Pharmacoepidemiological study and costs analysis of oral antidiabetic drugs and insulins in Lithuania on 2006-2009 year

MASTER WORK

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ABBREVIATIONS

AACE  American Association of Clinical Endocrinologists;
ADA  American Diabetes Association
ATC  Anatomical Therapeutic Chemical classification
BG  Blood Glucose
CI  Confidence Interval;
DDD  Defined Daily Dose
DDD/TID  Defined Daily Dose per 1000 Inhabitants per Day
DM  Diabetes Mellitus
FPG  Fasting Plasma Glucose
GDM  Gestational Diabetes Mellitus;
HbA1c  Hemoglobin A1c;
HDL-C  High-Density Lipoprotein Cholesterol;
IDF  International Diabetes Federation
IGT  Impaired Glucose Tolerance
LDL-C  Low-Density Lipoprotein Cholesterol;
LOE  Level-of-Evidence;
NPH  Neutral Protamine Hagedorn;
OGTT  Oral Glucose Tolerant Test
T1DM  Type 1 Diabetes Mellitus;
T2DM  Type 2 Diabetes Mellitus;
WHO  World Health Organization
1. INTRODUCTION

Diabetes is now one of the most common non-communicable diseases globally. It is the fourth or fifth leading cause of death in most developed countries and there is substantial evidence that it is epidemic in many developing and newly industrialized nations. Complications from diabetes, such as coronary artery and peripheral vascular disease, stroke, diabetic neuropathy, amputations, renal failure and blindness are resulting in increasing disability, reduced life expectancy and enormous health costs for virtually every society. Diabetes is certain to be one of the most challenging health problems in the 21st century [1].

What has changed and what is driving the diabetes epidemic? The answers are complex. Some reflect factors we cannot change (genetic, ethnic differences, ageing) while others are clearly environmental and involve changes in diet, decreased physical activity, increases in overweight and obesity as well as profound changes in our living environment which include changes in work practices, globalization, urbanization, town planning, transport, schooling, sport, and the development of mega-cities [1].

Thus the world is facing a growing diabetes epidemic of potentially devastating proportions. Diabetes is a major threat to global public health that is rapidly getting worse, and the biggest impact is on adults of working age in developing countries [2]. It means that people loose capacity for work thereby they lose incomes.

According to the official statistic data of diabetes mellitus morbidity in Lithuania in 2008 it is estimated that 1.1 children (0-17 years)/1000 inhabitants and 25.1 adult/1000 inhabitants suffer from diabetes. In comparison with statistic data in 2004, where 0.8 children (0-17 years)/1000 inhabitants and 19.7 adult/1000 inhabitants suffer from this disease, these figures defines a rapid increasing of prevalence of diabetes in Lithuania [3].

Moreover it is now becoming recognized that diabetes in children is becoming a global public health issue with potentially serious health outcomes. The risk of type 2 diabetes is clearly linked to an increasing prevalence of obesity. This in turn is associated with changing dietary and lifestyle patterns. In particular an increase in fatty foods as well as a reduction in activity levels both at home and in the school [4].

Diabetes is associated with an increased risk for a number of serious, sometimes life-threatening complications and certain populations experience an even greater threat. Good diabetes control can help reduce the risk, however many people are not even aware that they have diabetes until they develop one of its complications [5]. It is estimated that diabetes with multiple complications and premature mortality, accounting for at least 10% of total health care expenditure in many countries [6]. Diabetes costs hundreds of billions of dollars to treat each year. World
treatment costs are growing more quickly than world population. Global health expenditures to treat and prevent diabetes and its complications total at least USD 376 billion in 2010, it is interesting to reflect that there were USD 232 billion in 2007. Also it is estimated that this figure will exceed [1].

Diabetes is a life-threatening condition [7]. Global excess mortality attributable to diabetes in adults 20-79 years old in the year 2010 is estimated at 3.9 million deaths (1.8 million men and 2.1 million women). Since most deaths attributable to diabetes occur in persons 20-79 years old, these 3.9 million deaths account for more than 6% of total world mortality [1]. It is estimated 3543 deaths attributable to diabetes in adults 20-79 years old in the year 2010 in Lithuania, it accounts for more than 7% of total mortality [1, 8].

In the meanwhile, there already exists a large battery of treatment strategies of proven efficacy in preventing diabetes-related morbidity and mortality. However, the degree of implementation of these treatments is suboptimal and varies widely [9].

Relevance and novelty of this work

The high and rising prevalence of diabetes, its impact on mortality and morbidity, its disproportionate effect on disadvantaged individuals, communities and nations, and its high human and economic costs clearly establish diabetes as a significant global public health problem [9].

Diabetes is certain to be one of the most challenging health problems in the 21st century. The consumption of medications for diabetes mellitus is increasing dramatically, likewise the expenses for them. There are a lot of studies published on that score worldwide. However, to date no studies have been published that define the consumption of antidiabetic drugs in all Lithuanian regions and the expenses for these medications.
2. DIABETES MELLITUS: DISEASE AND MANAGEMENT

2.1. Definition of diabetes

Diabetes mellitus is a metabolic disorder characterized by the presence of hyperglycemia due to defective insulin secretion, defective insulin action or both. The chronic hyperglycemia of diabetes is associated with significant long-term sequelae, particularly damage, dysfunction and failure of various organs – especially the kidneys, eyes, nerves, heart and blood vessels [10].

In type 1 diabetes, it is due to a virtually complete lack of endogenous pancreatic insulin production, whereas in type 2 diabetes, the rising blood glucose results from a combination of genetic predisposition, unhealthy diet, physical inactivity, and increasing weight with a central distribution resulting in complex pathophysiological processes. Traditionally, diagnosis of diabetes was based on symptoms due to hyperglycaemia, but during the last decades much emphasis has been placed on the need to identify diabetes and other forms of glucose abnormalities in asymptomatic subjects. DM is associated with development of specific long-term organ damage (diabetes complications) including retinopathy with potential blindness, nephropathy with a risk of progression to renal failure, neuropathy with risk for foot ulcers, amputation, and Charcot joints and autonomic dysfunction such as sexual impairment. Patients with diabetes are at a particularly high risk for cardiovascular, cerebrovascular, and peripheral artery disease [11].

2.2. Epidemiology

The number of studies describing the epidemiology of diabetes over the last 30 years has been done. In 2004, there were published the study “Global prevalence of diabetes: estimates for the year 2000 and projections for 2030”. According to this study, 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 was projected to rise from 171 million in 2000 to 366 million in 2030 [4].

Though diabetes is a common condition and its frequency is dramatically rising all over the world. In the end of 2009 year, there were published new study about global prevalence of diabetes [12]. There were shown estimations for 2010 and projections for 2030. According to this study and International Diabetes Federation Diabetes Atlas statistic data basis [1], it is estimated that the world prevalence of diabetes among adults (aged 20–79 years) will be 6.4%, affecting 285 million adults, in 2010, and will increase to 7.7%, and 439 million adults by 2030 [1]. Between
2010 and 2030, there will be a 69% increase in numbers of adults with diabetes in developing countries and a 20% increase in developed countries.

These projections of the number of people with diabetes in 2030 take into account the fact that there will be more people in the world (population growth) and that there will be more elderly people (population ageing). They also take into account trends in urbanization - the fact that people are moving from rural areas to cities, particularly in developing countries. This affects the number of people who are likely to have diabetes, because people living in cities in developing countries tend to be less physically active and have higher levels of overweight and obesity than people in rural areas [2].

There are known regional estimates for diabetes (20-79 age group), in the year of 2010 (Table 1) [1]. The highest comparative prevalence of diabetes is 10.2% in North America and Caribbeans (NAC), and 9.3% in Middle East and North Africa (MENA). The lowest comparative prevalence of diabetes is 3.8% in Africa (AFR) and 4.7% in Western Pacific (WP). In Europe (EUR) comparative prevalence of diabetes is 6.9%, this is not so far from an average- 6.4%, but the regional prevalence is much higher- 8.6%.

Table 1. Regional estimates for diabetes (20-79 age group), 2010 Regions: Europe (EUR), Africa (AFR); Middle East and North Africa (MENA); North America and Caribbeans (NAC); South and Central America (SACA); South-East Asia (SEA); Western Pacific (WP). Regional prevalence is based on regional population; comparative prevalence is based on total population in the world

<table>
<thead>
<tr>
<th>EUR</th>
<th>AFR</th>
<th>MENA</th>
<th>NAC</th>
<th>SACA</th>
<th>SEA</th>
<th>WP</th>
<th>World</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total population (millions)</td>
<td>891</td>
<td>825</td>
<td>617</td>
<td>477</td>
<td>465</td>
<td>1439</td>
<td>2237</td>
</tr>
<tr>
<td>Adult population (20-79 years, millions)</td>
<td>646</td>
<td>379</td>
<td>344</td>
<td>320</td>
<td>287</td>
<td>838</td>
<td>1531</td>
</tr>
</tbody>
</table>

Prevalence of diabetes

| Regional prevalence (%) | 8.6 | 3.2 | 7.7 | 11.7 | 6.3 | 7 | 5 | 6.55 |
| Comparative prevalence (%) | 6.9 | 3.8 | 9.3 | 10.2 | 6.6 | 7.6 | 4.7 | 6.4 |
| Number of people with diabetes (millions) | 55.4 | 12.1 | 26.6 | 37.4 | 18 | 58.7 | 76.7 | 284.9 |

Diabetes mortality (20-79 years)

| Number of deaths, male (thousands) | 297.6 | 122.2 | 117 | 141 | 83.5 | 476.9 | 588.3 | 1826.5 |
| Number of deaths, female (thousands) | 336.5 | 210.4 | 177 | 172.2 | 87.8 | 666 | 486.7 | 2136.6 |
| Total | 634.1 | 332.6 | 294 | 313.2 | 171.3 | 1142.9 | 1075 | 3963.1 |

Health expenditure for diabetes (USD)

| Total health expenditure, R=2, (billions) | 105.5 | 1.4 | 5.6 | 214.2 | 8.1 | 3.1 | 38.2 | 376.1 |

It is estimated, that in developing countries three-quarters of all people with diabetes are under 65 years old and 25% of all adults with diabetes are younger than 44. In developed countries,
more than half of all people with diabetes are older than 65, and only 8% of adults with diabetes are younger than 44 [2]. It leads to the fact that in developed countries most people with diabetes are above the age of retirement, whereas in developing countries those most frequently affected are aged between 35 and 64 [2].

Diabetes is classified into types. Type 1 diabetes usually accounts for only a minority of the total burden of diabetes in a population; it is the predominant form of the disease in younger age groups in most developed countries. Type 1 diabetes is increasing in incidence in both developing and developed countries [1]. Type 2 diabetes constitutes about 85 to 95% of all diabetes in developed countries, and accounts for an even higher percentage in developing countries [2].

USA

There are 23.6 million people in the United States, or 8% of the population, who have diabetes. The total prevalence of diabetes increased 13.5% from 2005-2007. While an estimated 17.9 million have been diagnosed, unfortunately, 5.7 million people are not aware that they have the disease. 57 million people have pre-diabetes. 1.6 million new cases of diabetes were diagnosed in people aged 20 years or older in 2007 [5].

Among adults with diagnosed diabetes, 14% take insulin only, 13% take both insulin and oral medication, 57% take oral medication only, and 16% do not take either insulin or oral medications [5].

European region

There exists a great diversity of populations and affluence among the 54 countries and territories in the European Region, with gross domestic product (GDP) varying from over US$60,000 per capita for Luxembourg to less than US$2,000 for several of the former socialist republics [13].

The same big diversity reflects on prevalence of diabetes. The number of people with diabetes in European region was estimated to reach 55.4 million, or 8.6% of the adult population in 2010. National prevalence rates for diabetes show a wide variation from 2.1% in Iceland to 12.4% in Portugal (Figure 1).

