr period and deals with an adequate number of reported cases; therefore, it could contribute to the international effort to determine the exact pathogenesis of DM1. [11]

2.2.3 An Epidemiologic Study on the Prevalence of Diabetes, Glucose Intolerance, and Metabolic Syndrome in the Adult Population of the Republic of Cyprus

The study was conducted in Cyprus (November 2003 through January 2005). Stratified random sampling was used to select 1,200 individuals aged 20–80 years (from a total population of 477,000). In all subjects, anthropometrical measurements were taken, fasting lipids were measured, eating habits were evaluated according to a standardized questionnaire, and an oral glucose tolerance test (OGTT) was performed (except in known diabetic patients).

In the absence of OGTT-diagnosed diabetes or impaired glucose tolerance (IGT), impaired fasting glucose (IFG) was defined by fasting plasma glucose ≥110 mg/dl and <126 mg/dl, whereas "new" IFG was defined by fasting plasma glucose ≥100 and <126 mg/dl. Metabolic syndrome was defined according to the National Cholesterol Education Program Adult Treatment Panel III criteria. [13]

Of the 1,200 subjects, 78 (6.5%) had known diabetes and 45 (3.8%) were newly diagnosed by the OGTT, which brought the total prevalence of diabetes to 123 (10.3%). Another 78 (6.5%) subjects had IGT, 36 (3.0%) had IFG, and 171 (14.2%) had "new" IFG. Logistic regression showed that significant risk factors for diabetes were age, male sex, family history of diabetes ($P < 0.001$), hypertension ($P = 0.004$), and obesity ($P = 0.003$). Risk factors for IGT were age and family history of diabetes ($P < 0.01$). Risk factors for IFG and "new" IFG were age and obesity ($P < 0.01$). [13]

The prevalence of metabolic syndrome was 22.2% overall, 68.5% among subjects with diabetes, 43.6% among those with IGT, 86.1% among subjects with IFG, 35.7% with "new" IFG, and 12.3% among subjects with normal glucose tolerance. The prevalence of metabolic syndrome increases with age, is higher in men than in women (26.5 vs. 18.3%, respectively, $P = 0.001$), and is higher in rural than in urban areas (26.0 vs. 20.6%, respectively, $P = 0.037$). [14]

The average daily energy intake was 2,509 kcal, to which carbohydrates contributed 53.3%, fats contributed 31.8%, and proteins contributed 14.9%. Comparing the OGTT(–) group with the three groups of various degrees of glucose intolerance, after age and sex adjustment, no differences were found regarding energy intake (range 2,551–2,231 kcal) or the qualitative composition of the diet (carbohydrates 53.1–54.9%, proteins 14.4–15.4%, and fats 30.7–32.1%). Moreover, the above parameters did not differ between subjects with or without metabolic syndrome. [14]

In conclusion, the study revealed a very high prevalence of diabetes and IGT in Cyprus, among the highest in Europe, compared with five centers of the DECODE (Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe) study (1) and higher than in the U.S. (2), while the prevalence of metabolic syndrome is comparable with that of other Western countries (3). Dietary habits, evaluated by cross-sectional analysis, do not seem to contribute to the development of glucose intolerance. Interventions aimed at IGT and the components of metabolic syndrome are urgently needed in order to reduce the incidence of diabetes. [13]

2.2.4 Genetic predisposition to DM 1 in the Greek-Cypriot population

Genetic linkage of diabetes mellitus type 1 (DM1) with certain HLA alleles is still of scientific interest. The aim of this study is to identify the association of HLA alleles with DM1 in Greek Cypriots.

101 DM1 patients with age of onset less than 15 years were HLA typed using PCR/SSOP and PCR/SSP methods and compared to 209 controls randomly selected from a population of healthy volunteer donors. Statistical analysis was performed using the SPSS statistical package. [15]

The results are shown in the table below:

HLA DM1 % CTL % Odds Ratio (95% CI) Fisher.s test

DR4 66 18 8.735 (5.076-15.033) P<0.001

DR3 50 13 6.741 (3.839-11.837) P<0.001
DR5 9 56 0.079 (0.38-0.166) P<0.001
DR2 25 46 0.385 (0.227-0.653) P<0.001
DR3 or 4 92 30 27.266 (12.486-59.542) P<0.001
DQ2 73 27 7.230 (4.237-12.337) P<0.001
DQ3 49 54 0.802 (0.499-1.289) P<0.214
DQ2 or 3 95 73 7.278 (2.819-18.792) P<0.001

High resolution testing of the DR4 and DR3 alleles revealed the predominant presence of the DRB1*0403 (0% vs 36%), similar frequency of the DRB1*0402 in both groups (19% vs 14%) and that DRB1*0301 was the only DR3 allele detected. The DQB1 alleles were nearly exclusively DQB1*0201 and DQB1*0302. [15]

DM1 in our population seems to be linked to HLA:
DRB1*0301 and DRB1*0405 which are associated with DQB1*0201 and DQB1*0302. A negative association and possible protection from DM1 of DR5 and DR2 antigens is also considered. Further studies on the HLA and other genes are needed to uncover the immunogenetic basis of DM1. [15]

2.2.5 Prevalence of type 2 diabetes and physical activity status in elderly men and women from Cyprus (the MEDIS Study).

The aim is to investigate the association of being physically active on the prevalence of Type 2 diabetes mellitus among elderly people.

There was enrollment of 53 men and 97 women, aged 65 to 100, from various areas of Cyprus. Physical activity was evaluated through a validated questionnaire (the short International Physical Activity Questionnaire, IPAQ). Prevalence of diabetes was 26% in men and 18% in women, while 55% of men and 50% of women were reported as being moderately or vigorously active. Furthermore, 5% of the participants reported that they smoked, 4% had stopped smoking, and 8% reported alcohol consumption. People in the upper tertile of the IPAQ score were 0.26 times less likely to

have diabetes ($p < 0.05$); on the other hand people in the lower tertile of the score were 1.7 times more likely to have diabetes ($p < 0.05$). [39]

Findings support the notion of a beneficial effect of physical activity on the burden of diabetes in the elderly. [39]

2.2.6 Case studies made in Cypriot patients

The aim of the following case studies was to show the connection of diabetes mellitus with different complications and the great importance of the preventable measures that must be taken to avoid these complications. These case studies were taken from the Makarios Hospital of Nicosia, in Cyprus.

1. J.K., a 45-year-old female, was 1.59m and weighed 73kg. She had urinary tract infections once or twice each month within the last 12 months. Her other symptoms and signs included constant thirst, increased fluid intake, increased frequency and volume of urination. She was diagnosed with diabetes mellitus after testing positive for high levels of blood glucose. She was prescribed Equilibrium, 4 capsules TID before meals. Two weeks after the initial treatment, she reported significant improvement of her signs and symptoms. Two months after the initial treatment, her blood glucose levels were within the ideal range. She did not have any urinary tract infections during these two months. She continues to take Equilibrium, 4 capsules TID before meals. [16]

Clinical Note: Urinary tract infection is a common complication of chronic diabetes. The frequency of infections, polydipsia and polyuria, in combination with her age and body weight, indicated possible diabetes. Prior to treating the urinary tract infection, her blood glucose levels must first be tested to rule out diabetes. In this case, persistent high levels of blood glucose levels confirmed the diagnosis of diabetes mellitus. After treatment

with Equilibrium for two months, both symptoms and complications of diabetes mellitus were under good control. [16]

2. A.G., a 60-year-old male, was 1.83m and weighed 127kg. He was always hungry and ate two or three bowls of rice with every meal. He noticed that his cuts or scratches required a longer period of time to heal, sometimes up to one month. His diagnoses were diabetes mellitus and high cholesterol. He was given Equilibrium, 4 capsules TID for his diabetes, and Cholisma, 4 capsules TID for his cholesterol. After taking the herbs for three months, his blood glucose levels were within the ideal range and his cholesterol level dropped from 260 to 220. His weight also dropped from 280 to 255 pounds. He ate less and did not feel constantly hungry. He continues to take both Equilibrium and Cholisma. [17]

Clinical Note: High cholesterol levels are a common complication of diabetes mellitus. If untreated, high cholesterol levels can lead to atherosclerosis, hypertension, coronary heart disease, angina, and myocardial infarction. Therefore, effective treatment must address both blood glucose levels and blood cholesterol levels. In combination with dietary changes, this patient showed excellent progress in reducing his blood glucose and cholesterol levels. [17]

2.2.7 Insulin in Cyprus

In Cyprus, it was reported that two of the main problems relating to insulin, are the gap between private and public health care and the lack of treatment guidelines. People with diabetes go to the hospital for their prescriptions, while going to the Private Sector for their consultations. In North Cyprus, insulin is free of charge but there is an issue regarding availability; not all insulins are available. If other types of insulin are needed, a request must be submitted to a panel of doctors. The decision often takes a long time. [18]

2.2.8 Cyprus Diabetic Association (CDA)

2.2.8.1 What care to expect when your child has diabetes

The main aim of treatment for diabetes is to relieve the unpleasant symptoms of high and low blood glucose by maintaining near-normal blood glucose levels. Good diabetes control is not always easy to achieve. Most young people- and their parents- have difficulties with this at one time or another. But, with the support of the " Children's Specialist Diabetes Team", the child will be able to lead an active, healthy life with normal growth and development. [21]

Children with diabetes have special needs to do with the fact that they are children. This is why it is essential that the child is looked after by a Specialist Children's Diabetes Team, and is seen at a special clinic just for children with diabetes. This way, the family of the child can meet other parents and children who are in the same position as them- and meet all the members of the team at one visit. [21]

The child and his/her family are important members of the team too- after all, the child and the family will be "living with diabetes" day to day. The family's and child's input and experience is just as important as their contact with the diabetes team. [21]

The Specialist Children's Diabetes Team in Cyprus includes:

1. **Consultant paediatrician with a special interest in diabetes**- he/she has overall responsibility for the child's diabetes care, hand in hand with the other members of the team. His/her experience in childhood conditions and special knowledge of diabetes mean that the children can have the best possible care and advice.
2. **Paediatric diabetes specialist nurse**- he/she has special expertise in children and diabetes, and can give advice and support for managing diabetes in hospital, at home, and at school.
3. **Paediatric dietitian**- food is an important part of a child's life, even more so when the child has diabetes. The paediatric dietitian can give advice and support on the subject of the family's food. This will help the child to have good diabetes control and healthy growth.

4. **Children's clinical psychologist**- diabetes affects many aspects of life for the child and the family, and this can lead to emotional stress. The family should be able to contact a children's clinical psychologist with experience in diabetes if needed.
5. **Family GP**- he/she will still look after the child for non-diabetes matters. There should be good communication between the child's GP and the diabetes team on the child's health.
6. **Senior paediatric ward nurse with experience in diabetes**- hopefully, the child will not have much contact with the hospital ward after diagnosis, but the senior ward nurse can give advice if other members of the team are not available, or if the child does not need to go into hospital again. [21]

Care at diagnosis (at hospital or at home)

These days with newly diagnosed diabetes, children may receive their initial care and treatment either at hospital, at home or a combination of both, depending on the child's health and the facilities available in Cyprus health authority. [21]

If the child is going to be cared for in hospital and is under 16, he/she should be admitted to a paediatric ward staffed by health care professionals experienced in childhood diabetes. There should be facilities for the parents to stay with their child at the hospital, and the amount of time the child spends away from home should be kept to a minimum. [21]

In some cases, the child may be treated at home by a children's specialist paediatric diabetes team, if he/she does not have ketoacidosis, (a complication of diabetes that needs to be treated in hospital). The child may be able to spend the day at home and sleep at the hospital at night. [21]

Such "home-based" diabetes services for children, though not widespread, are being developed in some areas of Cyprus especially in the capital city Nicosia. [21]

Whether the child is to be at hospital or at home in the first few days after diagnosis, there are certain things that should happen:

1. The family should be given an explanation of diabetes from a senior member of the medical team, and appropriately written information on diabetes to back this up.

2. The family should be given time to absorb the fact that the child has diabetes, and a chance to talk over the emotional impact of diabetes on the child and the rest of the family.
3. The family should be able to talk over their concerns with senior staff while the child is in hospital or being looked after at home.
4. One of the diabetes team should inform the family's GP about their child's diabetes, and offer to get in contact with the school.
5. The family should have several sessions with a paediatric dietitian who can give them dietary advice and help them make any changes that are needed to the child's diet.
6. The family should be seen by a paediatric diabetes specialist nurse.
7. The family should be given information about the CDA (Cyprus Diabetic Association), family support groups in their area, and how to claim Disability Living Allowance to help cover the home supervision of their child now that he/she has diabetes. [21]

Continuous care

At diagnosis and in the weeks and months following the child's diagnosis, members of the diabetes team will give the family and the child more detailed information on how to control and manage diabetes. This should include:

1. Information and advice on how and where to inject, injecting devices, and how to dispose of needles and finger pricking lancets.
2. How and when to test blood for glucose levels and urine for ketones, what the results of these tests mean, and when to seek advice.
3. Information about how insulin, food, exercise, stress and excitement interact, and how they affect blood glucose levels.
4. A discussion about hypoglycaemia (hypos) with clear information about its causes, symptoms and treatment. This should include the use of Glucagon and/or Hypostop. The family should be given information on convulsions (fits) which can occasionally be caused by hypos, and how to deal with them.
5. An explanation of what is called the "honeymoon" phase- the time shortly after diagnosis when the child may need less insulin.
6. An explanation that the child may find it hard to adjust to early day to day life with diabetes.
7. The family should be given a telephone number to call for 24-hour advice from members of the diabetes team or the paediatric ward. [21]

Once the child's diabetes is reasonably controlled

After a time, the family will become more confident in managing their child's diabetes. However, the diabetes team should always be available when and if the family need them. They will maintain contact to continue their education programme and to support the family. The family should not hesitate to ask for more help or information. [21]
Then the following could be expected:

1. The family and their child should see a paediatric diabetes specialist nurse, consultant and dietitian frequently in the weeks and months after diagnosis. Once the family feels more confident in managing their child's diabetes, they will need to visit the clinic at least 3 or 4 times a year as part of their child's regular diabetes care.
2. At the visits, the child's general health will be checked and his/her blood glucose will be reviewed by looking at the family's home records, and by some extra tests of long term blood glucose control.
3. The family, especially the parents, should have a chance to get further education about diabetes, and discuss any other concerns that the family may have about diet, insulin, hypoglycaemia or any other aspect of living with diabetes.
4. As the child gets older there will be opportunities to discuss how he/she is coping with diabetes and life in general. There may be some emotional or behavioural problems that the family is finding difficult to manage on their own; perhaps the child is refusing to do blood tests, or worried about being bullied at school. If this is the case, the family should be able to get help from a psychologist or counsellor as part of the child's diabetes care. [21]

2.2.8.2 Child's annual review

Children with diabetes should have a complete medical check by the diabetes team. This may take the form of a yearly review or it may take place at each visit. This will show how the child is managing with injections, diet and diabetes control. It also allows the team to check for any signs of diabetes "complications", which can affect the feet, eyes and kidneys. [21]

Complications are rare in children, and we know that good diabetes control greatly reduces the risk. However, it is sensible for the child to have regular checks (at least once a year) so that any problems can be picked up and treated. [21]
This review includes:

1. Blood tests
2. Urine tests
3. A blood pressure check
4. Check of injection sites
5. A food examination
6. A review of diet
7. A check of weight and height
8. An eye examination(from the age of 12 onwards)
9. The diabetes team should note how many hypos, admissions to hospital and days missed from school due to diabetes the child has had in the past year.
10. Discussion of any worries the family may have, and setting realistic targets for control and management for the coming year. [22]

2.2.8.3 Emotional support

Learning that your child has diabetes is a traumatic event for any family. Adapting to and managing diabetes upsets the normal routine at home and can place a strain on family relationships. Diabetes can be fitted into an active and healthy life, and settled home life, but the family needs help and support to do this. This is why diabetes care in Cyprus should also include input from a psychologist and/or counsellor if needed. Extra support may be needed, for example, to help the child make the change to an adult diabetes team. [22]

Diabetes at school

It is important that there is good communication between the child's school staff and the diabetes team. In most instances the diabetes nurse specialist will visit the school to talk to the child's teacher and other staff about diabetes. He/she can explain about hypoglycaemia, the child's meal

and snack times, exercise and who to contact in an emergency. The CDA (Cyprus Diabetic Association) can supply a free **School Pack** for school staff. This is also useful for the paediatric diabetes specialist nurse, who can take it on school visits and leave it for the staff. [21]

Changing to an adult clinic

As the child gets older, the diabetes team will be trying to encourage him/her to take on more responsibility for doing their own injections and blood tests and keeping a record of their test results. In this way, the child will start to understand how food, exercise and insulin affects their diabetes, and how to make adjustments to " keep in control". [22]

When the child reaches the mid teenage years (generally 16 and over) he/she will probably come under the care of a new diabetes team, specialising in adults with diabetes. Exactly when this happens depends on the individual child and the facilities available in his/her area. [21]

It can be a difficult time for the child, as he/she will have got used to the paediatric team and perhaps made friends with other children attending. [21]

But the paediatric team and the adult team should work together to make sure the transfer is as smooth as possible. [22]

2.2.8.4 How the CDA can help

The Cyprus Diabetic Association is an excellent source of support and information for Cypriots living with diabetes, which includes the parents. Families with a child under 16 years old can join the CDA free for the first year. [21]

1. **Balance,** the CDA's magazine for members, is full of interviews, features, research updates and recipes, showing the people that diabetes needn't hold them back from a healthy, active lifestyle. They can also receive **Young Balance,** a series of pages especially for children with diabetes.
2. The CDA's **Balance for Beginners** range is designed to help people who are newly diagnosed with diabetes. The CDA has magazines for parents of children with diabetes, for children, teenagers, and for

adults with insulin dependent diabetes. The CDA also has a large selection of leaflets and books on all aspects of diabetes.

3. The CDA can offer reassurance through their confidential information and support service, **Careline.** Through **Careline,** CDA can provide Cypriots with general information on diet, hypoglycaemia, injections and testing, disability living allowance, employment issues and much more – for individual medical advice, the patient's diabetes nurse specialist and diabetes team are best qualified to help. There are number of self help groups especially for parents of children with diabetes, within CDA's nationwide branch network.
4. The Youth & Family Services department at the CDA runs a range of fun and educational holidays for children and teenagers, giving the child the chance to meet others the same age with diabetes and learn more about their condition.
5. CDA's Family Weekends are open to the whole family. Children are entertained by experienced helpers while the family has a chance to meet paediatricians, nurses and dietitians in an informal setting.
6. The CDA runs the Parent Network, which sends out a newsletter, *Link Up,* four times a year. There are special groups within this which discuss their own needs, including single parents, parents of children under five, parents of children with diabetes and another condition. [21]

2.2.9 Diabetes control in Cyprus and other Mediterranean East countries

The scale of the problem that diabetes poses to regional health is still widely under-recognized and presents a daunting public health challenge. Recent estimates predict that if current trends continue, the number of persons with diabetes will more than double, especially in the less developed countries of the Region. Recent studies from Bahrain, Oman and Saudi Arabia showed that diabetes prevalence ranges between 13% and 15%. The Regional Office supported efforts towards enhanced surveillance, epidemiology and prevention of diabetes mellitus, and financial support was offered for surveys and studies in Islamic Republic of Iran, Jordan, Lebanon, Oman and Saudi Arabia. Significant progress in early detection and

treatment of complications was made in Bahrain, Cyprus, Kuwait, Oman and Saudi Arabia, and in promoting healthy lifestyles, in a healthy nutritional strategies workshop held in Lebanon in June 2000. The majority of countries of the Region have established, published and distributed guidelines on diabetes education materials focusing on community-based aspects. Bahrain, Jordan, Oman and Saudi Arabia made progress in developing national diabetes programmes, with emphasis on primary health care implementation and community awareness. Workshops on diabetes control for physicians were conducted in Bahrain, Egypt, Jordan, Lebanon, Oman, Pakistan, Saudi Arabia, Sudan and Tunisia, for both ministry of health staff and the private sector. [18]

More efforts are needed, especially to accord high priority to diabetes control, provide adequate budgetary resources and conduct national community-based surveys. [19]

The aim of the following table is to show the present prevalence of diabetes mellitus among East Mediterranean countries, and in what extend it will be in the future. The data were collected from the World Health Organization (WHO).

Table3. Prevalence of diabetes in the WHO Eastern Mediterranean Region

Country	2000	2030
Afghanistan	468,000	1,403,000
Bahrain	37,000	99,000
Cyprus	50,000	87,000
Djibouti	7,000	9,000
Egypt	2,623,000	6,726,000
Islamic Republic of Iran	2,103,000	6,421,000

Iraq	668,000	2,009,000
Jordan	195,000	680,000
Kuwait	104,000	319,000
Lebanon	146,000	378,000
Libyan Arab Jamahiriya	88,000	245,000
Morocco	427,000	1,138,000
Oman	113,000	343,000
Pakistan	5,217,000	13,853,000
Qatar	38,000	88,000
Saudi Arabia	890,000	2,523,000
Somalia	97,000	331,000
Sudan	447,000	1,277,000
Syrian Arab Republic	627,000	2,313,000
Tunisia	166,000	388,000
United Arab Emirates	350,000	684,000
Yemen	327,000	1,286,000
Total	15,188,000	42,600,000

Resource: http://www.who.int/diabetes/facts/world_figures/en/index.html.

The prevalence is estimated to be increased:

- By 43% in Cyprus
- By 63% in Bahrain

- By 61% in Egypt
- By 67% in Iran

2.3 DIABETES MELLITUS IN THE EU

The aim of the following description is to show the general situation concerning diabetes mellitus in the EU, including the prevalence of diabetes mellitus among EU countries, the costs of this disease, the plans taken for the prevention and diabetes care, and the policy recommendations for diabetes prevention and control at EU and national levels.