According to Diabetes Atlas, in Europe the highest regional prevalence rate is 12.4% in Portugal. Above 10% is in Germany(12%), Switzerland (11.3%), Austria (11.2), Liechtenstein (11%) and Cyprus(10.4%). The lowest ones are 2.1% in Iceland, 3.6% in Tajikistan and 4% in Uzbekistan. There are similar prevalence rate in Baltic States (Estonia, Latvia, Lithuania).

Moreover, it is disappointing that the morbidity of diabetes in Lithuania is one of the highest rates in Europe, as only ten countries (out of 54) had higher values. Despite the high
prevalence of diabetes in Lithuania, it is lower than in other Baltic States. There are 239,800 people, who suffer from diabetes in Lithuania, it tally with 9.7% of all population.

![Figure 1. Regional prevalence of diabetes mellitus in some European countries](image)

2.3. **Burden of the disease**

Diabetes costs hundreds of billions of dollars to treat each year. World treatment costs are growing more quickly than world population. However, the larger costs of diabetes arise from disability and loss of life caused by its preventable complications, including heart, kidney, eye and foot disease [1].

More than 80% of expenditures for medical care for diabetes are made in the world’s economically richest countries, not in the low- and middle-income countries where 80% of persons with diabetes will soon live. In the world’s poorest countries, not enough is spent to provide even the least expensive lifesaving diabetes drugs [1].

In industrialized countries, about a quarter of the medical expenditures for diabetes is spent for the control of elevated blood sugar. Another quarter goes to treat long-term complications (largely cardiovascular disease), and half is consumed by the additional general medical care that accompanies diabetes and diabetic complications, including intensified efforts to prevent cardiovascular and microvascular complications [14].

In middle-income countries, a higher proportion of expenditures — half — goes for blood sugar control, which is essential for the prevention of acute life-threatening hyperglycaemia. The remainder is split between general medical care and chronic complications [15]. Most persons in
these countries do not receive a great deal of medical care once complications appear, and many may not survive acute hyperglycaemic crises to develop longer term sequellae [1].

Diabetes affects all persons living in society, not just those who live with diabetes. Many studies have tried to measure this larger societal impact by adding a category of effects called indirect costs. The ADA estimated that the US economy lost USD 39.8 billion or USD 3,290 per person with diabetes in 2002, as a result of lost earnings due to lost work days, restricted activity days, mortality and permanent disability caused by diabetes [16]. Indirect costs of diabetes in Germany have been estimated at EUR 1,328 per person for the year 2001 [17].

Three-quarters of global expenditures for the care of diabetes are used for persons who are between 50 and 80 years of age. This is because the prevalence of diabetes is much higher in older age groups, and because persons who have lived with diabetes for many years have higher rates of complications, which are expensive to treat. Also, the countries that spend the most per capita for diabetes have older populations [1].

Diabetes is one of the world’s most important causes of expenditure, mortality, disability and lost economic growth. Global health expenditures to treat and prevent diabetes and its complications total at least USD 376 billion in 2010. To mention the fact that there were USD 232 billion in 2007. By 2030, this number is projected to exceed some USD 490 billion.

North America and Caribbeans (NAC) is estimated to spend more than half of this amount (USD 214.4 billion, or 57%). The European Region (EUR) – USD 105.5 billion, or 28% and Western Pacific Region (WP), which includes Australia, China, Japan and Korea – USD 38.2 billion, or 10% of global spending [1].

Countries vary widely in the resources they spend on diabetes per person. In 2010, according to the IDF formula, it is estimated that the US spent an average of USD 7,383 for diabetes for each person who had the condition, Norway spent USD 6,933 and Switzerland spent USD 5,995. However, spending at this level is uncommon. Globally, the mean of each country’s average 2007 expenditure was USD505 (there are no estimations for the year 2010) [1].

There exits a great variety of health expenditure per person with diabetes in European region (Figure 2). The highest level of expense is USD 7,268 in Luxembourg, USD 7,001 in Iceland and USD 6,933 in Norway. It is quite a lot spent in Denmark, Ireland, France, Sweden. There are a sharp leap between Western European countries and Baltic States. Estonia (USD 584), Latvia (USD 493) and Lithuania (USD 521) barely reach an average of expenditure for diabetes (USD505). But in Montenegro or Tajikistan is even much worse. Montenegro is estimated to spent USD 14 and Tajikistan – USD 31 per person with diabetes.
Assigning a type of diabetes to an individual often depends on the circumstances present at the time of diagnosis, and many diabetic individuals do not easily fit into a single class. For example, a person with gestational diabetes mellitus (GDM) may continue to be hyperglycemic after delivery and may be determined to have, in fact, type 2 diabetes. Thus, for the clinician and patient, it is less important to label the particular type of diabetes than it is to understand the pathogenesis of the hyperglycemia and to treat it effectively [18].

Classification of diabetes includes both aetiological types and different clinical stages of hyperglycaemia as suggested by Kuzuya and Matsuda. Four main aetiological categories of diabetes have been identified as diabetes type 1, type 2, other specific types, and gestational diabetes [11].

**Aetiological classification**

**Type 1 diabetes mellitus**

This form includes cases due to an autoimmune process (immune-mediated diabetes) and those for which the etiology of beta cell destruction is unknown (idiopathic diabetes) [18].

Figure 2. Health expenditure per person with diabetes in European region in 2010 (USD)

2.4. Diabetes mellitus: classification, diagnostic criteria, prognosis and complications
Immune-mediated diabetes. Typically, this form of diabetes occurs in young subjects with acute-onset with typical symptoms of diabetes together with weight loss and propensity to ketosis, but type 1 diabetes may occur at any age, sometimes with slow progression [11]. It accounts for only 5–10% of those with diabetes, previously encompassed by the terms insulin-dependent diabetes, type I diabetes, or juvenile-onset diabetes, results from a cellular-mediated autoimmune destruction of the β-cells of the pancreas. Markers of the immune destruction of the β-cell include islet cell autoantibodies, autoantibodies to insulin, autoantibodies to glutamic acid decarboxylase (GAD65), and autoantibodies to the tyrosine phosphatases IA-2 and IA-2α. One and usually more of these autoantibodies are present in 85–90% of individuals when fasting hyperglycemia is initially detected. Also, the disease has strong HLA associations, with linkage to the DQA and DQB genes, and it is influenced by the DRB genes. These HLA-DR/DQ alleles can be either predisposing or protective [18].

In this form of diabetes, the rate of β-cell destruction is quite variable, being rapid in some individuals (mainly infants and children) and slow in others (mainly adults). Some patients, particularly children and adolescents, may present with ketoacidosis as the first manifestation of the disease. Others have modest fasting hyperglycemia that can rapidly change to severe hyperglycemia and/or ketoacidosis in the presence of infection or other stress. Still others, particularly adults, may retain residual β-cell function sufficient to prevent ketoacidosis for many years; such individuals eventually become dependent on insulin for survival and are at risk for ketoacidosis [18].

Autoimmune destruction of β-cells has multiple genetic predispositions and is also related to environmental factors that are still poorly defined. These patients are also prone to other autoimmune disorders such as Graves’ disease, Hashimoto’s thyroiditis, Addison’s disease, vitiligo, celiac sprue, autoimmune hepatitis, myasthenia gravis, and pernicious anemia [18].

Idiopathic diabetes. Some forms of type 1 diabetes have no known etiologies. Some of these patients have permanent insulinopenia and are prone to ketoacidosis, but have no evidence of autoimmunity. Although only a minority of patients with type 1 diabetes fall into this category. Individuals with this form of diabetes suffer from episodic ketoacidosis and exhibit varying degrees of insulin deficiency between episodes. This form of diabetes is strongly inherited, lacks immunological evidence for β-cell autoimmunity, and is not HLA associated. An absolute requirement for insulin replacement therapy in affected patients may come and go [18].

Type 2 diabetes mellitus

This form of diabetes, which accounts for 90–95% of those with diabetes, previously referred to as non-insulindependent diabetes, type II diabetes, or adult-onset diabetes, encompasses
individuals who have insulin resistance and usually have relative (rather than absolute) insulin deficiency [18].

It is caused by a combination of complex metabolic disorders that result from coexisting defects of multiple organ sites such as insulin resistance in muscle and adipose tissue, a progressive decline in pancreatic insulin secretion, unrestrained hepatic glucose production, and other hormonal deficiencies. Before the appearance of clinical symptoms, a degree of hyperglycemia may be present, causing pathologic and functional changes in various target tissues [19].

Typically, the early stage of type 2 diabetes is characterized by insulin resistance and decreased ability for insulin secretion causing excessive post-prandial hyperglycaemia. This is followed by a gradually deteriorating first-phase insulin response to increased blood glucose concentrations. Type 2 diabetes, comprising over 90% of adults with diabetes, typically develops after middle age. The patients are often obese or have been obese in the past and have typically been physically inactive. Ketoacidosis is uncommon, but may occur in the presence of severe infection or severe stress [11].

At least initially, and often throughout their lifetime, these individuals do not need insulin treatment to survive. There are probably many different causes of this form of diabetes. Although the specific etiologies are not known, autoimmune destruction of β-cells does not occur, and patients do not have any of the other causes of diabetes listed above or below. Most patients with this form of diabetes are obese, and obesity itself causes some degree of insulin resistance. Patients who are not obese by traditional weight criteria may have an increased percentage of body fat distributed predominantly in the abdominal region. Ketoacidosis seldom occurs spontaneously in this type of diabetes; when seen, it usually arises in association with the stress of another illness such as infection.

This form of diabetes frequently goes undiagnosed for many years because the hyperglycemia develops gradually and at earlier stages is often not severe enough for the patient to notice any of the classic symptoms of diabetes. Nevertheless, such patients are at increased risk of developing macrovascular and microvascular complications.

Whereas patients with this form of diabetes may have insulin levels that appear normal or elevated, the higher blood glucose levels in these diabetic patients would be expected to result in even higher insulin values had their cell function been normal. Thus, insulin secretion is defective in these patients and insufficient to compensate for insulin resistance. Insulin resistance may improve with weight reduction and/or pharmacological treatment of hyperglycemia but is seldom restored to normal. The risk of developing this form of diabetes increases with age, obesity, and lack of physical activity. It occurs more frequently in women with prior GDM and in individuals with hypertension or dyslipidemia, and its frequency varies in different racial/ethnic subgroups. It
is often associated with a strong genetic predisposition, more so than is the autoimmune form of type 1 diabetes. However, the genetics of this form of diabetes are complex and not clearly defined [18].

**Gestational diabetes mellitus**

It constitutes any glucose perturbation that develops during pregnancy and disappears after delivery [11]. Long-term follow-up studies, recently reviewed by Kim et al., reveal that most, but not all, women with gestational diabetes do progress to diabetes after pregnancy. Long-term studies that have been conducted over a period of more than 10 years reveal a stable long-term risk of — 70% [20]. In some cases, type 1 diabetes may be detected during pregnancy.

**Other specific types**

Other specific types include a wide variety of relatively uncommon conditions, primarily specific genetically defined forms of diabetes or diabetes associated with other diseases or drug use [10].

**Clinical classification**

The clinical classification also comprises different stages of hyperglycaemia, reflecting the natural history of absolute or relative insulin deficiency progressing from normoglycaemia to diabetes. It is not uncommon that a non-diabetic individual may move from one category to another in either direction. Usually, a progression towards a more severe glucose abnormality takes place with increasing age. This is reflected by the increase in the 2-hPG level with age. The currently valid clinical classification criteria have been issued by WHO and ADA. The WHO recommendations for glucometabolic classification are based on measuring both fasting and 2-hPG concentrations and recommend that a standardized 75 g OGTT should be performed in the absence of overt hyperglycaemia [11].

**Diagnostic criteria**

The diagnostic criteria for diabetes and the plasma glucose thresholds for other diagnostic categories are summarized in Table 2.
Table 2. Diagnosis of diabetes mellitus

<table>
<thead>
<tr>
<th>FPG ≥7.0 mmol/L (126 mg/dl)</th>
<th>Casual PG≥11.1 mmol/L (200 mg/dl) + symptoms of diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting = no caloric intake for at least 8 hours</td>
<td>Casual = any time of the day, without regard to the interval since the last meal</td>
</tr>
<tr>
<td>Or</td>
<td>Classic symptoms of diabetes = polyuria, polydipsia and unexplained weight loss</td>
</tr>
<tr>
<td>Or</td>
<td>2hPG in a 75-g OGTT≥11.1 mmol/L (200 mg/dl)</td>
</tr>
</tbody>
</table>

A confirmatory laboratory glucose test (an FPG, a casual PG or a 2hPG in a 75-g OGTT) must be done in all cases on another day in the absence of unequivocal hyperglycemia accompanied by acute metabolic decompensation. However, in individuals in whom type 1 diabetes is a possibility (younger individuals and lean, older individuals), to avoid rapid deterioration, confirmatory testing should not delay initiation of treatment.

Recent estimates suggest that 195 million people throughout the world have diabetes and that this number will increase to 330, maybe even to 500 million, by 2030 [21]. Many patients, up to 50% in most investigations, with type 2 diabetes are undiagnosed since they remain asymptomatic and therefore are undetected for many years. Detecting people with undiagnosed type 2 diabetes is important because early detection of diabetes can improve prevention of cardiovascular complications. In addition, there is an increasing interest in identifying people with impaired glucose tolerance (IGT), who might benefit from lifestyle or pharmacological intervention to reduce or delay the progression to diabetes [22].

**Prognosis and complications of diabetes mellitus**

It is serious identify diabetes mellitus as early as it is possible. Early detection and treatment can bring successful results. If patients execute prescriptions, take care of themselves carefully, they can improve their health also avoid a lot of complications.

Patients often develop T2DM 9 to 12 years before the disease is diagnosed. Findings from the United Kingdom Prospective Diabetes Study (UKPDS) show that affected individuals have already lost 50% of β-cell function at the time T2DM is diagnosed [19].

Diabetes increases the prevalence of coronary artery disease (CAD) approximately 2- to 3-fold compared to individuals without diabetes [23]. Coronary and cerebrovascular events are responsible for >75% of the deaths in people with diabetes, and are 40 times more likely to occur than the serious consequences of microvascular disease such as end-stage renal failure [24]. When a
person with diabetes has an acute coronary event, the short- and long-term outcomes are considerably worse than for the person without diabetes [25].

Classical risk factors for CAD, such as smoking, hypertension and hyperlipidemia (elevated low-density lipoprotein cholesterol [LDL-C] and low high-density lipoprotein cholesterol), add to the risk conferred by diabetes alone. Diabetes-related risk factors such as duration of diabetes >15 years and hyperglycemia (as determined by glycated hemoglobin A1C levels), as well as the presence of microvascular disease (micro- or macroalbuminuria, impaired renal function or retinopathy) and features of metabolic syndrome, add to the risk of premature CAD events [10].

Type 1 diabetes is an independent risk factor for premature CVD and mortality in young adults (20 to 39 years). The presence of CAD in people with type 1 diabetes is related to age, duration of diabetes, presence of retinopathy, higher A1C levels and higher albumin excretion rates, as well as to traditional CAD risk factors such as elevated total cholesterol and LDL-C cholesterol, smoking and excess body weight [26].

Thus, it is very important for patients to achieve glycemic levels as near normal as possible to avoid any disorders, microvascular and macrovascular complications, such as coronary artery disease, dyslipidemia, hypertension, heart failure, chronic kidney disease, diabetic retinopathy and neuropathy, foot ulceration, erectile dysfunction.

2.5. Treatment of diabetes mellitus

The therapeutic cornerstones to treat T1DM and T2DM are proper nutrition, exercise, education, and appropriate pharmacologic therapy [27]. Early and aggressive management of glycemia by addressing mean glucose levels and glucose level variability, is vital to preventing or delaying the development of diabetic complications [28]. Therapy should be tailored to the individual to maximize the likelihood of attaining and maintaining appropriate glycemic goals and to reduce the frequency of adverse effects [27].

2.5.1. Non-medicinal treatment

Nutrition

Healthy eating is a critical component in the management of type 1 and type 2 diabetes. In over 50% of people presenting with type 2 diabetes restriction of energy intake, increased activity and weight reduction will initially normalise blood glucose levels. Medication is likely to be needed later [29].

In people with type 2 diabetes increased activity and elimination of concentrated sources of energy with substitution with high fibre, carbohydrate foods will often bring the condition under
control. Unless the patient is very symptomatic, a trial of at least 6 to 8 weeks of lifestyle modification is wise before oral hypoglycaemic agents are considered [29].

Loss of body weight will often result in near normal glycaemic, blood pressure and lipid profiles. Many studies suggest that a weight loss of 5 to 20% will improve glycaemic control. Therefore it is important to encourage any degree of weight loss.

Carbohydrate foods which are rich in fibre and have a low energy density are the basis of the eating plan and it is recommended that they contribute up to 50% of the total energy intake. It is recommended that people with diabetes have one high fibre, low glycaemic index carbohydrate food at each meal. This would include wholegrain breads, rolled oats, low fat, low sugar breakfast cereals, pasta, beans, lentils and temperate fruits.

It is recommended that fat contribute to less than 30% of total energy intake. This has a beneficial effect on serum lipids and helps with weight reduction. Also it is important to reduce alcohol intake. It is recommended ≤2 standard drinks (20g) per day for men and women.

It is recommended that protein contribute 10–20% of total energy. Selection of type of protein depends on patient preferences taking into consideration the fat content of each source. Vegetable sources of proteins such as beans and pulses are very low in fat [29].

**Physical activity**

Regular physical activity improves metabolic control and reduces other cardiovascular risks. Even low level aerobic exercise (eg: brisk walking for half an hour per day) has the following benefits [29]:

- Improved glucose tolerance as insulin sensitivity increases
- Increased energy expenditure resulting in weight loss
- Increased feeling of well being
- Increased work capacity
- Improved blood pressure and lipid profiles

In time, duration and frequency of physical activity should be increased up to 30-45 minutes on 3-5 days per week, or an accumulation of 150 minutes of physical activity per week.

### 2.5.2. Medicinal treatment

#### 2.5.2.1. Insulins

Near-normalization of blood glucose concentrations in patients with T1DM also in patients with T2DM (if oral antidiabetics do not give expected results) can be achieved safely by
intensive insulin therapy. Insulin plays a key role in the regulation of carbohydrate, fat, and protein metabolism. It is a polypeptide hormone of complex structure. There are differences in the amino-acid sequence of animal insulins, human insulins and the human insulin analogues. Insulin may be extracted from pork and beef pancreas, but now are rarely used. Human sequence insulin may be produced semisynthetically by enzymatic modification of porcine insulin or biosynthetically by recombinant DNA technology using bacteria or yeast [30]. However human recombinant DNA insulins are gradually being replaced because of the superior efficacy of insulin analogues.

Analogue insulins are available in both rapid- and long-acting preparations. Currently available rapid-acting insulins are lispro, aspart and glulisine, and the currently available long-acting analogue basal insulins are detemir and glargine. The rapid-acting insulin analogues are also available in combination with protamine in fixed-dose pre-mixed insulins to provide a more sustained action [31].

Maximal utilisation of analogue insulins will result not only in better glycaemic control, but will also minimise the frequency and severity of hypoglycaemic episodes. In addition, maximisation of glycaemic control will result in prevention, delay of onset or amelioration of both the microvascular and perhaps the macrovascular complications of diabetes [31].

Insulin is inactivated by gastro-intestinal enzymes, and must therefore be given by injection; the subcutaneous route is ideal in most circumstances [30].

Currently available insulins

Rapid-Acting Insulins

The three currently available rapid-acting (ultra short-acting) insulins are insulin lispro, insulin aspart and insulin glulisine. They are available in vials, pre-filled disposable pens.

Insulin lispro because of the configuration resembled the structure of insulin-like growth factor, which tends not to self-associate, and when injected subcutaneously remains in monomeric form rather than forming dimmers and hexamers as regular insulin does. The configuration of insulin aspart and insulin glulisine, resulted in decreased hexamer formation following subcutaneous injection. Therefore they diffuse into the circulation quickly and are immediately available to cover the postprandial glycaemic excursion. The onset of action of rapid-acting insulin analogues given subcutaneously is 5-15 minutes, the peak action is between 30 - 90 min and the duration of action is up to 5 hours (Table 3) [31].

The pharmacodynamic effect of insulins aspart, lispro and glulisine can be declared equivalent. Clinical trials have demonstrated equivalence in efficacy and safety among rapidly acting insulin analogues. No difference concerning absorption or elimination for time to maximal
insulin concentration, time to half-maximum insulin concentration, and time to decrease to 50% of maximum insulin concentration was observed [32]. Several studies indicated a statistically significant decrease of hemoglobin A1C (A1C) with glulisine compared with regular insulin (0.10 decrease); however, no difference in A1C control was found compared with insulin aspart or lispro [33].

Rapid-acting insulin analogues have a rapid onset of action accompanied by a rapid return to baseline. In this way, postprandial hyper-glycaemia and later postprandial hypoglycaemia are avoided or at least ameliorated [31]. This is the reason, why rapid-acting analogues are more preferable than short acting human insulin.

Table 3. Pharmacokinetics of Available Insulin Preparations

<table>
<thead>
<tr>
<th>Insulin, Generic Name (Brand)</th>
<th>Onset</th>
<th>Peak</th>
<th>Effective Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rapid – Acting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin aspart injection (NovoLog)</td>
<td>5-15 min</td>
<td>30-90 min</td>
<td>&lt;5 h</td>
</tr>
<tr>
<td>Insulin lispro injection (Humalog)</td>
<td>5-15 min</td>
<td>30-90 min</td>
<td>&lt;5 h</td>
</tr>
<tr>
<td>Insulin glulisine injection (Apidra)</td>
<td>5-15 min</td>
<td>30-90 min</td>
<td>&lt;5 h</td>
</tr>
<tr>
<td><strong>Short – Acting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular (Actrapid, Humulin R)</td>
<td>30-60 min</td>
<td>2-3 h</td>
<td>5-8 h</td>
</tr>
<tr>
<td><strong>Intermediate – Acting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isophane NPH (Humulin N, Protophane)</td>
<td>2-4 h</td>
<td>4-10 h</td>
<td>10-16 h</td>
</tr>
<tr>
<td><strong>Long – Acting,</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin glargine injection (Lantus)</td>
<td>2-4 h</td>
<td>No peak</td>
<td>20-24 h</td>
</tr>
<tr>
<td>Insulin detemir injection (Levemir)</td>
<td>3-8 h</td>
<td>No peak</td>
<td>5.7-23.2 h</td>
</tr>
<tr>
<td><strong>Premixed</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>75% insulin lispro protamine suspension/25% insulin lispro injection (Humalog Mix 75/25)</td>
<td>5-15 min</td>
<td>Dual</td>
<td>10-16 h</td>
</tr>
<tr>
<td>50% insulin lispro protamine suspension/50% insulin lispro injection (Humalog Mix 50/50)</td>
<td>5-15 min</td>
<td>Dual</td>
<td>10-16 h</td>
</tr>
<tr>
<td>70% insulin aspart protamine suspension/30% insulin aspart injection (Novomix 70/30)</td>
<td>5-15 min</td>
<td>Dual</td>
<td>10-16 h</td>
</tr>
<tr>
<td>70% NPH/30% regular (Mixtard 30, Humulin M3)</td>
<td>30-60 min</td>
<td>Dual</td>
<td>10-16 h</td>
</tr>
</tbody>
</table>

**Short-Acting Insulins**

Currently, the only available short-acting insulin is regular insulin, which is manufactured by the recombinant DNA process utilising either E. coli or a yeast, so that it is identical to native human insulin. Regular insulin is, without question, the insulin of choice for intravenous use. However, the rapid-acting and more physiological rapid-acting insulin analogues are preferable for
subcutaneous use [31].