2.3.1 The size of the diabetes epidemic in the EU

Diabetes mellitus is a mounting public health issue. Being a chronic and progressive process from hyperglycemia at its beginning to cardiovascular and so-called microangiopathic complications, the consequences of "the diabetes process" cannot be overestimated. The severity of the problem is largely accentuated by the growing prevalence of type II diabetes, and, to a lesser extend, type I diabetes. [26]

Today, over 25 million people living with diabetes within the 27 EU member states are affected by the disease. The current EU average prevalence rate is estimated to be 7.5% of the total population aged 20 and above with all indications pointing to a continued increase in the coming years. [26]

Prevalence rates in the new member states lie around 9% and beyond. [26]

Based on population screening programmes, it is estimated that up to 50% of all people with diabetes are undiagnosed: for every known diabetes case, an unknown one is detected. [26]

There is an alarming rise in the number of children diagnosed with type II diabetes. This audit revealed the incompleteness of existing data regarding this problem, and moreover, the lack of specific programmes to address it. [26]

2.3.2 The personal and budgetary costs of the diabetes problem in the EU

Diabetes mellitus is a major and growing epidemic with high cost and negative health implications, yet several EU governments lack a clear view of the disease's epidemiological burden, economic, personal, and societal impact. [27]

The total cost of diabetes across the EU is estimated to account for 2.5-15% of total healthcare spending (over half of member states have reported estimates of their spending on diabetes). [27]

Evidence of the dramatic costs of treating diabetes and its complications are found in the CODE-2 study, which estimated the total direct costs of type II diabetes to be 29 billion Euros in 1998 for 10 million people with type II diabetes in eight EU countries (Belgium, France, Germany, Italy, the Netherlands, Spain, Sweden and the UK). [27]

Around 50% of the people with type II diabetes have already developed at least one complication by the time of diagnosis. Cardiovascular diseases leading to myocardial infarction and/or stroke, eye disease or retinopathy (the leading cause of blindness), kidney failure, neuropathy and diabetic foot disease(predisposing to ulceration and limb amputation) are some of the most common complications of diabetes. [27]

On average, those with type II diabetes will die 5-10 years before those without diabetes; most of this excess mortality is due to cardiovascular disease. About 80% of all people living with diabetes die of cardiovascular disease. [27]

Cardiovascular disease consumes by far the greatest proportion of direct costs and more than half of the mortality-related costs of diabetes. [27]

The largest single item of diabetes expenditure is hospital admissions for the treatment of long-term complications such as heart disease, stroke, kidney failure and foot problems. Many of these complications are potentially preventable given prompt diagnosis of diabetes, effective patient and professional education and comprehensive long term care of people with diabetes. [27]

The cost-effectiveness of diabetes management programmes depends on several factors such as diabetes epidemiology, healthcare organization and delivery of care. [27]

With regard to general screening, questions remain over long-term benefits. Experts suggest that a more targeted approach towards high risk groups is probably the best and most profitable way forward. [27]

2.3.3 Policies in place to address the diabetes problem in the EU

11out of the 27 member states (Austria, Czech Republic, Denmark, Finland, France, Germany, Italy, Portugal, Slovakia, the Netherlands and United Kingdom) are reported to provide a national framework or plan for diabetes prevention and care. Spain is unique as it has several regional diabetes plans but no national framework. [28]

10 member states are addressing diabetes, either under the national obesity plan, or by developing national diabetes plans or screening programmes. Of these, seven member states are expected to have national diabetes plans in place by 2006 (Austria, Ireland, Germany, Lithuania, Luxembourg, Spain and Poland). [28]

Finland is a model for other member states because it has addressed the high prevalence of diabetes and associated healthcare costs. Germany and Slovenia have indicated their intention to model national programmes of

the Finnish example: however, outcome data from the Finnish programme are not available. [28]

The Netherlands report one of the lowest prevalence rates (3.7%) and the lowest healthcare diabetes costs (2.5% of total healthcare budget) among all EU member states. Nevertheless, it has recently developed a national plan for improved diabetes care focusing on a multidisciplinary approach. [28]

Most member states (19 out of 27) have nationwide clinical evidence-based guidelines for type I and/or type II diabetes. [28]

Prevention of obesity together with secondary prevention and intervention measures are key factors in delaying and reducing the risk of complications such as cardiovascular disease, blindness or amputations. [28]

All 27 member states of the EU (with the exception of Cyprus) adopted the St Vincent Declaration in 1989. Even when member states have established national plans, these as such are not a measure of success unless they are being implemented; the level of resources and implementation of plans was reported to be unsatisfactory in many countries. [28]

Progress made with strategies addressing cancer and cardiovascular disease, at both national and international levels, demonstrates the wisdom of addressing equally devastating conditions such as diabetes in a similarly co-ordinated, strategic and comprehensive way. [28]

2.3.3.1 Identified gaps in diabetes policies

The starting point for any comprehensive and credible policy is the availability of data on the extent and magnitude of the problem, i.e. an accurate diagnosis is the key. There is a lack of cost data in many countries, such as Cyprus, Estonia, Greece, Latvia, Luxembourg, Malta, Slovakia, Slovenia and Sweden. Governments, diabetes associations, health professionals and people living with diabetes need to be aware of the current and future economic impact of the disease. National diabetes registers (NDRs) of people with diagnosed diabetes are helpful so that effective

diabetes care can be delivered and outcomes monitored as outlined in the targets of the St Vincent Declaration. We found that very few countries have developed NDRs. Furthermore, according to experts the lack of electronic record linkage or sophisticated monitoring facilities should not prevent diabetologists and general practitioners continuing to refine their data collection on these patients. 13 Several member states have *ad hoc* screening programmes to reduce complications. However, only a few member states have set national screening targets, such as the UK, Finland and France. There is no collection of data on hard outcomes following the implementation of programmes; CVD and mortality rates are not measured, leading to inability to assess cost-effectiveness of programmes. The development of information technology is necessary if the scale of the epidemic and outcomes are to be properly recorded. [26]

2.3.3.2 Policy recommendations for diabetes prevention and control

POLICY RECOMMENDATIONS AT EU LEVEL

Article 152 of the EU Treaty of Nice provides that EU action is to complement national policies and be directed towards improving public health, preventing human illness and diseases and obviating sources of danger to human health. Such action shall support the fight against the major health scourges by promoting research into their causes and their prevention as well as health information and education. EU action in public health shall respect fully the responsibilities of member states for the delivery of health services and medical care. In this context, the proposed EU Programme of action in the field of health and consumer protection 2007 – 2013 seeks to improve the health of citizens throughout their lives, improve health as a human right and encourage investment in health, including the promotion of policies that lead to a healthier way of life and help to reduce the incidence of major diseases. However, as it stands this programme fails to address diabetes specifically as a disease that requires attention and community action. There is a definite need to identify diabetes as a priority disease at EU and national level and to encourage the exchange of best practice to

optimise resources while raising the standards across Europe as regards prevention, screening and treatment. Currently there is no forum of exchange of such practices within the EU other than ad hoc forums created by Council Presidencies. It is urged the European Commission and European Parliament to examine the current epidemiological evidence and the policy gaps across Europe with regard to diabetes. The European Commission should address the European epidemic by developing a coordinated and comprehensive EU strategy for diabetes which could make a significant contribution to the reduction of public health expenditures in all 27 EU member states. Based on the precedent of EU action in the field of cancer and the EU Council Recommendation on Cancer Screening, it is specifically encouraged the EU Commission to present an EU Council Recommendation on diabetes prevention and screening for adoption by member states. Although nonbinding for member states, such a Recommendation would provide an EU legal framework for action to improve the collection of data, to take appropriate primary prevention measures, to encourage the development of screening programmes and finally to monitor and evaluate outcomes – while respecting member states' responsibility for the delivery of health services and medical care. [27]

POLICY RECOMMENDATIONS AT NATIONAL LEVEL

It is crucial that member states improve the collection of epidemiological data on a regular basis. The EU should provide common criteria for the collection of such data so as to be able to compile and report comparative data at EU level. National registers of diabetes patients are a useful tool both from an individual perspective – they enable all those with diabetes to be identified – as well as from a public health perspective. All member states should gather comprehensive economic data about the costs of diabetes prevention and treatment. This is essential if policy decisions are to be taken to optimise limited resources. Such data are also needed to evaluate the effectiveness of different approaches to prevention and disease management. Member states should each have a national plan for diabetes prevention and care with measurable targets and an evaluation system to track health outcomes and cost-effectiveness of measures. Specific primary prevention programmes covering the whole population should be developed to promote a healthy lifestyle. Specific policies for school children should be developed, and particularly for children at increased risk of developing

obesity and diabetes (genetic and/or socio-economic factors, overweight, poor diet and lack of exercise). The development of primary screening and diagnosis programmes should be encouraged. Member states need to define targeted populations – based on local epidemiology and available resources – and screening policies to identify individuals at risk of developing diabetes and those with undiagnosed diabetes who risk developing costly complications. The implementation of secondary screening and prevention of complications in patients with diagnosed diabetes should be encouraged. Nationally-agreed guidelines with targets for disease management should be established and measured for health outcomes. A holistic approach to management of the disease is required where healthcare professionals work with patients and across sectors, i.e. Primary care, Community care, Secondary care, Social Services and Education institutes. Diabetes care requires an integrated approach. Investment in specific education and training of healthcare professionals in this disease area (physicians, diabetes specialist nurses, specialist dieticians, and other specialists) is essential to ensure that they can deliver high quality prevention, screening and care. Additional education and training at regular intervals should be made available to nonspecialist healthcare professionals to maintain safe practice. All people with diabetes should have an agreed individualised care plan which includes education, self management plan, review schedule and a named healthcare specialist. Member states need to make the political commitment to invest in the systems of care and infrastructure to ensure adequate implementation of national frameworks and to provide quality of care. Information technology is also needed to ensure good implementation and measurement of outcome data. Healthcare systems could save lives as well as billions of Euros annually with widespread use of healthcare information technology. [29]

The main goal of the following table is to show the prevalence of diabetes mellitus nowadays among European countries and the extent that the disease will take in the future years. It is seen that in some countries the prevalence will be doubled in some years and in some countries it will be even 3 times more than the present situation. The data were taken from the World Health Organization (WHO).

Table 4. Prevalence of diabetes in the WHO European Region

Country	2000	2030
Albania	86,000	188,000
Andora	6,000	18,000
Armenia	120,000	206,000
Austria	239,000	366,000
Azerbaijan	337,000	733,000
Belarus	735,000	922,000
Belgium	317,000	461,000
Bosnia and Herzegovina	111,000	180,000
Bulgaria	472,000	458,000
Croatia	155,000	180,000
Czech Rep.	336,000	441,000
Denmark	157,000	232,000
Estonia	46,000	43,000
Finland	157,000	239,000
France	1,710,000	2,645,000

Georgia	200,000	223,000
Germany	2,627,000	3,771,000
Greece	853,000	1,077,000
Hungary	333,000	376,000
Iceland	6,000	12,000
Ireland	86,000	157,000
Israel	257,000	500,000
Italy	4,252,000	5,374,000
Kazakstan	452,000	668,000
Kyrgyzstan	98,000	222,000
Latvia	82,000	90,000
Lithuania	114,000	146,000
Luxembourg	12,000	21,000
Malta	39,000	57,000
Monaco	2,000	3,000
Netherlands	426,000	720,000
Norway	130,000	207,000
Poland	1,134,000	1,541,000
Portugal	662,000	882,000
Republic of Moldova	171,000	243,000
Romania	1,092,000	1,395,000
Russian Federation	4,576,000	5,320,000

San Marino	2,000	3,000
Slovakia	153,000	220,000
Slovenia	66,000	87,000
Spain	2,717,000	3,752,000
Sweden	292,000	404,000
Switzerland	219,000	336,000
Tajikistan	93,000	246,000
The Former Yugoslav Republic of Macedonia	54,000	96,000
Turkey	2,920,000	6,422,000
Turkmenistan	80,000	222,000
Ukraine	1,629,000	1,642,000
United Kingdom of Great Britain and Northern Ireland	1,765,000	2,668,000
Uzbekistan	430,000	1,165,000
Yugoslavia	324,000	393,000
Total	33,332,000	47,973,000

Resource: http://www.who.int/diabetes/facts/world_figures/en/index.html.

The prevalence is estimated to be increased:

- By 30% in Germany
- By 34% in UK
- By 36% in France
- By 41% in Netherlands
- By 28% in Spain

2.4 Diabetes mellitus in Cyprus in comparison with EU

As it is seen there are a lot of differences between Cyprus and the EU as it concerns diabetes mellitus. Prevalence of diabetes is slightly higher in Cyprus than in the EU. The extend that the disease will take up to 2030 is similar for Cyprus and some member states, and for other member states the prevalence will be increased but not at the same extend but lower. As it concerns cost of diabetes from the total health care spending, EU has approximately 15% while in Cyprus it is not estimated precisely. The prevalence of undiagnosed patients with diabetes is slightly higher in the EU, and the same exists for the mortality and the risk for developing complications due to diabetes. EU has advantage over Cyprus in the guidelines and actions taken for prevention of diabetes and diabetes care, eg Czech Republic. All EU member states adopted the St. Vincent Declaration in 1989, with the exception of Cyprus. EU has also developed better strategies for preventing complications caused by diabetes. Cyprus has lack of cost data but this is not seen in most of the EU member states. Few member states have developed National Diabetes programmes, with Cyprus being in the process of doing it. [33]

2.5 Diabetes mellitus in Czech Republic

2.5.1 General facts

The objective of the following table is to show the total prevalence of diabetes among citizens of Czech Republic in 2003, the costs of this disease, and the actions taken from the state against the disease. The data were collected from the European Association for Study of Diabetes (EASD).

Table 5. Prevalence, cost and national plans for diabetes in Czech Republic

FACTS	
Estimated prevalence (% of total population above 20 years old)	9.5%
Total diabetes prevalent cases	534,000-687,000
Cost of diabetes (% of total healthcare budget)	15%
POLICY FRAMEWORK	
National Plan	1996 National Diabetes Programme
Guidelines	(Czech Diabetes Society) Standards of Care
Planned Actions	NDP evaluated in 2006 Epidemiological survey/Assessment of Guidelines – expected in 2007

Resource: European Association for the Study of Diabetes. www.easd.org.

2.5.1.1 Incidence/Prevalence of diabetes

The prevalence rate is estimated to be 9.5% according to the IDF Atlas. Over the last 30 years the number of people living with diabetes has more than doubled. [26]

In 1975 there were 234,000 people living with diabetes, rising to 687,137 in 2003. In 2003 type II diabetes represented 91.6% of cases. There is a growing incidence rate in both type II and type I diabetes, notably among children. Between 2000 and 2003, the number of people with diabetes increased by 5%. If this trend continues, by 2010 there will be an estimated 800,000 people living with diabetes, with a considerable number of undiagnosed, and an estimated 1,100,000 by 2020 (or a prevalence of 11%). [33]

Of major concern is that each year there is a growing number of patients with complications (173,000 in 2002 and 178,000 in 2003). The most frequent complications are retinopathy, nephropathy and insufficient blood supply in the legs. Women constitute a consistently higher proportion of people living with diabetes (by about 10%). [33]

2.5.1.2 Cost of diabetes care

According to the Czech Diabetes Society there are no accurate data, but estimates show that total expenditure on diabetes accounts for about 15% of the total budget for healthcare. [28]

2.5.1.3 Government priorities

Diabetes is seen as a government priority in addition to oncology and cardiology and the cooperation with the states' administration in this field is satisfactory. However, there remains room for improvement in prevention and early detection. [27]

2.5.1.4 Policy framework

The Ministry of Health approved the 2nd National Diabetes Programme (NDP) prepared by the Czech Diabetes Society (representing doctors) in 1996. The 1st NDP dated from the 1980s. [26]

The NDP was based on the St. Vincent Declaration and covers treatment and prevention, education of healthcare workers, social and legal aspects and science and research. The NDP is implemented in cooperation with the Ministry of Health, the Czech Diabetes Society, patients associations, the Coordination Group of the St. Vincent Declaration, the Ministry of Social Affairs and scientific and research centres. The Programme is due to be assessed in 2006. [29]

Through a well-functioning monitoring system, the Czech Republic has a relatively good picture of the evolution of diabetes. [26]

2.5.1.5 Guidelines

The NDP is complemented by a comprehensive set of standards prepared by the Czech Diabetes Society. These guidelines, published in 2004 in the Czech Journal "Diabetes, Metabolism, Endocrinology, Nutrition", cover, *inter alia*, standards for diagnosis and care of type I and type II diabetes during pregnancy, self-control levels for blood sugar, care of diabetic nephropathy, care of patients with diabetic foot, treatment of diabetic retinopathy and its complications, and nutrition recommendations for people with diabetes. The guidelines are implemented nationwide and are subject to an update every two years. [27]

The Czech Diabetes Society is currently undertaking a study of the "Evaluation of Diabetes Care in the Czech Republic" to measure the effectiveness of the guidelines. This epidemiological survey will cover a sample of 3,600 patients and will be repeated in 2006. Full results of the study are expected in 2007. [27]

2.5.1.6 Reimbursement

Health insurance provides nearly 100% reimbursement for diabetes care (insulin is covered by 90-100%; basic oral agents by 100%, and 400 glucose strips by 100%). Since 1st July 2005 the number of strips has been

increased as a consequence of negotiations between the Czech Diabetes Society and the Ministry of Health. [29]

2.6 Diabetes mellitus in Cyprus in comparison with Czech Republic

There are some similarities and some differences concerning diabetes mellitus between Cyprus and Czech Republic. From the above mentioned for both EU member states it is seen that the prevalence of diabetes in Cyprus is slightly higher than in Czech. The same is for the extent that the prevalence of diabetes will take in the future years. Concerning the cost of diabetes, it is estimated that in Czech is approximately 15% of the total health care budget (same as in EU), while in Cyprus the total cost is not estimated precisely but it is estimated that each person with diabetes is paying annually around 5000 Euros for therapy. Czech Republic has the advantage over Cyprus in the guidelines given, in that Czech Diabetes Society has evaluated diabetes Care with the Standards of Care, while Cyprus is still in progress for newly created diabetes clinics. Czech has developed a national plan which is the 1996 National Diabetes Programme (NDP), while Cyprus is in the process of developing a national plan. Planned actions in Czech Republic is the evaluation of the NDP in 2006, and also an Epidemiological Survey, with the assessment of guidelines expected in 2007. [26]

Reimbursement for diabetes mellitus is one of the most important features in the treatment of diabetics in Cyprus and Czech Republic. In the case of Cyprus, there is reimbursement of insulin (all types with the pen injector), also for tablets for monitoring of diabetes, and other drugs for complications caused by diabetes, and strips for blood glucose analyses. All of them are provided by government hospitals with 53% benefit in the price of them. Unlike Cyprus, reimbursement for diabetes in Czech Republic is almost 100%. Insulin is covered by 90-100%, basic oral agents by 100%, and more than 400 glucose strips by 100%. [29]

2.7 Global Diabetes Problem

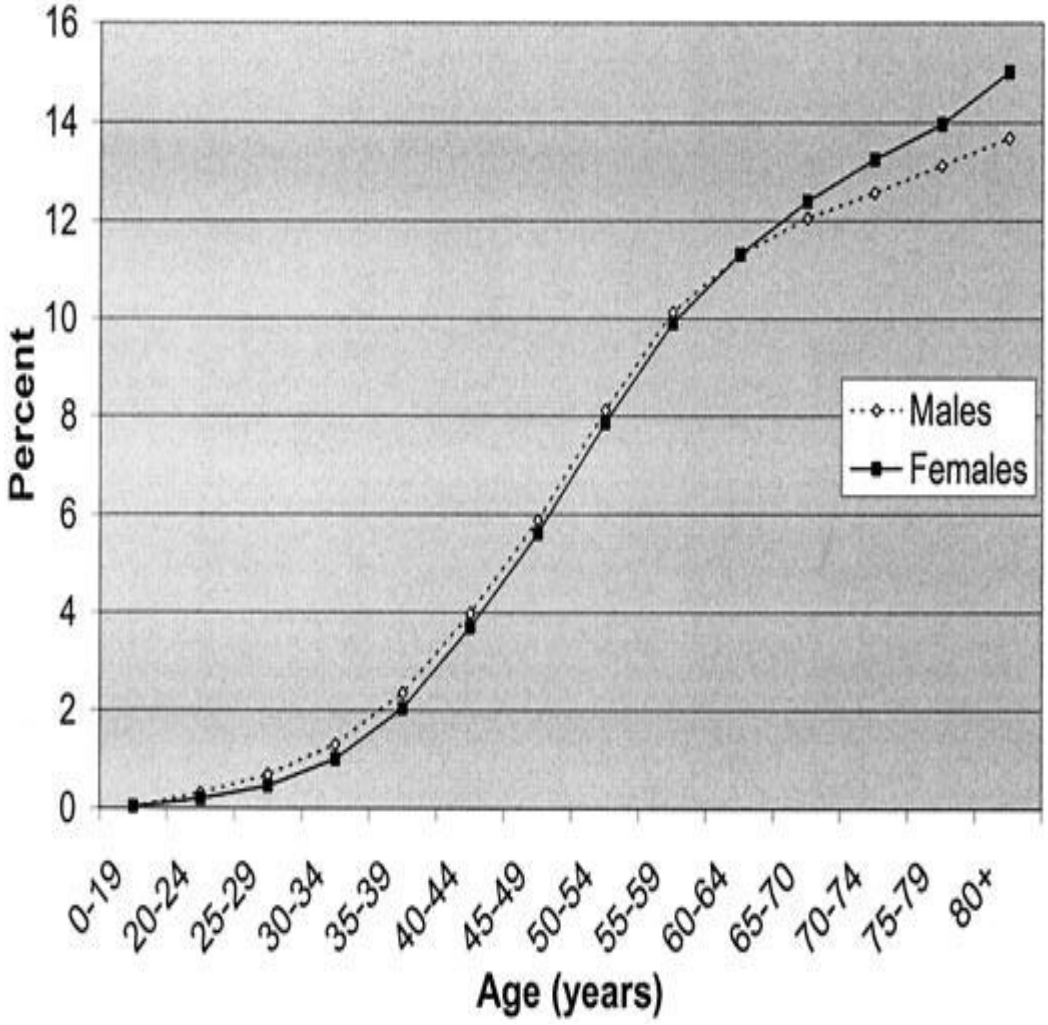
2.7.1 Global prevalence of diabetes

The goal of this study was to estimate the prevalence of diabetes and the number of people of all ages with diabetes for years 2000 and 2030. Data on diabetes prevalence by age and sex from a limited number of countries were extrapolated to all 191 World Health Organization member states and applied to United Nations' population estimates for 2000 and 2030. Urban and rural populations were considered separately for developing countries.