Some people prefer regular insulin over a rapid-acting insulin, because the effect of rapid-acting analogues is too short and is exhausted long before the next meal. The onset of action of regular insulin given subcutaneously is 30 minutes, the peak action is between 2.5 and 5 hours and the duration of action is up to 8 hours [34].

**Intermediate-Acting Insulins**

Since lente insulins are no longer available, the only intermediate-acting insulin available at present is human insulin isophane suspension or NPH insulin. The onset of action of human NPH is within 1–2 hours, it peaks at 2–12 hours and its duration of action is 14–24 hours [35]. Use of NPH insulin has diminished because of its variable intra-patient absorption rate (10–55% from injection to injection), its pronounced and variable peak, its dose-dependent duration of action, and the availability of the long-acting insulins (detemir and glargine), which have a lesser coefficient of variation and a more predictable and lower peak [31].

Thus, NPH insulin with its variable pharmacodynamics and pharmacokinetics is not the ideal insulin for insulin-requiring diabetic patients and in many situations has been replaced with long-acting insulins and mixtures that include both rapid-acting and protaminated rapid-acting insulins [31].

**Long-Acting Insulins**

The currently available long-acting insulins are insulin glargine and insulin detemir. Insulin glargine, the first long-acting analogue, is produced by substituting glycine for asparagine at position 21 of the α chain and by adding two arginine molecules at position 30 of the β chain of insulin. With these substitutions, there is a shift in the isoelectric point so that glargine is acidic. With subcutaneous injection, there is a shift towards a neutral pH, which decreases the solubility of the injected insulin, so that precipitation occurs from which an insulin depot is formed. Insulin is slowly released from this depot, making insulin glargine a long-acting insulin analogue [36].

The more recently available long-acting basal insulin analogue is insulin detemir. Unlike insulin glargine, insulin detemir is soluble at a neutral pH and, therefore, does not precipitate or form a depot on subcutaneous injection so stinging at the injection site does not occur. The prolonged action of insulin detemir is due to its attachment in the extracellular and vascular spaces to albumin. Therefore, there is a slow systemic absorption of insulin detemir from the subcutaneous injection site and a slower release to target tissues as a result of binding to albumin [37].
The onset of action of insulin glargine is 1.5 hours and of insulin detemir 0.8–2.0 hours. The action of neither of these insulins is without a peak but the peak is much flatter with both insulins than that seen with NPH. The duration of action of both of these insulins is up to 24 hours, with the duration of action being directly proportional to the dose of insulin that is injected. The termination of the pharmacological effect of insulin glargine ranges between 10.8 and more than 24 hours, while it varies from 5.7 to 23.2 hours with insulin detemir [38, 39]. Insulin detemir is approved for both once and twice daily injections, whereas insulin glargine is only approved for once-daily administration despite a similar dose-related duration of action.

Some clinical trials [40, 41] have shown, that detemir was noninferior to glargine in terms of overall glycemic control (HbA1c) in patients with T1DM. When used according to the approved labeling, detemir and glargine did not differ in tolerability or in terms of the occurrence of hypoglycemia. Glucose monitoring profiles and dosing requirements were shown to be statistically equivalent between the two insulins.

Pre-Mixed Insulin

The currently available pre-mixed, fixed ratio insulins are mixtures of intermediate- and short-acting insulins and mixtures of rapid-acting insulin analogues with an intermediate-acting component obtained through the addition of protamine. The former are mixtures of human NPH insulin and regular insulin, while the latter are the result of the addition of protamine to a rapid-acting insulin analogue (insulin lispro or insulin aspart) to prolong the duration of action of a fixed proportion of the preparation. The onset of action with the rapid-acting insulin mixtures is 15–30 minutes, the peak action is at 2.5 hours and the duration of action is for up to 24 hours [42].

Pre-mixed insulins have the advantage of convenience and accuracy. When there is retained endogenous insulin production, as occurs early in the course of type 1 diabetes, adequate control can be obtained with two or three injections of pre-mixed insulin per day [43]. When oral therapy has failed and insulin is first added to oral therapy in patients with type 2 diabetes, one to three injections of pre-mixes containing rapid-acting insulin have been shown to control type 2 diabetes adequately. Pre-mixes that include a rapid-acting insulin produce the best results and should therefore be utilised.

Premixed insulin preparations provide both basal and prandial coverage because of their biphasic pharmacokinetic properties. Clinical trials have shown that these agents improve glycemic control, are associated with an acceptably low rate of severe hypoglycemia, and have a high degree of patient acceptance [44].
2.5.2.2. Oral antidiabetic agents

Near-normalization of blood glucose levels in patients with T2DM can be achieved safely by monotherapy or intensive combination therapy—either dual-oral or triple-oral combinations and/or oral-insulin combinations. If oral antidiabetic agents can not ensure the right glucose control, patients need insulin therapy.

Insulin secretagogues
Sulphonylureas

Sulphonylureas lower blood glucose concentrations primarily by directly stimulating insulin secretion from the β-cells of the pancreatic islets. The blood glucose-lowering efficacy of sulphonylureas has been evaluated in many retrospective and prospective studies, and from decades of collective worldwide clinical experience.

Sulphonylureas can be a choice as first-line oral therapy for patients with type 2 diabetes who are not overweight and have not achieved or maintained adequate glycaemic control using nonpharmacological measures. They can be used as a monotherapy and in combination with agents from other classes of antidiabetic agents (metformin, thiazolidinedione, α-glucosidase inhibitor), with the exception of other insulin secretagogues. Daytime sulphonylurea treatment may be used in combination with bedtime insulin, and can reduce insulin doses by up to 50% [45].

When used as monotherapy in patients inadequately controlled by nonpharmacological measures, sulphonylureas can be expected to reduce fasting plasma glucose by an average of 2–4 mmol/L accompanied by a decrease in HbA1c of 1–2% [46]. However, individual responses are variable. When a sulphonylurea is used in combination with another antidiabetic agent, the glucose-lowering efficacy of the sulphonylurea is approximately additive to the effect of the other agent. Though response is crucially dependent on the presence of adequate β-cell function.

The currently available sulphonylureas in Lithuania belongs to second generation. The principal distinguishing feature between different sulphonylureas relates to their pharmacokinetic characteristics. Duration of action varies from 12 to 24 hours because of differences in rates of metabolism; activity of metabolites; and rates of elimination [47]. These properties have important implications for the risk of hypoglycaemia associated with various sulphonylureas, an issue that is further complicated by retarded release preparations of some compounds. All sulphonylureas are well absorbed and most reach peak plasma concentration in 2–4 hours.

Clinical trials have shown that gliclazide and glimepiride are equally effective in terms of glycaemic control. It was concluded that a 1mg dose of glimepiride has equivalent efficacy to an
80mg dose of gliclazide [48, 49]. In a large randomised study on type 2 diabetic patients, once daily gliclazide modified release 30-120mg was as effective as twice daily gliclazide 80-320mg in reducing HbA1c, with fewer side effects and less risk of hypoglycemia [50]. As a result, 30mg dose of gliclazide MR is equivalent to 80mg dose of gliclazide. There is a paucity of studies for some other comparisons, of the sulfonylureas (excluding studies of gliclazide modified release) [51]. Though according to NICE guidelines, it can be prescribed any of sulfonylurea with a low acquisition cost (but not glibenclamide), when an insulin secretagogue is indicated. In conclusion, all sulfonylureas (but not glibenclamide) should provide similar efficacy in equivalent DDD doses.

**Rapid-Acting Prandial Insulin Releasers- Glinides**

Glinides employ a mechanism of action similar to sulfonylureas to facilitate glycemic control; however, they have a much shorter metabolic half-life. Glinides stimulate a rapid but short-lived release of insulin from pancreatic β-cells that lasts 1 to 2 hours [19]. When taken at meals, these agents attenuate postprandial glucose excursions and decrease the risk of hypoglycemia during the late postprandial phase because less insulin is secreted several hours after the meal [52]. Therefore, use of glinides should target postprandial blood glucose levels rather than fasting blood glucose levels [19].

The currently available glinide in Lithuania is repaglinide. Repaglinide is rapidly and almost completely absorbed after oral administration, with peak plasma concentrations achieved in about 1 hour [53]. The drug is rapidly metabolised in the liver to inactive metabolites, which are mainly excreted in bile. When taken about 15 minutes before a meal, repaglinide produces a prompt insulin-releasing effect, which is limited to a period of about 3 hours, roughly coinciding with the duration of meal digestion [54].

Repaglinide can be used as monotherapy or with metformin to control post prandial hyperglycaemia. It should not be used in combination with sulphonylureas [29]. Overall reductions in HbA1c are similar in magnitude to those observed with sulphonylureas that is 1–2%. In head-to-head comparisons with sulfonylureas, metiglinides failed to demonstrate better glucose control and led to a similar number of hypoglycaemic events. No significant differences were observed in terms of lipid profile and body weight reduction [51].

**α-Glucosidase Inhibitors**

α-Glucosidase inhibitors provide postprandial glucose control by decreasing the absorption of carbohydrates from the gastrointestinal tract. These agents work by inhibiting α-
glucosidase, an enzyme that breaks down disaccharides and more complex carbohydrates. Through competitive inhibition of this enzyme, α-glucosidase inhibitors delay intestinal carbohydrate absorption, thus attenuating postprandial glucose excursions [19]. Acarbose is absorbed only to a trivial degree (<2%) [37].

It is useful when blood glucose values remain high after meals despite dietary modification. An α-glucosidase inhibitor can reduce peak concentrations of blood glucose and reduce interprandial troughs. Used as monotherapy to patients who comply appropriately with dietary advice, an α-glucosidase inhibitor will typically reduce postprandial glucose concentrations by 1–4 mmol/L. The decrease in HbA1c is usually about 0.5–1.0%, provided that a high dose of the drug is tolerated and dietary compliance is maintained. There may be a trivial alteration in the gastrointestinal absorption of other oral antidiabetic agents when used in combination therapy. In general, the extra benefit to glycaemic control achieved by addition of an α-glucosidase inhibitor to another antidiabetic agent is additive [45].

**Insulin sensitisers**

**Biguanides**

Metformin is the therapy of choice for overweight and obese patients with type 2 diabetes. It can be equally effective in normal weight patients. In some guidelines [10, 19, 52], it is recommended to prescribe metformin as the first choice medication in people with diabetes.

Metformin has a variety of metabolic effects, some of which may confer clinical benefits that extend beyond glucose lowering.

Since metformin lowers blood glucose concentrations without causing overt hypoglycaemia it is most appropriately classed as an anti-hyperglycaemic – as distinct from hypoglycaemic – agent. The clinical efficacy of metformin in patients with type 2 diabetes requires the presence of insulin. The drug does not stimulate insulin release, but reduces hepatic glucose output and insulin resistance [46].

Metformin is a stable hydrophilic biguanide that is quickly absorbed and eliminated unchanged in the urine. The drug is contraindicated in patients with impaired renal function (i.e. serum creatinine >120-130 µmol/L, depending on lean body mass), as a precaution against drug accumulation [45]. Peak plasma metformin concentrations are short-lived: in patients with normal renal function the plasma half-life (t1/2) for metformin is 2–5 hours, and almost 90% of an absorbed dosage is eliminated within 12 hour [55].

The long-term blood glucose-lowering efficacy of metformin is broadly similar to sulphonylureas. As monotherapy in patients who are not adequately controlled on
nonpharmacological therapy, optimally titrated metformin therapy typically reduces fasting plasma glucose by 2–4 mmol/L, corresponding to a decrease in HbA1c by approximately 1–2% [55]. Drug can also be used in combination with any other class of oral antidiabetic agent or with insulin.

Metformin should be taken with meals or immediately before meals to minimise possible gastrointestinal adverse effects. Treatment should be started with 500 or 850mg once daily, or 500mg twice daily. The dosage is increased at intervals of about 2 weeks. The maximal effective dosage appears to be about 2000 mg/day, given in divided doses with meals, the absolute maximum being 2550 or 3000 mg/day in different countries [45].