The prevalence of diabetes for all age-groups worldwide was estimated to be 2.8% in 2000 and 4.4% in 2030. The total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030. The prevalence of diabetes is higher in men than women, but there are more women with diabetes than men. The urban population in developing countries is projected to double between 2000 and 2030. The most important demographic change to diabetes prevalence across the world appears to be the increase in the proportion of people 65 years of age. [32]

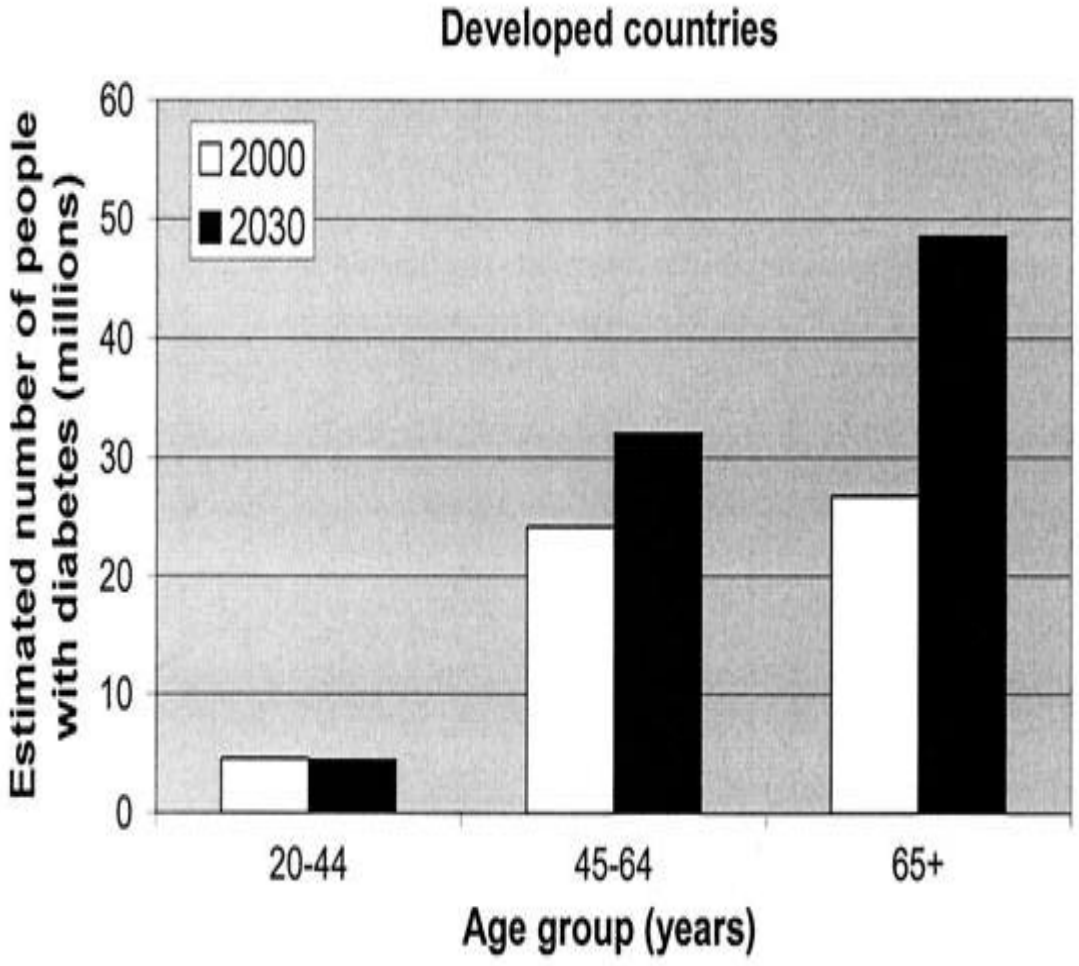
These findings indicate that the "diabetes epidemic" will continue even if levels of obesity remain constant. Given the increasing prevalence of obesity, it is likely that the following figures provide an underestimate of future diabetes prevalence. [32]

Figure 1. Global diabetes prevalence by age and sex for 2000.



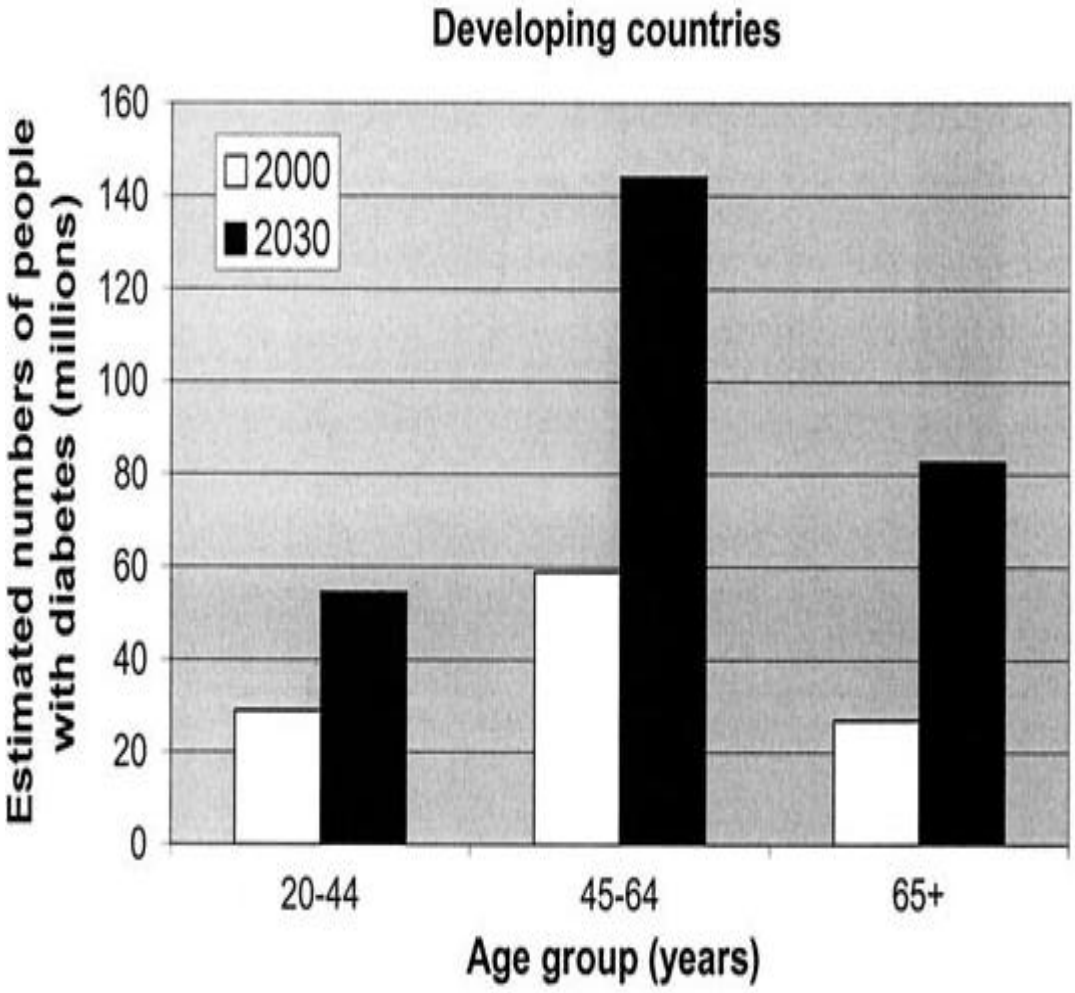
Resource: King H, Aubert RE, Herman WH: Global burden of diabetes, 1995-2025: prevalence, numerical estimates, and projections. Diabetes Care 21:1414-1431, 1998.

Figure 2. Number of people with diabetes by age in 2000 and 2030 in developed countries.



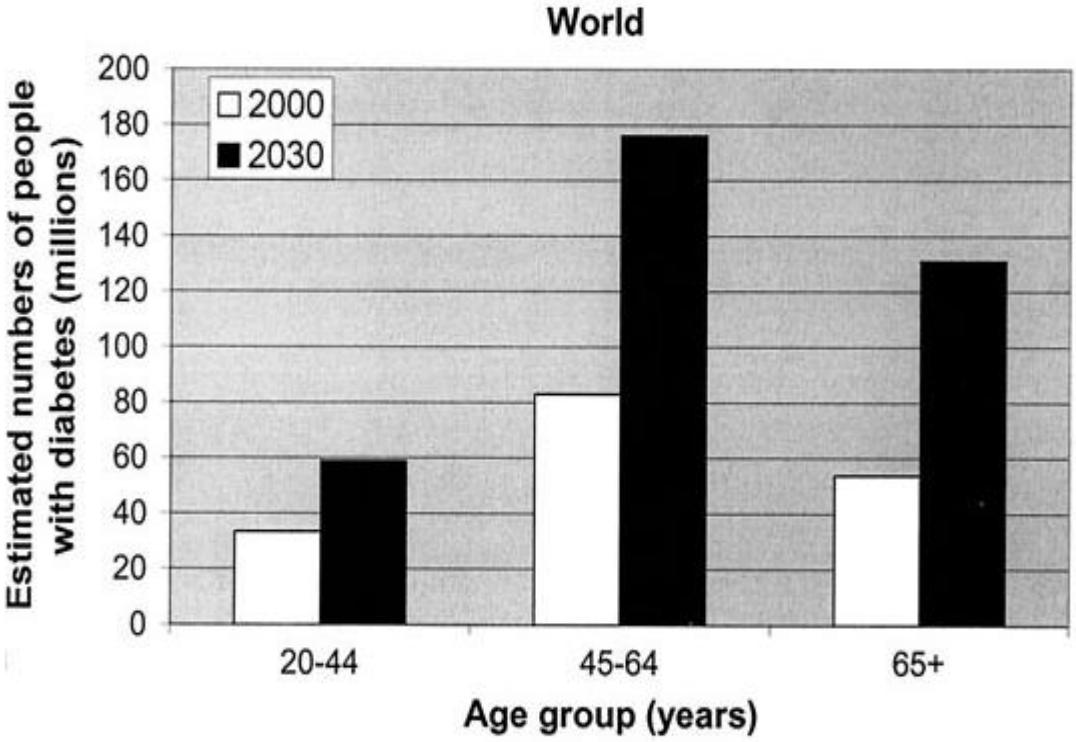
Resource: King H, Aubert RE, Herman WH: Global burden of diabetes, 1995-2025: prevalence, numerical estimates, and projections. Diabetes Care 21:1414-1431, 1998.

Figure 3. Number of people with diabetes by age in 2000 and 2030 in developing countries.



Resource: King H, Aubert RE, Herman WH: Global burden of diabetes, 1995-2025: prevalence, numerical estimates, and projections. Diabetes Care 21:1414-1431, 1998.

Figure 4. Number of people with diabetes by age in 2000 and 2030 in the world.



Resource: King H, Aubert RE, Herman WH: Global burden of diabetes, 1995-2025: prevalence, numerical estimates, and projections. Diabetes Care 21:1414-1431, 1998.

The aim of the following table is to show the total number of diabetics nowadays in the world and how it will be in the future years. The data were taken from the International Diabetes Federation (IDF).