Metformin has several features that mark it out as a good choice for first-line monotherapy. The anti-hyperglycaemic action of metformin means that it is unlikely to cause severe hypoglycaemia. This may be explained in part because metformin does not stimulate insulin secretion. Also bodyweight tends to stabilise or decrease slightly during metformin therapy [45]. Consumption of metformin is increasing and for one more reason, metformin has been shown to significantly reduce the risk of diabetes-related morbidity and mortality in overweight patients [29].

**Thiazolidinediones**

Thiazolidinediones improve whole-body insulin sensitivity via multiple actions on gene regulation. These effects result from stimulation of a nuclear receptor peroxisome proliferator-activated receptor-γ (PPARγ), for which thiazolidinediones are potent synthetic agonists [56].

Reductions in plasma insulin concentrations and lowering of circulating triglycerides are additional indirect mechanisms that may help to improve whole-body insulin sensitivity. Thiazolidinediones, like metformin, are anti-hyperglycaemic agents and require the presence of sufficient insulin to generate a significant blood glucose-lowering effect [45].

The currently available thiazolidinediones in Lithuania, rosiglitazone and pioglitazone, seem to have similar efficacy on glycemic control. As judged by the available literature, these agents have similar glucose-lowering effects, reducing HbA1c by around 0.5-1.5% [57]. In addition to variety of metabolic effects that lower glycemia, these agents modestly reduce blood pressure, enhance fibrinolysis, and improve endothelial function [18].

Thiazolidinediones are rapidly, and nearly completely absorbed (1–2 hours to peak concentration), although absorption is slightly delayed when taken with food. Both agents are extensively metabolised by the liver [45]. In Europe, rosiglitazone and pioglitazone can be used as monotherapy if the patient is contraindicated for or intolerant of metformin. Also drugs can be used in combination with metformin or sulphonylurea, or as part of triple therapy with metformin and a sulfonylurea. Pioglitazone can be used in combination therapy with insulin [51]. Some comparison
studies were done and shown that there are no significant differences between thiazolidinediones in terms of HbA1c and FPG values [51].

Use of thiazolidinediones in patients with any evidence of congestive heart disease or heart failure is contraindicated. Also pre-existing liver disease, the development of clinical hepatic dysfunction or elevated ALT levels >2.5 times the upper limit for the laboratory serve as contraindications to thiazolidinediones.

**New agents for type 2 diabetes management**

Normal glucose metabolism involves a balancing act between insulin and glucagon. But it was found, that other hormones also play key roles in regulating glucose homeostasis. Incretin hormones are released from the gut after a meal. One of these incretin hormones, glucagon-like peptide-1 (GLP-1), binds to the beta-cell membrane in the pancreas, thereby stimulating insulin secretion by the beta cell. GLP-1 is not activated when glucose concentrations are below a certain threshold, thereby preventing glucose levels from becoming too low. Studies have shown that GLP-1 also appears to increase cell glucose sensitivity and aids in insulin synthesis and beta-cell function [58].

Amylin, a neuroendocrine hormone, has also been found to be important for glucose metabolism. Amylin is released from the beta cells of the pancreas in conjunction with insulin secretion. It binds to receptors in the brain to aid in the regulation of glucose by inhibiting glucagon secretion. This allows the body to use glucose recently ingested instead of glucose via gluconeogenesis [59].

**Exenatide**

Exenatide (Byetta, Amylin Pharmaceuticals), is an incretin mimetic similar to one of these incretin hormones, similar to glucagon-like peptide-1 (GLP-1). Exenatide binds to the GLP-1 receptor in the gut, but it has increased potency and a longer duration of action than endogenous GLP-1. It has been shown to potentiate insulin secretion, decrease glucagon secretion, decrease gastric emptying time, and enhance satiety [60]. Exenatide is a new treatment option for the management of type 2 diabetes that works by a novel mechanism of action.

Exenatide is available as pre-filled pens that deliver 60 doses of medication (either 5 mcg or 10 mcg per dose). Like insulin, exenatide is administered by subcutaneous injection. However, it is dosed in micrograms rather than units. Exenatide therapy should be initiated at 5 mcg twice daily, administered within the 60-minute period before the 2 largest meals of the day (at least 6 hours
If a patient is able to tolerate exenatide 5 mcg twice daily after 1 month, and additional blood glucose lowering is needed, the dose may be increased to 10 mcg twice daily [61].

In short-term trials, it has been shown to be safe and effective for patients with type 2 diabetes who are either at the maximum doses of or cannot tolerate metformin, sulfonylurea, and/or thiazolidinedione therapy and still need to decrease their A1C by at least 0.5% to 1.0%. It may also be a good choice for those patients concerned with weight gain from other antidiabetic medications or in those needing to lose weight to improve glycemic control since it has been shown to lead to weight loss. While clinical trials published to date have shown promising results, the trials primarily studied patients who were relatively healthy with no serious comorbidities. Post-marketing studies will provide a better picture of the long-term efficacy and safety profile of exenatide. While exenatide is a viable option for adjunctive therapy, it requires 2 injections daily, has a moderate effect on A1C relative to insulin, and is quite costly [61].

**Pramlintide**

Pramlintide (Symlin, Amylin Pharmaceuticals) is an analog of the neuroendocrine hormone, amylin, which appears to be at least as potent as endogenous amylin. It decreases post-prandial glucagon secretion, slows gastric emptying, and increases satiety. Because amylin dysfunction occurs in patients with diabetes, providing exogenous amylin could attenuate the issues of satiety and increased glucagon secretion, which affect patients with type 2 diabetes [61].

Pramlintide should be administered in conjunction with mealtime insulin in patients who have failed to achieve desired glucose control despite optimal insulin therapy, with or without concurrent metformin and/or a sulfonylurea agent [62]. Pramlintide offers a novel mechanism of action and can result in modest weight loss. While studies conducted to date have shown it to be effective as adjunctive therapy, lowering A1C by approximately 0.6%, in patients who are receiving concomitant insulin therapy [61].

Patients with type 1 or type 2 diabetes require different initial doses. In type 1 diabetes, patients should be started with a subcutaneous injection of 15 µg before meals, and the dose should be titrated at 15-µg increments to reach a maintenance dose of 30-60 µg before meals. As is the case with insulin in type 2 diabetes, patients taking pramlintide will require higher doses. In these patients, the dose should start at 60 µg before meals and be titrated to 120 µg before meals, as tolerated. The time pramlintide achieve maximum concentration is 20 minutes, with the effect lasting up to 3 hours after drug administration [63].

**Sitagliptin**

Sitagliptin (Januvia, Merck & Co., Inc.) is a dipeptidyl peptidase-4 (DPP-4) inhibitor. By
blocking this enzyme, insulin production increases, glucose production in the liver goes down, and blood sugar levels decrease [64]. While it does not act by mimicking the actions of natural neuroendocrine hormones, it is yet another new class of agents for the treatment of type 2 diabetes [61]. It is used for the treatment of type 2 diabetes as monotherapy or adjunctive therapy in combination with metformin, sulfonylureas, or a thiazolidinedione when the existing regimen no longer provides adequate blood glucose control [64].

The recommended dose of sitagliptin (in patients with an estimated creatinine clearance ≥ 50 mL/min) is 100 mg once daily, either as monotherapy or combined with metformin or pioglitazone. No dosage adjustment is necessary for the elderly. If taken in combination with a sulfonylurea, the dose of sulfonylurea may need to be reduced to decrease the risk of hypoglycemia. In clinical trials, sitagliptin has been shown to reduce A1C by 0.6% to 1%, but it does not appear to have a positive effect on weight loss [61].

2.5.3. Recommendations for glycemic management

All Patients with Diabetes Mellitus
- Encourage patients to achieve glycemic levels as near normal as possible without inducing clinically significant hypoglycemia; glycemic targets include:
  - HbA1c <7%
  - Fasting plasma glucose concentration <6.7 mmol/l
  - 2-hour postprandial glucose concentration <8.9 mmol/l
- Refer patients for comprehensive, ongoing education in diabetes self-management skills, physical activities and nutrition therapy;
- Initiate self-monitoring of blood glucose levels, detection and management of hypoglycaemia [18].

Patients with Type 1 Diabetes Mellitus
Initiate intensive insulin therapy, regimen options include:
- 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.

Oral glucose-lowering drugs should generally not be used in the management of adults with type 1 diabetes [65].

According to Lithuanian guidelines for Type 1 diabetes [66], when Type 1 diabetes is diagnosed, intensive insulin therapy must be started immediately and continued whole patients life. It is recommended to start with rapid–acting or short–acting insulin before the main meals + intermediat – acting insulin one or two times a day. If this regimen is not effective for the patient, it can be suggested a combination of long–acting and short–acting insulin injections.

Patients with Type 2 Diabetes Mellitus

According to NICE [51] - National Institute for Health and Clinical Excellence (it is an independent organisation responsible for providing national guidance on promoting good health and preventing and treating ill health), there is such recommendations for glucose control therapies (Figure 3):
Figure 3. Scheme for the pharmacotherapy of glucose lowering in people with Type 2 diabetes
* or as individually agreed

**Metformin**

- Start metformin treatment in a person who is overweight or obese and whose blood glucose is inadequately controlled by lifestyle interventions (nutrition and exercise) alone.
- Consider metformin as an option for first-line glucose-lowering therapy for a person who is not overweight.
- Continue with metformin if blood glucose control remains or becomes inadequate and another oral glucose-lowering medication (usually a sulfonylurea) is added.
- Step up metformin therapy gradually over weeks to minimise risk of gastrointestinal side effects (See the main side effects for oral antidiabetics in Table 4).
- Review the dose of metformin if the serum creatinine exceeds 130 micromol/l or the eGFR is below 45 ml/minute/1.73 m².
• Stop the metformin if the serum creatinine exceeds 150 micromol/l or the eGFR is below 30 ml/minute/1.73 m².

• The benefits of metformin therapy should be discussed with a person with mild to moderate liver dysfunction or cardiac impairment so that:
  o due consideration can be given to the cardiovascular-protective effects of the drug
  o an informed decision can be made on whether to continue or stop the metformin.

**Insulin secretagogues**

• Consider a sulfonylurea as an option for first-line glucose lowering-therapy if:
  o the person is not overweight
  o the person does not tolerate or is contraindicated
  o a rapid response to therapy is required because of hyperglycaemic symptoms

• Add a sulfonylurea as second-line therapy when blood glucose control remains, or becomes, inadequate with metformin.

• Continue with a sulfonylurea if blood glucose control remains, or becomes, inadequate and another oral glucose-lowering medication is added.

• Prescribe a sulfonylurea with a low acquisition cost (but not glibenclamide) when an insulin secretagogue is indicated.

• When drug concordance is a problem, offer a once daily, long-acting sulfonylurea.

• Educate a person being treated with an insulin secretagogue, particularly if renally impaired, about the risk of hypoglycaemia.

**Rapid-acting insulin secretagogues**

• Consider offering a rapid-acting insulin secretagogue to a person with an erratic lifestyle.

**Acarbose**

• Consider acarbose for a person unable to use other oral glucose-lowering medications.

**Thiazolidinediones (glitazones)**

• If glucose concentrations are not adequately controlled (to HbA1c <7.5% or other higher level agreed with the individual), consider, after discussion with the person, adding a thiazolidinedione to:
  o the combination of metformin and a sulfonylurea where insulin would otherwise be considered but is likely to be unacceptable
  o a sulfonylurea if metformin is not tolerated
  o metformin as an alternative to a sulfonylurea where the person’s job or other issues make the risk of hypoglycaemia with sulfonylureas particularly significant.

• Do not commence or continue thiazolidinedione in people who have evidence of heart failure, or who are at higher risk of fracture.
**Gliptins: GLP-1 enhancers**
- No recommendations are made on the use of gliptins as these drugs are not covered in this guideline.

**Exenatide: GLP-1 mimetics**
- Exenatide is not recommended for routine use in Type 2 diabetes.

**Insulin**
- When other measures no longer achieve adequate blood glucose control to HbA1c <7.5% or other higher level agreed with the individual, discuss the benefits and risks of insulin therapy. Start insulin therapy if the person agrees.
- Insulin therapy should be initiated from a choice of a number of insulin types and regimens.
  - Preferably begin with human NPH insulin, taken at bedtime or twice daily according to need.
  - Consider, as an alternative, using a long-acting insulin analogue (insulin glargine) for a person who falls 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 once daily basal insulin injections in combination with oral glucose-lowering medications.
  - Consider twice-daily biphasic human insulin (pre-mix) regimens in particular where HbA1c is elevated above 9.0 %. A once-daily regimen may be an option when initiating this therapy.
  - Consider pre-mixed preparations of insulin analogues rather than pre-mixed human insulin preparations when:
    - immediate injection before a meal is preferred, or
    - hypoglycaemia is a problem, or
    - there are marked postprandial blood glucose excursions.
- When starting basal insulin therapy:
  - continue with metformin and the sulfonylurea (and acarbose, if used)
  - review the use of the sulfonylurea if hypoglycaemia occurs.
- When starting pre-mixed insulin therapy (or mealtime plus basal insulin regimens):
  - continue with metformin
  - continue the sulfonylurea initially, but review and discontinue if hypoglycaemia occurs.
Consider combining pioglitazone with insulin therapy for:

- a person who has previously had a marked glucose lowering response to thiazolidinedione therapy
- a person on high-dose insulin therapy whose blood glucose is inadequately controlled.
- Warn the person to discontinue pioglitazone if clinically significant fluid retention develops.

Table 4. The main side effects for oral antidiabetics

<table>
<thead>
<tr>
<th>Side effects of metformin are:</th>
<th>Side effects of sulphonylureas are:</th>
<th>Side effects of glitazones are:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anorexia, nausea, vomiting</td>
<td>Weight gain</td>
<td>Increased subcutaneous fat and/or fluid</td>
</tr>
<tr>
<td>Diarrhoea, abdominal cramps, flatulence</td>
<td>Symptomatic hypoglycaemia</td>
<td>Decreased haemoglobin levels</td>
</tr>
<tr>
<td>Lactic acidosis (if renal, liver or cardiovascular disease exist)</td>
<td>Anorexia, nausea, diarrhoea, skin rashes</td>
<td>Increased risk of peripheral fractures in women</td>
</tr>
</tbody>
</table>

**Side effects of GLP-1 agents are:**

Occasionally blood dyscrasias

**‘Mimetics’ exenatide:**

Possible increased risk of myocardial infarction (rosiglitazone)

**Side effects of repaglinide are:**

Increased LDL-C (rosiglitazone)

**Side effects of acarbose are:**

Non response to carbohydrates than glucose if hypoglycaemic other

**‘Enhancers’ sitagliptin:**

(Rare) hepatitis and/or jaundice

According to Lithuanian guidelines for Type 2 diabetes [66], first of all should be suggested non-pharmacological management: diet and physical activity. If it is not effective alone, there should be added monotherapy of oral antidiabetics. First choice medication should be metformin, if it is not tolerated, it can be either a sulphonylurea or thiazolidinedione. If monotherapy is not effective, start with combinations of metformin and sulphonylurea. If glycemic control is not obtained, there can be added thiazolidinediones or insulin.
3. OBJECTIVE AND AIMS

Objective:

To evaluate consumption of drugs for diabetes mellitus treatment in Lithuania on 2006-2009 year and to perform a pharmaco economical analysis of antidiabetic drugs.

Aims:

1. To evaluate utilization of antidiabetic drugs in Lithuania by the means of the ATC/DDD methodology.
2. To evaluate and to compare utilization of insulins and oral hypoglycaemic drugs in Lithuania by the means of the ATC/DDD methodology.
3. To compare antidiabetics’ utilization data in Lithuania with other European countries.
4. To evaluate direct cost of antidiabetic drugs in Lithuania by using retail prices from the National Patient Funds Price List on 2006-2009 years.
5. To perform a pharmaco economical analysis of insulins and oral hypoglycaemic drugs by the cost minimization and reference price methodologies.
4. MATERIAL AND METHODS

4.1 The purpose of the ATC/DDD system

The purpose of the ATC/DDD system is to serve as a tool for drug utilization research in order to improve quality of drug use. One component of this is the presentation and comparison of drug consumption statistics at international and other levels. A major aim of the Centre and Working Group is to maintain stable ATC codes and DDDs over time to allow trends in drug consumption to be studied without the complication of frequent changes to the system. There is a strong reluctance to make changes to classifications or DDDs where such changes are requested for reasons not directly related to drug consumption studies. For this reason the ATC/DDD system by itself is not suitable for guiding decisions about reimbursement, pricing and therapeutic substitution [67].

4.2 The ATC classification – structure and principles

Structure

In the Anatomical Therapeutic Chemical (ATC) classification system, the drugs are divided into different groups according to the organ or system on which they act and their chemical, pharmacological and therapeutic properties. Drugs are classified in groups at five different levels. The drugs are divided into fourteen main groups (1st level), with one pharmacological/therapeutic subgroup (2nd level). The 3rd and 4th levels are chemical/pharmacological/therapeutic subgroups and the 5th level is the chemical substance. The 2nd, 3rd and 4th levels are often used to identify pharmacological subgroups when that is considered more appropriate than therapeutic or chemical subgroups [67].

Principles for classification

Medicinal products are classified according to the main therapeutic use of the main active ingredient, on the basic principle of only one ATC code for each pharmaceutical formulation (i.e. similar ingredients, strength and pharmaceutical form). A medicinal product can be given more than one ATC code if it is available in two or more strengths or formulations with clearly different therapeutic uses.

A medicinal product may be used for two or more equally important indications, and the main therapeutic use of a drug may differ from one country to another. This will often give several classification alternatives. Such drugs are usually only given one code, the main indication being
decided on the basis of the available literature. Problems are discussed in the WHO International Working Group for Drug Statistics Methodology where the final classification is decided. Cross-references will be given in the guidelines to indicate the various uses of such drugs.

The ATC system is not strictly a therapeutic classification system. At all ATC levels, ATC codes can be assigned according to the pharmacology of the product. Subdivision on the mechanism of action will, however, often be rather broad, since a too detailed classification according to mode of action often will result in having one substance per subgroup which as far as possible is avoided. Some ATC groups are subdivided in both chemical and pharmacological groups. If a new substance fits in both a chemical and pharmacological 4th level, the pharmacological group should normally be chosen.

Substances classified in the same ATC 4th level cannot be considered pharmacotherapeutically equivalent since their mode of action, therapeutic effect, drug interactions and adverse drug reaction profile may differ [67].

4.3 The DDD – definition and principles

The basic definition of the unit is:

The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults. A DDD will only be assigned for drugs that already have an ATC code.

It should be emphasised that the defined daily dose is a unit of measurement and does not necessarily reflect the recommended or prescribed daily dose. Doses for individual patients and patient groups will often differ from the DDD and will necessarily have to be based on individual characteristics (e.g. age and weight) and pharmacokinetic considerations.

Drug consumption data presented in DDDs only give a rough estimate of consumption and not an exact picture of actual use. DDDs provide a fixed unit of measurement independent of price and formulation enabling the researcher to assess trends in drug consumption and to perform comparisons between population groups.

DDDs are not established for topical preparations, sera, vaccines, antineoplastic agents, allergen extracts, general and local anesthetics and contrast media.

The DDD is nearly always a compromise based on a review of the available information including doses used in various countries when this information is available. The DDD is sometimes a dose that is rarely if ever prescribed, because it is an average of two or more commonly used dose sizes [67].
4.4 DDD for comparison of consumption

Use of the ATC/DDD system allows standardisation of drug groupings and a stable drug utilization metric to enable comparisons of drug use between countries, regions, and other health care settings, and to examine trends in drug use over time and in different settings [67].

Sales or prescription data presented in DDD/1000 inhabitants/day provide a rough estimate of the proportion of the population within a defined area treated daily with certain drugs. As an example, the figure 10 DDDs/1000 inhabitants/day indicates that 1 % of the population on average might get a certain drug or group of drugs every day. This estimate is most useful for chronically used drugs when there is good agreement between the average prescribed daily dose and the DDD. Usually the general utilization is calculated for the total population including all age groups [68].

4.5 Drug utilization

The ATC/DDD system can be used for collection of drug utilization statistics in a variety of settings and from a variety of sources. Examples are:

- **Sales data** such as wholesale data at a national, regional or local level.
- **Dispensing data** either comprehensive or sampled. In many countries pharmacies are computerised and advantage can be taken of this to collect data on drugs dispensed. Alternatively, sample data can be collected manually. Reimbursement systems, which operate in a number of countries at the national level provide comprehensive dispensing data down to the individual prescription level, as all prescriptions are submitted and recorded for reimbursement. This is generally called "claims" data. Similar data are often available through health insurance or health maintenance organisations. These databases can sometimes allow collection of demographic information on the patients, and information on dose, duration of treatment and co-prescribing. Less commonly, linkage to hospital and medical databases can provide information on indications, and outcomes such as hospitalisation, use of specific medical services and adverse drug reactions.
- **Patient encounter based data.** This is usually collected by specially designed sampling studies such as those carried out by market research organisations. However, increasing use of information technology at the medical practice level will make such data available more widely in the near future. These methods have the advantage of potentially providing accurate information on Prescribed Daily Doses, patient demographics, duration of therapy, co-prescribing, indications, morbidity and co-morbidity, and sometimes outcomes.
- **Patient survey data.** Collection of data at the patient level can provide information about actual drug consumption and takes into account compliance in filling prescriptions and taking medications as prescribed. It can also provide qualitative information about perceptions, beliefs and attitudes to the use of medicines.

- **Health Facility data.** Data on medication use at all the above levels is often available in health care settings such as hospitals and health centres at regional, district or village level [67].

### 4.6. Definition of cost-minimization analysis

Cost-minimization analysis (CMA) compares the costs of two or more therapies that have equivalent treatment outcomes. To declare therapies equivalent, a proper equivalency trial is necessary. The objective of an equivalency trial is to demonstrate that drug A is at least as good as drug B.

Before undertaking this type of trial, a minimally clinically important difference (MCID) in the treatment outcome must be estimated. The MCID is defined as the smallest improvement in the outcome measure that is perceived as beneficial. In the case of mortality, there is no consensus as to what constitutes a MCID, but it is generally accepted that if the treatment benefit from two competing therapies does not differ by more than 1% in total mortality, the therapies can be considered to be-equivalent. To determine the MCID for treatment outcomes other than mortality, a formal literature search and/or a consensus conference is required. Using this a priori estimate of a MCID, the number of patients required to demonstrate equivalency can then be calculated.

Sample size calculations for equivalency trials are performed using a statistical power of 90% or greater. In this way, when the trial reports no statistically significant difference between the two therapies, the reader can be at least 90% sure that a difference greater than the MCID does not exist. Equivalency trials and thus cost-minimization studies, are very difficult to conduct and as a basic rule, if a MCID is not defined in advance or if a sample size calculation is not performed using at least 90% power, the two therapies cannot be declared equivalent. Since equivalency trials can be complex to design, conduct and report, the excellent paper by Massel provides a detailed approach to a critical review of the topic.

If an appropriate sample size calculation is performed using at least 90% power and if a MCID is defined in advance, the cost minimization study resolves to a simple, direct comparison of the difference between the total costs recorded in both arms of the trial.

CMA uses monetary units to measure its outcomes. When two or more interventions result in identical outcomes, a CMA is the appropriate tool for deriving the cost associated with each
outcome. Because the outcomes of two different drugs are rarely, if ever, equal, this type of study is applicable and most useful for evaluating different dosage forms of the same drug, or for evaluating generically equivalent drugs for which outcomes have been demonstrated to be equivalent. A determination of preference is then made between the two or more alternatives based on cost minimization [69].