Table 6. Prevalence of diabetes worldwide

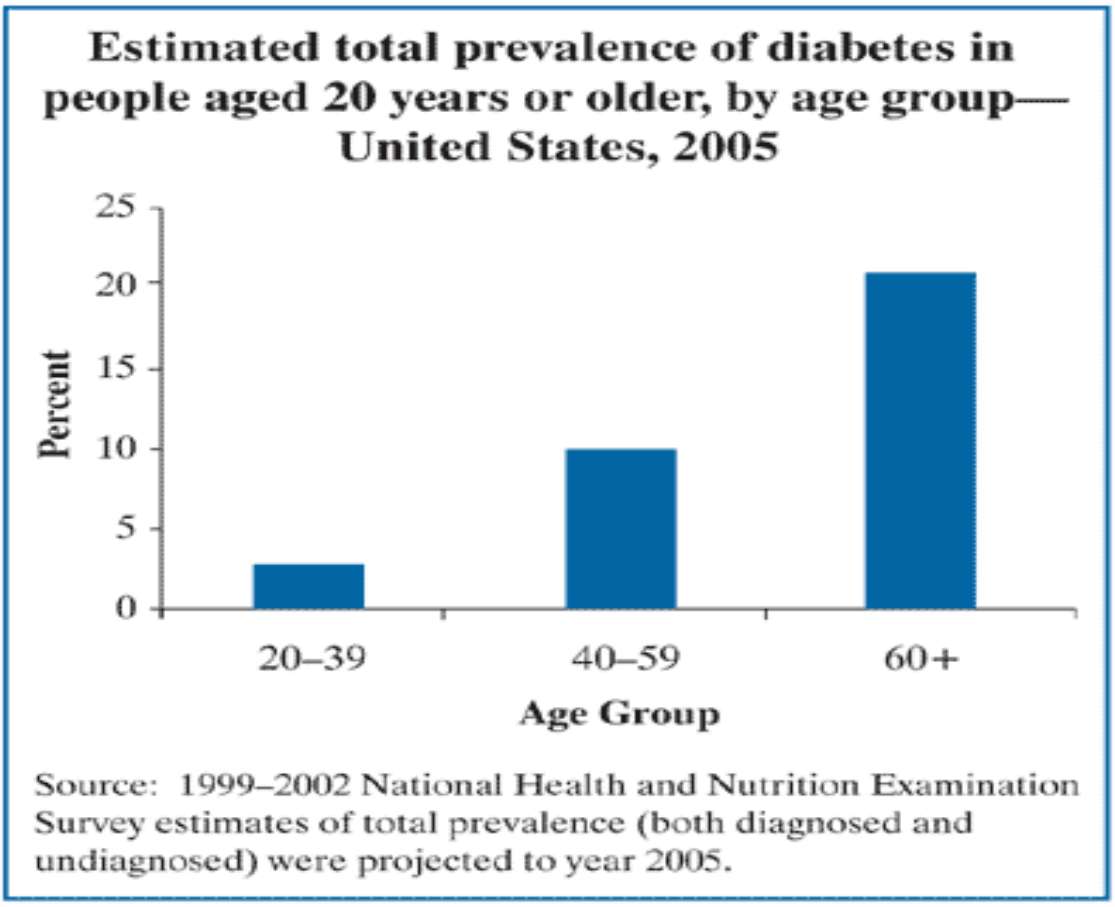
2000	**2030**	
World	171,000,000	366,000,000

Resource: Diabetes Atlas, 3rd Edition, International Diabetes Federation, 2006.

2.7.2 Diabetes mellitus in USA

The data were collected from the National Health and Nutrition Survey. The aim of the following figure is to show that prevalence of diabetes is increasing with age.

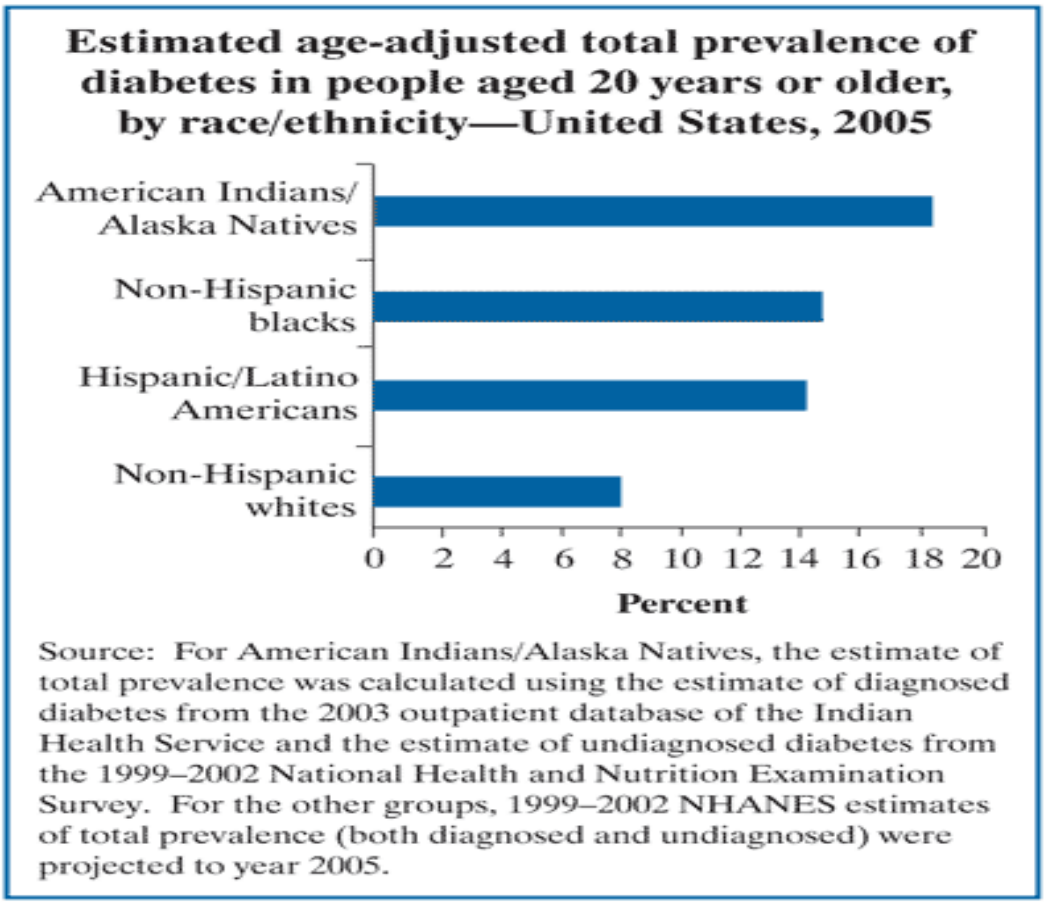
Figure 5. Prevalence of diabetes in 2005 in USA according age.



Resource: U.S. Census Bureau, resident population estimates for 03/01/05. www.census.gov/popest/national/asrh/2004_nat_res.html.

The data were collected from the National Health and Nutrition Examination Survey (NHANES), and the aim is to show what is the prevalence of diabetes among people of different ethnicities that live in USA.

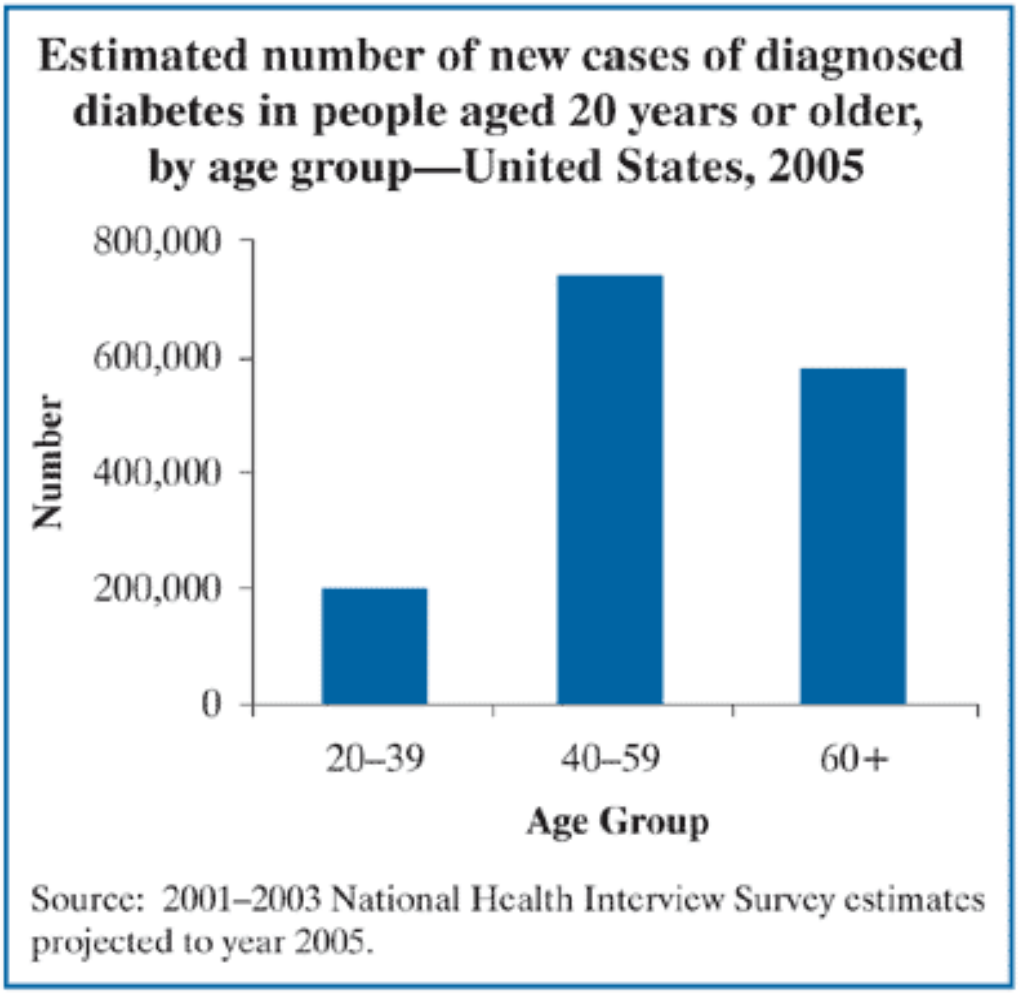
Figure 6. Prevalence of diabetes in 2005 in USA according ethnicity.



Resource: National Centre for Health Statistics, Centres for Disease Control and Prevention. 1999-2002, National Health and Nutrition Examination Survey (NHANES). www.cdc.gov/nchs/nhanes.htm.

The data were collected from the National Health Interview Survey. The aim of the following figure is to show the number of newly diagnosed diabetes among people living in USA according age group.

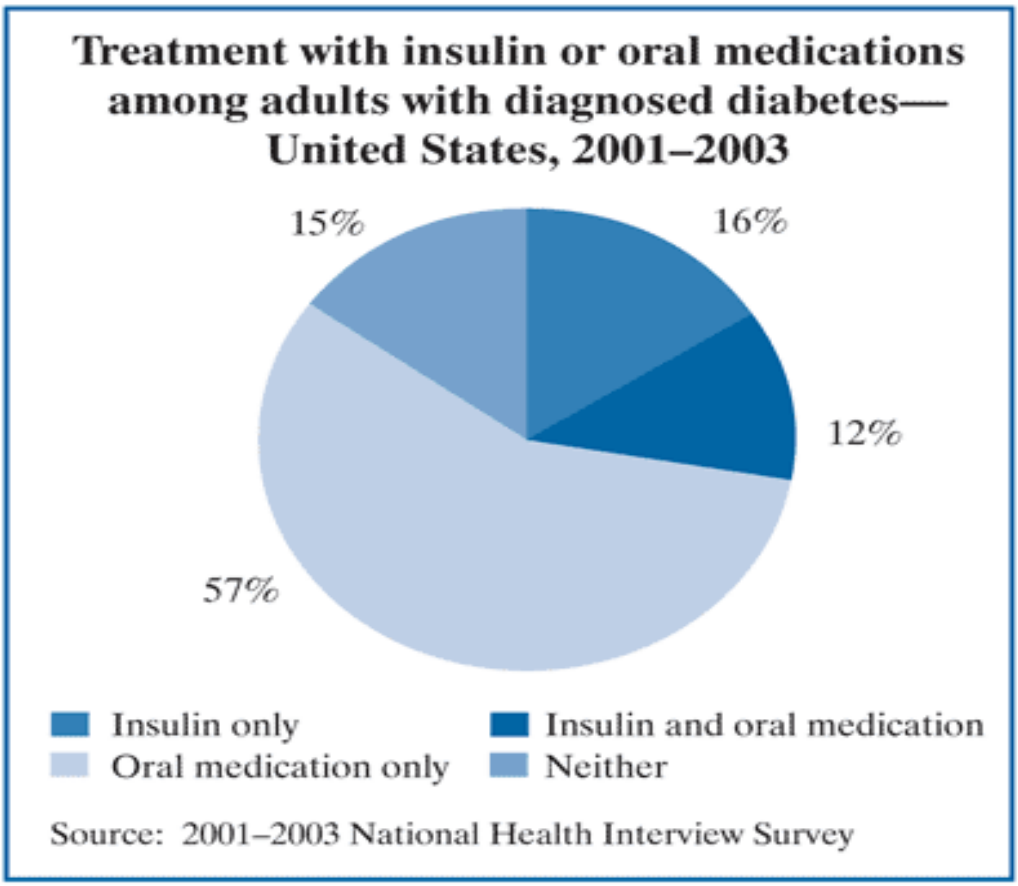
Figure 7. New cases of diagnosed diabetes in USA



Resource: National Centre for Health Statistics, Centres for Disease Control and Prevention. 1999-2003, National Health Interview Survey (NHIS). www.cdc.gov/nchs/nhis.htm.

The data were taken from the National Health Interview Survey. The aim of the following figure is to show what pharmacotherapy are adults with diagnosed diabetes in USA take. The figure shows that more than 50% are treated only with oral hypoglycemics and 15% follow other therapy than with insulin or oral hypoglycemics.

Figure 8. Treatment of adults with diagnosed diabetes in USA



Resource: National Centre for Health Statistics, Centres for Disease Control and Prevention. 1999-2003, National Health Interview Survey (NHIS). www.cdc.gov/nchs/nhis.htm.

2.8 Diabetes mellitus in the world in comparison with Cyprus

If comparison is made between the global diabetes problem and the problem of diabetes in Cyprus, some similarities and some differences can be found. The prevalence of diabetes for all age-groups worldwide was estimated to be 2,8% in comparison with Cyprus which is higher (5-10%). By 2030 it is estimated that approximately 4,4% in the world will suffer with diabetes, while in Cyprus it will be more than 2 times the recent prevalence. Some similarities can also be observed. Both in Cyprus and the world there are more women with diabetes mellitus than men. In both cases there is increasing of the prevalence of diabetes with increasing age, especially in population above 65 years of age. [33]

2.9 Diabetes in the year 2010 – what will the future bring?

The main goal of the following article is to evaluate the significance of the prevention against diabetes mellitus and its complications, and if not taken, how the incidence of the disease will be increased in the next years. Also is to give some strategies concerning the pharmacotherapy of diabetes mellitus in the future.

Although there are no definitive preventative measures that can be taken against diabetes at this time, except for identifying persons at high risk and encouraging appropriate dietary and exercise guidelines, research into the causes and control of this disease continues to provide the possibility of new cures. With the discovery of insulin in the 1920's and the development of oral hypoglycaemic drugs in the 1950's, a person who has diabetes can live an active and productive life. The importance of early detection and proper management of this chronic disease cannot, however, be emphasised too strongly. [38]

The therapy of insulin-dependent diabetes will surely be altered dramatically over the next few decades. One can project that there will be improved strategies for glucose control in established IDDM. This will include the widespread use of mechanical devices, which will involve both implantable glucose sensors and implantable insulin infusion systems; and successful pancreas, islet or beta cell transplantation, in the absence of the need of immunosuppressive therapy to prevent rejection. [33]

An inhaled form of insulin, under development for several years, appears to be ready for wide scale application by the year 2000. Recent studies conducted at the Universities of Miami and Vermont involving Type I and Type II patients demonstrated that inhaled insulin is at least as effective as injected insulin in controlling the symptoms of diabetes and has no side effects. The delivery system, whereby a finely powdered form of insulin is inhaled directly into the lungs, promises to greatly simplify management of both forms of diabetes. Powdered insulin requires no refrigeration and since it is absorbed into the bloodstream though the lungs, there will generally be no need for hypodermic needles. Type I patients will

still require an injection of slow-acting insulin at bedtime12. In the future it may also be possible to administer insulin in the form of a pill or patch. All of these advances will change the face of diabetes, as we know it. [9]

Moreover, it will be seen the application of immune intervention strategies at the time of onset of IDDM, with the reversal of the disease process. Ultimately, these strategies will be applied earlier in the sequence during a stage that we do not yet recognise as clinical diabetes. In these individuals otherwise destined to develop IDDM, the disease will be prevented. [30], [33]

III. DISCUSSION

The prevalence and the risk for complications of diabetes mellitus have been increased by the years and it's expected to be increased more in the future years, unless actions against its prevention are to be taken.

NICE guidelines and recommendations against diabetes mellitus are from the best available nowadays, and they are one important measure against prevention of the disease, and if the disease exists, against prevention of complications associated with diabetes mellitus. In this thesis are described the guidelines that NICE provides for:

- Management of type 1 and type 2 diabetes mellitus after diagnosis, including education, monitoring glycaemic control, management of diabetic ketoacidosis, screening for complications and associated conditions, arterial risk-factor control and psychological support.
- Non-pharmacological treatment of both types with diet and exercise.
- Pharmacological treatment of both types, including the insulin preparations (short-acting, intermediate-acting, long-acting insulin analogues), the insulin regimens, the types of insulin administration, the oral hypoglycemic drugs (metformin, sulphonylureas, acarbose), the newer agents in the market (thiazolidinediones, exenatide, liraglutide, sitagliptin, vidagliptin), and the combinations of these agents.

Following these guidelines can help diabetic patients to control the status of the disease and increase their quality of life.

The problem of diabetes mellitus has been described as the global problem, and more impact was given in the situation of the disease in Cyprus and EU. Some similarities and some differences were observed in the comparisons made between diabetes in Cyprus and EU, diabetes in Cyprus and Czech Republic, and finally diabetes in Cyprus against the global diabetes problem. These had to do with:

- The Incidence/Prevalence of the disease.
- The cost of diabetes care.

- The government priorities.
- The Policy framework.
- The guidelines given for prevention and control of diabetes.
- The reimbursment of insulin and oral hypoglycemic agents.

The prevalence of Diabetes mellitus in Cyprus in 2003 according IDF Atlas for population above 20 years old was estimated to be 5.1% and today has reached 10.3%. It represents approximately the 2.1% of the disease burden in Cyprus and 2.3% of total deaths. Cardiovascular disease which is one of the many serious complications associated with diabetes, represents 17% of the disease burden in Cyprus and is estimated to account for around 41% of deaths in the country.

The incidence for children below 20 years old with type 1 diabetes mellitus in 1990-1994 according a study was estimated to be 10.5/100000 and until 2000 was increased to 11.32/100000.

Cost of diabetes care in Cyprus has reached 5.8% of GDP in 2002 against 2.8% in 1980. The growth rate for the last 5 years is estimated at 2.3%.

The prevalence of Diabetes mellitus in Czech Republic according IDF Atlas in 2003 for population above 20 years old was estimated to be 9.5%. In 2003, type 2 diabetes represented 91.6% of all cases. By the year 2020 prevalence is estimated to increase by 11%. The most frequent complications seen in Czech diabetic patients are retinopathy, nephropathy, and insufficient blood supply in the legs. Women constitute a consistently higher proportion of people living with diabetes by about 10%.

The current average prevalence rate of Diabetes mellitus in EU is estimated to be 7.5% of the total population aged 20 years old and above. Prevalence rates in the new member states lie around 9% and beyond. It is also estimated that 50% of all people with diabetes are undiagnosed. Very important point is that there is an alarming rise in the number of children diagnosed with type 2 diabetes. About 80% of all people living with diabetes die of cardiovascular disease.

According WHO the incidence of diabetes mellitus by the year 2030 will be increased in most of the countries, eg by 43% in Cyprus, by 30% in Germany, by 34% in UK, by 36% in France, by 41% in Netherlands, by 28% in Spain.

The prevalence of diabetes for all age-groups worldwide was estimated to be 2.8% in 2000 and 4.4% in 2030. There are more women with diabetes than men.

It is clear from the results that actions have to be taken immediately for prevention of the disease because diabetes is estimated to be increased by 2 times and in some countries by 3 times, in the next 20 years.

In most of the EU member states, the cost for diabetes care is almost 15% of the total health care budget. This indicates the severity of the disease, and how important is the reimbursement of the specific pharmacotherapy.

What is very interesting is that in Czech Republic and many EU member states, the reimbursement for management and pharmacotherapy of diabetes mellitus, including insulin, pen injectors, strips for blood glucose monitoring, and oral antidiabetic agents, is almost 100%. In Cyprus exists the reimbursement of all these but in a less extent (53%). In Cyprus the diabetic patients have to pay some amount of money for their pharmacotherapy.

Another interesting point is that Czech Republic and some EU member states have developed national plans against diabetes mellitus, while Cyprus and most of the EU countries are still in the process of developing national plans against the disease.

Case studies made in Cypriot diabetic patients were described to show the connection of diabetes mellitus with different complications and what measures must be taken to prevent these complications.

One very interesting point is the diabetic care that Cyprus Diabetic Association (CDA) provides to the Cypriot diabetic patients and especially to the children with diabetes. It includes:

- Care of children with diabetes at hospital and at home.
- Regular annual checks for children with diabetes.
- Emotional support.
- Help through publication of various journals and with support services.

CONCLUSION

The main goal of this diploma thesis was to give the most effective guidelines and recommendations concerning non-pharmacological and pharmacological treatment for both types of diabetes mellitus, and to show the differences and the similarities about situation of diabetes in Cyprus, the EU and generally the world. Among this goal was to show the severity that mainly type 2 diabetes mellitus has taken the recent years with the development of this disease not only in adults but also in children.

Diabetes mellitus as the disease was described according its definition, classification, clinical manifestations, complications diagnosis, non-pharmacological and pharmacological treatment.

Evidence-based guidelines and recommendations were provided from NICE for the management, non-pharmacological and pharmacological treatment of type 1 and type 2 diabetes in children and adults.

More impact was given for type 2 than type 1 diabetes mellitus and type 2 diabetes in children was also described.

The general situation of diabetes mellitus, including its prevalence and incidence, cost of diabetes care, government priorities, policy framework, guidelines and reimbursement, was described for Cyprus, for EU, for Czech Republic and also for the world. Comparisons were made between Cyprus and EU, Cyprus and Czech Republic and finally Cyprus and the rest of the world.

The results show that diabetes has become a leading cause of death in Europe and an increasingly uncontrolled health problem. It carries with it the risk of major cardiovascular complications and is now the commonest cause of hearth attack and stroke, a major cause of peripheral vascular disease and peripheral neuropathy leading to amputation and cause of micro vascular disease in the kidney and the eye. Diabetes is also the commonest cause of renal failure and blindness in Europe.

The European Union has leading role to play in shaping policy and action to encourage member states to provide adequate prevention, diagnosis and control of diabetes. Despite today's unhealthy lifestyles and poor nutritional habits, few appropriate public health measures are currently being taken to address the increasing prevalence and cost burden of diabetes.

The Cyprus Diabetic Association (CDA), in cooperation with the Ministry of Health should focus not only in the pharmacotherapy of diabetes mellitus but it is of great importance, among their national plans to focus on the prevention of the disease and to find ways to inform not only the patients but generally the population about the severity of the disease and the ways to prevent it.

One very important measure is that national plans against the disease should be developed as soon as possible from the government of Cyprus and more diabetic clinics should be built so that the disease would be better tollerated and diabetic patients should have the best possible care to be able to control their disease.

While many current and future European Union Member States, eg. Czech, have established national diabetes plans, the European Union still lacks an overall public health framework that calls for the sharing of best practices and benchmarking of national approaches to the direct benefit of the individual patient. Such a framework could also encourage the creation of minimum standards for diabetes prevention, diagnosis and control, including early screening and appropriate intervention on glycaemic control, hypertension and dyslipidaemia.