4.7. Reference pricing

The immediate intuitive appeal of reference pricing is clear – to pay a similar price for products that provide a similar benefit. From the payer’s perspective, it provides an opportunity to reduce the cost of higher-priced products – to pay only the lowest common denominator, the generic price. Analysis of the factors contributing to the growth in pharmaceutical expenditure in major markets shows that the biggest factor is innovation, as physicians switch from older to newer and more effective medicines [70].

The Structure of Reference Price Systems

Any reference price system requires several key structural decisions: criteria for grouping drugs; criteria for setting and updating reference prices; and incentives for patients, doctors and pharmacists. Decisions on each of these dimensions involve a trade-off between low current prices, on the one hand, and incomplete protection for patients and/or undermining of incentives for innovation, on the other [71].

No two references pricing schemes are identical, but the essential elements are:

- The grouping together of medicines into identical or similar classes (often known as clusters), whether by active substance or therapeutic class. In most countries this clustering is restricted to generic medicines, but in Germany and the Netherlands patent-protected medicines may be included. The assumption is that products in a cluster are interchangeable.
- A fixed maximum reimbursement price is set for all the medicines within the cluster, irrespective of their actual prices. Usually this is set by reference to the cheapest medicines within the cluster.
- Manufacturers are free to set the price of their products above the reference price (the reimbursed amount), but patients are responsible for paying co-payments where the price exceeds the reference price.

In countries where generic prescribing is not well-established, reference pricing is one of the main tools used by governments to implement this switch to generics, or at least to achieve generic prices even if doctors persist in prescribing brands.

However, reference pricing has negative consequences for both patients and pharmaceutical
innovation. What it fails to take into account is the variety of both products and patients. Products within the same class may have characteristics that differ in clinically significant ways, and much innovation comes from incremental improvement within therapeutic classes. But, if new products will be clustered with existing products there is no incentive for companies to invest in such incremental improvement. The almost infinite variability of patients may mean that, for an individual patient, only one medicine in a class may be effective or appropriate [70].

In contrast with positive or negative lists, the choice of medicines available to the patients and their physicians is not restricted. If a doctor prescribes a product that is more expensive than the fixed payment level, then the patient will pay the difference.

4.8. Data sources

The search for all literature relating to pharmacokinetic and pharmacodynamic characteristics of drugs for diabetes mellitus was done in MEDLINE database.

The data on total sales of antidiabetic drugs in Lithuania over 2006-2009 years period were obtained from Softdent UAB, data base. Data were calculated by DDD methodology and expressed in DDDs per 1000 inhabitants per day. Calculations of drug prices and total expenditures for antidiabetic drugs were made by using retail prices from the National Patient Funds Price List on 2006-2009 years.
5. RESULTS

5.1. Analysis of total consumption of antidiabetic agents

Calculated data of antidiabetic agents (ATC A10) consumption in Lithuania over a four-year period (2006 – 2009) are shown in Figure 4. Antidiabetic drugs are classified using the therapeutic classification in the British National Formulary (BNF). The usage of antidiabetic agents (including insulin) was analyzed using the value of the defined daily doses per 1000 inhabitants per day (DDD/TID). Drug consumption measuring according to the DDD/TID shows the general utilization and makes possible comparisons between areas with different number of population.

![Figure 4](image-url)  
Figure 4. Total consumption of antidiabetic drugs (including insulins) by DDD/TID units in Lithuania, 2006 – 2009

The estimations have demonstrated the general growth of antidiabetic agents consumption in Lithuania during the study period. The Figure 4 illustrates the increase in total antidiabetics consumption by 33.4% reaching the value of 28.72 DDD/TID in 2009.

The separate consumption of insulins and oral antidiabetic agents are represented in Figure 5. The estimations showed that consumption of insulins have increased by 30% (2.18 DDD/TID) from 7.25 DDD/TID (2006) to 9.43 DDD/TID (2009), likewise the consumption of oral hypoglycaemic drugs have risen by 35.1% (5 DDD/TID) reaching the value of 19.29 DDD/TID in 2009. The total increase in oral antidiabetic agents was two times higher than insulins.
In comparison with consumption of antidiabetic agents, the total amount of money spent for these drugs have increased by 23.4% during the four-year period (Figure 6). In the year of 2007, the total expenses have increased by 5.822mln Lt (10.2%), alike in 2008- by 6,282mln Lt (10%), though in 2009 there have just been 1.289mln Lt (1.9%) increase. In comparison, the total consumption during the last year (2009) increased by 8.7%.

Despite the fact that expenses for insulin preparations have been increasing during all
four-year period (by 12% in 2007; 10.6% in 2008; 6.4% in 2009), expenses for oral antidiabetic agents have declined during the last year (by 6.4% in 2009) (Figure 7).

Figure 7.Expenditures for oral antidiabetic agents and insulins by million Litas in Lithuania, 2006 – 2009

5.1.2. Analysis of consumption of human insulin and insulin analogues

Calculated data of human insulin and insulin analogues (ATC A10A) consumption during the four-year period (2006 –2009) are shown in Figures (Figure 8, Figure 9). Short-acting insulin group includes rapid-acting insulin analogues and short-acting soluble insulin according to BNF classification [30]. Figure 8 demonstrates the increase in almost all insulins consumption in different groups (biphasic, short-acting, long-acting insulin preparations), just in intermediate-acting group there are seen small variations during 2006-2009.

Instead of total increase in insulins utilization every year, a great difference between the consumption of human insulin and insulin analogues exists. Figure 9 represents the general tendency to decline the consumption of human insulin and increase the consumption of insulin analogues. During the four-year period, the consumption of human insulin has decreased five times from 2.6 DDD/TID in 2006 to 0.54 DDD/TID in 2009, while the utilization of insulin analogues has increased by two times reaching the value of 8.89 DDD/TID in 2009.
Figure 8. Consumption of insulin groups by DDD/TID units in Lithuania, 2006 – 2009

Figure 9. Consumption of human insulin and insulin analogues by DDD/TID units in Lithuania, 2006 – 2009

Variation of insulins consumption in 2009 is represented in Figure 10. Mixed (biphasic) insulin preparations took the biggest part of insulin market in Lithuania – 54%. Second place went to short-acting insulin – 24%. Whereas intermediate-acting insulin encompassed just 6% of the market.
Figure 10. Variation of insulins consumption in 2009

Figure 11 demonstrates variation of biphasic insulin consumption by certain substance over the study period. The proportion of consumption of insulin aspart increased from 46% in 2006 to 58% in 2009 and took the biggest part of biphasic insulin market in Lithuania. Though the biggest increase was made by insulin lispro, the consumption has grown two and a half times from 16% in 2006 to 42% in 2009. The situation with human (isophane) insulin was different comparing with other insulins in biphasic insulin group: the estimations have shown a huge decrease in human insulin consumption from 38% in 2006 to 0% (0.00325 DDD/TID) in 2009.

Figure 11. Variation of biphasic insulin consumption by certain substance in Lithuania, 2006 – 2009 by percent

*Preparations contain two forms of substances – soluble form and form of protamine

Variation of short-acting insulin consumption by certain substance over the study period is represented in Figure 12. The proportion of consumption of insulin aspart increased from 43% in
2006 to 50% in 2009 and took a half of short-acting insulin market in Lithuania. The biggest increase was made by consumption of insulin glulisine, it has grown three times reaching the value of 18% in 2009. The usage of insulin lispro remained rather stable. However the estimations have shown a sharp decrease in the consumption of human (soluble) insulin during the whole study period.

![Bar chart showing variation of short-acting insulin consumption by certain substance in Lithuania, 2006–2009 by percent.](image)

Figure 12 Variation of short-acting insulin consumption by certain substance in Lithuania, 2006–2009 by percent

**Preparations contain just soluble form of the substance.

Variations of long- and intermediate-acting insulin groups by certain substance do not differ so much like in the previous groups during the study period. But it is important to mention, that in intermediate-acting insulin group there were just human insulin available. Since 2009, the protamined form of insulin lispro (intermediate-acting) was introduced to Lithuanian market and took 26% of it at once.

### 5.1.2 Analysis of consumption of oral antidiabetic agents

Calculated data of consumption of oral antidiabetic agents (ATC A10B) during the four-year period (2006–2009) are shown in Figures (Figure 13, Figure 14, Figure 15). Figure 13 illustrates the sharp increase in biguanide consumption during this period. The utilization has risen almost two times reaching the value of 8.21 DDD/TID in 2009. The increase in metformin consumption took 69.4% of total increase in oral antidiabetic drugs. The estimations show general but not sharp increase of consumption of sulphonylureas, glinides, thiazolidinediones during the four-year period. New agent Sitagliptin have been introduced to the market in 2008, the
consumption has not grown a lot.

Figure 13. Consumption of oral antidiabetic agents shared by groups by DDD/TID units in Lithuania, 2006 – 2009

Figure 14 demonstrates the tendencies in growth of certain substance of oral antidiabetic drug. The estimations show that the biggest increase belongs to metformin (the only substance in the group of biguanides in Lithuania), while the biggest decrease belongs to glibenclamide. The consumption of gliclazide has increased by almost 20%, consumption of glimepiride and pioglitazone has increased a bit. In utilization of other substances there are seen small variations during the year of 2006-2009.
Figure 14. Consumption of oral antidiabetic agents by DDD/TID units in Lithuania, 2006 – 2009

The percentage variation of total consumption for certain oral antidiabetic agent group in 2009 is represented in Figure 15. The estimations have shown that the values of sulphonylureas and biguanides consumptions were the highest- 52% and 43%, respectively. The utilization of glinides and new agents were very low, reaching the values of 0.06 DDD/TID and 0.04 DDD/TID,
The findings have shown medication gliclazide being the most popular of sulphonylureas. According to the data, the utilization has reached more than a half – 55% of all sulphonylureas market, leaving glimepiride (37%) in the second place. The consumption of glibenclamide has been the lowest one - 0.012 DDD/TID - 0% (Figure 16).

It is important to mention that the major part of total oral antidiabetic agents consumption takes the consumption of pure drugs, just 4% is taken by combined medications, containing two substances inside (Figure 17).
Combined medications, containing two substances

One substance in the drug

Figure 17. Variation of oral antidiabetic drug consumption shared by pure and combined drugs in 2009

5.2. Reference pricing

5.2.1. Reference price for human insulin and insulin analogues

The financial analysis of insulin showed that the sum of money spent on these medications was LTL 47.415 million in Lithuania in 2009 (Figure 7) (all calculations are made by using retail prices from the National Patient Funds Price List for 2009). The biggest part of total expenditures took biphasic insulin - 50%. Short-acting and long-acting insulin took almost equal parts of total expenditures – 23% and 22%. The least expenditures were for intermediate-acting insulin – 5% (Figure 18). The average price per DDD paid for certain group of insulin is demonstrated in Figure 19. The costs per DDD of certain insulin group ranged from 2.97 LTL/DDD to 5.67 LTL/DDD in Lithuania in 2009.

Figure 18. Distribution of money spent on insulins by groups in Lithuania, 2009
There are not concentrated meta-analysis among all groups of insulin, analysing the main diabetes parameters (HbA1c reduction, ratio of major and minor hypoglycaemic events, adverse affects, adherence, compliance, quality of life etc. in T1DM and T2DM.) Insufficient evidence of efficacy and safety among all groups of insulin existance do not let adjust cost minimization analysis and use of reference price among them all.

However there were long- and intermediate- acting insulins compared in type 1 diabetes [72] (twenty-three randomised controlled trials were identified) and meta analysis done in type 2 diabetes [73] (fourteen randomized controlled trials). In type 1 diabetes long- acting insulin preparations seem to exert a beneficial effect on nocturnal glucose levels, though their effect on the overall diabetes control is clinically unremarkable versus intermediate acting insulin. In type 2 diabetes long-acting analogues also did not produce any significant improvement of HbA1c, in comparison with NPH human insulin, whereas it reduces the risk of nocturnal and symptomatic hypoglycemia. Detemir, but not glargine, could be associated with smaller weight gain than NPH insulin.