New data from the International Diabetes Federation show that more than 230 million people, almost 6% of the world's adult population, now live with diabetes. Previous figures underestimated the diabetes threat and the total is expected to rise.

The number of people living with diabetes is expected to grow to 350 million in less than 20 years if action is not taken. Diabetes is increasing faster in the world's developing economies than in developed countries. Seven out of ten countries with the highest number of people living with diabetes are in the developing world. IDF predicts that by 2025 almost 80% of all diabetes cases will be in low- and middle-income countries. If nothing is done, diabetes will place severe economic, social and health burdens on the countries that can least afford it. The disease threatens to subvert the gains of economic advancement.

Diabetes is emerging fast as one of the biggest health catastrophes the world has ever seen. The diabetes epidemic will overwhelm healthcare resources everywhere if governments do not wake up and take action now.

Despite its alarming human toll, claiming as many lives as HIV/AIDS, there is an extraordinary lack of awareness of the global scale of the diabetes threat. The 'Unite for Diabetes' campaign aims to gain support from governments for a United Nations Resolution on diabetes in order to raise awareness of the disease and improve diabetes care globally.

Diabetes is one of the major causes of premature death worldwide. Every 10 seconds a person dies from diabetes-related causes. The death rates are predicted to rise by 25% over the next decade. According to the World Health Organization, the disease could reduce life expectancy globally for the first time in 200 years.

Despite these alarming figures, little political effort has been made. The international community needs to start taking the threat seriously. Diabetes can be effectively managed, its impact reduced and its onset in many cases prevented completely. Some 80% of type 2 diabetes is preventable by improving the living environment. This includes dietary changes and increased physical activity. Type 1 diabetes (insulin dependent) however is not preventable. It predominantly affects youth and is rising alarmingly worldwide at a rate of 3% per year.

Reversing the current trend is not just a health issue. It will require a whole-of-government approach and the attention of the international community. A United Nations Resolution on diabetes will recognise the global burden of diabetes and focus world attention on the need for immediate action. IDF hopes that a UN Resolution on diabetes will prompt decision-makers to take preventive actions against the growing health challenge.

There is now extensive evidence on the optimal management of diabetes, offering the opportunity of improving the immediate and long-term quality of life of those with the condition. Unfortunately such optimal management is not reaching many, perhaps the majority, of the people who could benefit. Reasons include the size and complexity of the evidence-base, and the complexity of diabetes care itself. One result is a lack of proven cost-effective resources for diabetes care. Another result is diversity of standards of clinical practice.

Guidelines are one part of a process that seeks to address those problems. Many guidelines have appeared internationally, nationally, and more locally in recent years, but most of these have not used the rigorous new guideline methodologies for identification and analysis of the evidence.

A global guideline presents a unique challenge. Many national guidelines address one group of people with diabetes in the context of one health-care system, with one level of national and health-care resources. This is not true in the global context where, although every health-care system seems to be short of resources, and the funding and expertise available for health-care vary widely between countries and even between localities.

Published national guidelines come from relatively resource-rich countries, and may be of limited practical use in less well resourced countries.

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APPENDIX I

TABLES AND FIGURES

APPENDIX II (TABLES)

Table 1. Prevalence of diabetes in the WHO African region

Country	2000	2030
Algeria	426,000	1,203,000
Angola	51,000	140,000
Benin	87,000	266,000
Botswana	25,000	45,000
Burkina Faso	124,000	388,000
Burundi	26,000	72,000
Cameroon	70,000	171,000
Cape Verde	7,000	24,000
Central African Republic	18,000	38,000
Chad	97,000	269,000
Comoros	4,000	15,000
Congo	14,000	39,000
Côte d'Ivoire	264,000	636,000
Democratic Republic of the Congo	291,000	910,000
Equatorial Guinea	8,000	21,000
Eritrea	47,000	142,000
Ethiopia	796,000	1,820,000

Gabon	8,000	14,000
Gambia	22,000	61,000
Ghana	302,000	851,000
Guinea	34,000	89,000
Guinea-Bissau	17,000	44,000
Kenya	183,000	498,000
Lesotho	31,000	42,000
Liberia	40,000	154,000
Madagascar	100,000	301,000
Malawi	55,000	118,000
Mali	140,000	405,000
Mauritania	34,000	103,000
Mauritius	111,000	233,000
Mozambique	133,000	273,000
Namibia	25,000	60,000
Niger	108,000	382,000
Nigeria	1,707,000	4,835,000
Rwanda	30,000	77,000
Sao Tome-Principe	1,000	2,000
Senegal	143,000	421,000
Seychelles	8,000	19,000
Sierra Leone	65,000	178,000

South Africa	814,000	1,286,000
Swaziland	13,000	21,000
Togo	64,000	184,000
Uganda	98,000	328,000
United Republic of Tanzania	201,000	605,000
Zambia	70,000	186,000
Zimbabwe	108,000	265,000
Total	7,020,000	18,234,000

Resource: http://www.who.int/diabetes/facts/world_figures/en/index.html.

- In Nigeria prevalence is estimated to be increased by 65%
- In South Africa prevalence is estimated to be increased by 47%

Table 2. Prevalence of diabetes in the WHO region of the Americas

Country	2000	2030
Antigua and Barbuda	3,000	5,000
Argentina	1,426,000	2,457,000
Bahamas	12,000	26,000
Barbados	11,000	22,000
Belize	5,000	15,000
Bolivia	207,000	562,000
Brazil	4,553,000	11,305,000
Canada	2,006,000	3,543,000
Chile	495,000	1,047,000
Colombia	883,000	2,425,000
Costa Rica	76,000	237,000
Cuba	480,000	855,000
Dominica	3,000	4,000
Dominican Republic	245,000	594,000
Ecuador	341,000	921,000
El Salvador	103,000	320,000
Grenada	4,000	7,000
Guatemala	139,000	447,000
Guyana	19,000	36,000
Haiti	161,000	401,000

Honduras	81,000	269,000
Jamaica	81,000	189,000
Mexico	2,179,000	6,130,000
Nicaragua	68,000	246,000
Panama	59,000	155,000
Paraguay	102,000	324,000
Peru	754,000	1,961,000
Saint Kitts and Nevis	2,000	2,000
Saint Lucia	5,000	11,000
Saint Vincent and the Grenadines	5,000	9,000
Suriname	9,000	20,000
Trinidad and Tobago	60,000	125,000
United States of America	17,702,000	30,312,000
Uruguay	154,000	224,000
Venezuela	583,000	1,606,000
Total	33,016,000	66,812,000

Resource: http://www.who.int/diabetes/facts/world_figures/en/index.html.

- In Mexico prevalence is estimated to be increased by 65%
- In Canada prevalence is estimated to be increased by 43%

- In USA prevalence is estimated to be increased by 41%

Table 3. Prevalence of diabetes in the WHO South-East Asia region

Country	2000	2030
Bangladesh	3,196,000	11,140,000
Bhutan	35,000	109,000
Dem. People's Rep. of Korea	367,000	635,000
India	31,705,000	79,441,000
Indonesia	8,426,000	21,257,000
Maldives	6,000	25,000
Myanmar	543,000	1,330,000
Nepal	436,000	1,328,000
Sri Lanka	653,000	1,537,000
Thailand	1,536,000	2,739,000
Total	46,903,000	119,541,000

Resource: http://www.who.int/diabetes/facts/world_figures/en/index.html.

- In India prevalence is estimated to be increased by 60%

Table 4. Prevalence of diabetes in the WHO Western Pacific region

Country	2000	2030
Australia	941,000	1,673,000
Brunei Darussalam	18,000	49,000
Cambodia	110,000	317,000
China	20,757,000	42,321,000
Cook Islands	700	1,300
Fiji	37,000	72,000
Japan	6,765,000	8,914,000
Kiribati	4,000	7,000
Lao People's Dem. Rep.	46,000	128,000
Malaysia	942,000	2,479,000
Marshall Islands	2,000	4,000
Federated States of Micronesia	5,000	13,000
Mongolia	34,000	81,000
Nauru	2,000	4,000
New Zealand	179,000	307,000
Niue	<100	<100
Palau	1,000	2,000
Papua New Guinea	152,000	392,000
Philippines	2,770,000	7,798,000
Republic of Korea	1,859,000	3,378,000

Samoa	4,000	7,000
Singapore	328,000	695,000
Solomon Islands	13,000	41,000
Tonga	3,000	6,000
Tuvalu	300	800
Vanuatu	6,000	17,000
Viet Nam	792,000	2,343,000
Total	35,771,000	71,050,100

Resource: http://www.who.int/diabetes/facts/world_figures/en/index.html.

- In China prevalence is estimated to be increased by 51%
- In Australia prevalence is estimated to be increased by 44%

ABBREVIATIONS

ACE	Angiotensin Converting Enzyme
ADA	American Diabetes Association
BMI	Body Mass Index
CDA	Cyprus Diabetic Association
CDC	Centres for Disease Control and Prevention
CVD	Cardiovascular disease
EASD	European Association for Study of Diabetes
ECG	Electrocardiogram
FDA	Food and Drug Administration
GDP	Gross Domestic Product
GFR	Glomerular Filtration Rate
GI	Gastrointestinal
GP	General Practitioner
HbA1c	glycosylated hemoglobin
HCF	High Carbohydrate high plant-fibre
HDL	High Density Lipoprotein
IDDM	Insulin Dependent Diabetes mellitus
IDF	International Diabetes Federation

IFG	Impaired Fasting Glucose
IGT	Impaired Glucose Tolerance
IPAQ	International Physical Activity Questionnaire
IV	Intravenous
LDL	Low Density Lipoprotein
NCHS	National Centre for Health Statistics
NDP	National Diabetes Programme
NDRs	National Diabetes Registers
NHANES	National Health and Nutrition Examination Survey
NHIS	National Health Interview Survey
NICE	National Institute for Health and Clinical Excellence
NIDDM	Non-insulin Dependent Diabetes Mellitus
NPH	Isophane insulin
OGTT	Oral Glucose Tolerance Test
SIGN	Scottish Intercollegiate Guidelines Network
TID	Three times per day
VLDL	Very Low Density Lipoprotein
WHO	World Health Organization

ABSTRACT

My topic was about diabetes mellitus in Cyprus in relation with the world. For my diploma work I used literature searches in electronic form from different databases and also books, journals, and published articles.

My diploma thesis was divided into two main parts, the theoretical part and the results.

In the theoretical part diabetes mellitus was described according its definition, classification, clinical manifestations, complications, diagnosis, non-pharmacological and pharmacological treatment.

In the results first were described evidence-based guidelines and recommendations from NICE for the management, non-pharmacological and pharmacological treatment for type 1 and type 2 diabetes mellitus in children and adults.

Then the general situation of diabetes was described for Cyprus, EU, Czech Republic and the world, according the incidence/prevalence of diabetes, cost of diabetes care, government priorities, policy framework, guidelines and reimbursement.

From the results it's obvious that the burden of diabetes is constantly increasing and immediate measures must be taken to prevent further increase. Also it exists the problem with reimbursement for the therapy of diabetes in many countries, including Cyprus.

Cyprus Diabetic Association (CDA) provides great help for the patients with diabetes, especially children, and their families. Among activities of CDA are the Diabetes care, child's annual review, emotional support, help provided from several magazines that CDA is publishing.

Most of EU member states have developed national plans against diabetes, eg. Czech Republic, but EU has still leading role to play in shaping policy and action to encourage member states to provide adequate prevention, diagnosis and control of diabetes.