Financial analysis has shown that DDD prices in long – acting insulin group (insulin detemir 5.69 LTL/DDD and insulin glargine 5.67 LTL/DDD) are equivalent. Though a sharp difference between DDD prices of long- actin insulin analogues and intermediate- acting human insulin exist. Long- acting insulins are the most expensive - 5.67 LTL/DDD, and intermediate-acting human insulin is the cheapest one – 2.97 LTL/DDD. According to meta-analysis data and difference between DDD prices, reference pricing would bring huge financial benefit. It would be
possible to reduce the costs of long-acting insulins by LTL 4.879 million, by choosing intermediate-acting insulin price for long-acting insulins as a reference price (Table 5).

Table 5. Pharmacoeconomic calculations based on consumption of insulin in suggesting the intermediate-acting human insulin price as the reference price for long-acting insulin analogues group in 2009

<table>
<thead>
<tr>
<th></th>
<th>Price For DDD</th>
<th>DDDs</th>
<th>Costs</th>
<th>Reference Price/DDD</th>
<th>Cost Using Reference Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermediate-acting (human)</td>
<td>2.97</td>
<td>535.518,75</td>
<td>1.590.490,69</td>
<td>2.97</td>
<td>1.590.490,69</td>
</tr>
<tr>
<td>Long-acting (detemir, glargine)</td>
<td>5.67</td>
<td>1.806.937,50</td>
<td>10.245.335,63</td>
<td>2.97</td>
<td>5.366.604,38</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>2.342.456,25</td>
<td>11.835.826,31</td>
<td>2.97</td>
<td>6.957.095,06</td>
</tr>
</tbody>
</table>

Estimations have shown that expenses for one DDD in the group of biphasic insulin ranged from 2.90 LTL/DDD for human insulin to 4.09 LTL/DDD for insulin aspart in Lithuania in 2009 (Figure 20) despite the similar efficacy and safety of these substances.

![Figure 20](image)

Figure 20. Dynamics of costs per DDD by Litas (LTL/DDD) for certain substance in the group of biphasic insulin in Lithuania, 2009
* Preparations contain a fixed proportion of soluble with protamined forms of insulin.

Data from various randomised trials show that both biphasic insulin lispro and insulin aspart provide more effective postprandial control of blood glucose than premixed human insulin or human insulin isophane suspension (NPH insulin). Longer-term glycaemic control, evaluated as changes in glycosylated haemoglobin (HbA1c), is comparable for premixed insulin analogues and premixed human insulin in most studies [74,75]. Hypoglycaemia and other adverse events were also similar between various premix insulins. Though analogues allow flexible injection timing, relative
to meal timing, thus improving adherence, compliance and quality of life compared with premixed human insulin [75]. The evidence of similar efficacy let adjust a reference price in order to lower the expenditures (Table 6, Table 7).

Table 6. Pharmacoeconomic calculations based on consumption of insulin in suggesting the human insulin price as the reference price in biphasic insulin and insulin analogues group in 2009

<table>
<thead>
<tr>
<th></th>
<th>Price For DDD</th>
<th>DDDs</th>
<th>Costs</th>
<th>Reference Price/DDD</th>
<th>Cost Using Reference Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biphasic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isophane*</td>
<td>2,90</td>
<td>4.012,50</td>
<td>11.619,13</td>
<td>2,90</td>
<td>11.619,13</td>
</tr>
<tr>
<td>Lispro*</td>
<td>3,51</td>
<td>2.656.162,50</td>
<td>9.310.094,40</td>
<td>2,90</td>
<td>7.691.538,29</td>
</tr>
<tr>
<td>Aspart*</td>
<td>4,09</td>
<td>3.626.250,00</td>
<td>14.825.077,00</td>
<td>2,90</td>
<td>10.500.653,00</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>6.286.425,00</td>
<td>24.146.790,53</td>
<td></td>
<td>18.203.810,42</td>
</tr>
<tr>
<td>Saved Money</td>
<td></td>
<td></td>
<td>5.942.980,11</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 7. Pharmacoeconomic calculations based on consumption of insulin in suggesting the lowest price of insulin analogues as the reference price in biphasic insulin and insulin analogues group in 2009

<table>
<thead>
<tr>
<th></th>
<th>Price For DDD</th>
<th>DDDs</th>
<th>Costs</th>
<th>Reference Price/DDD</th>
<th>Cost Using Reference Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biphasic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isophane*</td>
<td>2,90</td>
<td>4.012,50</td>
<td>11.619,13</td>
<td>2,90</td>
<td>11.636,25</td>
</tr>
<tr>
<td>Lispro*</td>
<td>3,51</td>
<td>2.656.162,50</td>
<td>9.310.094,40</td>
<td>3,51</td>
<td>9.310.094,40</td>
</tr>
<tr>
<td>Aspart*</td>
<td>4,09</td>
<td>3.626.250,00</td>
<td>14.825.077,00</td>
<td>3,51</td>
<td>12.710.340,51</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>6.286.425,00</td>
<td>24.146.790,53</td>
<td></td>
<td>22.032.071,16</td>
</tr>
<tr>
<td>Saved Money</td>
<td></td>
<td></td>
<td>2.114.719,37</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The estimations showed if the reference price would be adjusted according to human insulin price (2.90 LTL/DDD), the expenses of biphasic insulin would decrease by 24.6% ( LTL 5.943 million). If the reference price would be taken according to the lowest price of insulin analogue, it would be possible to save LTL 2.115 million (8.76%).

Short-acting insulin took 23% - 10.754mln Lt of all expenditures for insulins. Estimations have shown that expenses per DDD in the group of short-acting insulin ranged from 2.63 LTL/DDD for human insulin to 4.09 LTL/DDD for insulin aspart in Lithuania in 2009 (Figure 21).

According to the newest (2009) meta-analysis study [76] about insulin analogues, that included 68 randomized controlled trials in the analysis of rapid-acting insulin analogues, in terms of hemoglobin A1c, it was found minimal differences between rapid-acting insulin analogues and regular human insulin in adults with type 1 diabetes. There were observed similar outcomes among patients with type 2 diabetes. However there were insufficient data to determine whether insulin
analogues are better than conventional insulins in reducing long-term diabetes-related complications or death.

Figure 21. Dynamics of costs per DDD by Litas (LTL/DDD) for certain substance in short-acting insulin group in Lithuania, 2009

**Preparations contain just soluble form of the substance.

To date, reviews of insulin analog studies have not found a dramatic overall improvement in glycosylated hemoglobin (HbA1c) outcomes compared to traditional human insulins, this is the reason to reduce the expenses by considering the human insulin price as a reference price (Table 8). However, insulin analogs have been shown in many instances to be associated with lower risks of hypoglycemia, lower levels of postprandial glucose excursions and better patient adherence [77]. It should be considerate in taking the lowest price of insulin analogues as the reference price (Table 9).

Table 8. Pharmacoeconomic calculations based on consumption of insulin in suggesting the human insulin price as the reference price in short-acting insulin and insulin analogues group in 2009
Table 9. Pharmacoeconomic calculations based on consumption of insulin in suggesting the lowest price of insulin analogues as the reference price in short-acting insulin and insulin analogues group in 2009.

<table>
<thead>
<tr>
<th></th>
<th>Price For DDD</th>
<th>DDDs</th>
<th>Costs</th>
<th>Reference Price/DDD</th>
<th>Cost Using Reference Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-Acting</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human**</td>
<td>2.63</td>
<td>124,125.00</td>
<td>326,860.20</td>
<td>2.63</td>
<td>326,448.75</td>
</tr>
<tr>
<td>Lispro**</td>
<td>3.60</td>
<td>792,742.50</td>
<td>2,855,204.47</td>
<td>3.60</td>
<td>2,855,204.47</td>
</tr>
<tr>
<td>Glulisine**</td>
<td>3.61</td>
<td>521,700.00</td>
<td>1,885,239.92</td>
<td>3.60</td>
<td>1,878,996.24</td>
</tr>
<tr>
<td>Aspart**</td>
<td>4.09</td>
<td>1,390,987.50</td>
<td>5,686,727.83</td>
<td>3.60</td>
<td>5,009,891.27</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>2,829,555.00</td>
<td>10,754,032.42</td>
<td></td>
<td>10,070,540.73</td>
</tr>
<tr>
<td><strong>Saved Money</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>683,491.69</td>
</tr>
</tbody>
</table>

The financial analyses have shown that the equalization of short-acting prices would also bring a huge financial benefit. Taking 2.63 LTL/DDD as a reference price would influence the decrease of the total expenses by 3.303mln Lt. 683 thousand would be saved by taking 3.60 LTL/DDD – the lowest price of insulin analogue – as a reference price in 2009.

There has been just human insulin in the group of intermediate-acting insulin till the year of 2009, the average DDD price was 2.97 LTL/DDD in 2009. Now it is possible to obtain insulin lispro in form of protamine (3.71 LTL/DDD) (Figure 22). This is a new preparation in the market, so there are not enough clinical trials done to compare their efficacy, therefore we can not adjust a reference price in this group of insulin.

![Figure 22. Dynamics of costs per DDD by Litas (LTL/DDD) for certain substance in intermediate-acting insulin group in Lithuania, 2009](image)

***Insulin lispro is in the form of protamine in these preparations.
****Human insulin group includes Humulin N and Protaphane insulin.

In conclusion, reference pricing would influence the huge reduction of the total expenses.
for insulins. Small corrections for one DDD prices would give extremely big money savings in general. During one year (2009) period, it could be saved from LTL 14.125 million to LTL 7.677 million (Table 10, Table 11).

Table 10. Comparison between total expenditures for insulins

<table>
<thead>
<tr>
<th></th>
<th>Expenditures 2009</th>
<th>Expenditures with reference pricing</th>
<th>Saved money</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long- acting insulin</td>
<td>10.245.335,63</td>
<td>5.366.604,38</td>
<td>4.878.731,25</td>
</tr>
<tr>
<td>Biphasic* insulin</td>
<td>24.146.790,53</td>
<td>18.203.810,42</td>
<td>5.942.980,11</td>
</tr>
<tr>
<td>Short- acting* insulin</td>
<td>10.754.032,42</td>
<td>7.451.109,07</td>
<td>3.302.923,35</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>45.146.158,58</td>
<td>31.021.523,86</td>
<td>14.124.634,71</td>
</tr>
</tbody>
</table>

* Pharmacoeconomic calculations based on consumption of insulin in suggesting human insulin prices as the reference prices in some groups of insulin.

Table 11. Comparison between total expenditures for insulins

<table>
<thead>
<tr>
<th></th>
<th>Expenditures 2009</th>
<th>Expenditures with reference pricing</th>
<th>Saved money</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long- acting insulin</td>
<td>10.245.335,63</td>
<td>5.366.604,38</td>
<td>4.878.731,25</td>
</tr>
<tr>
<td>Biphasic** insulin</td>
<td>24.146.790,53</td>
<td>22.032.071,16</td>
<td>2.114.719,37</td>
</tr>
<tr>
<td>Short- acting** insulin</td>
<td>10.754.032,42</td>
<td>10.070.540,73</td>
<td>683.491,69</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>45.146.158,58</td>
<td>37.469.216,26</td>
<td>7.676.942,32</td>
</tr>
</tbody>
</table>

** Pharmacoeconomic calculations based on consumption of insulin in suggesting the lowest price of insulin analogues as the reference prices in some groups of insulin.

5.2.2. Reference price for oral antidiabetic agents

The financial analysis of antidiabetic agents showed that the sum of money spent on these medications was LTL 23.115 million in Lithuania in 2009 (Figure 7). The biggest part of total expenditures 40% took sulphonylureas and 29 % - biguanides (Figure 23). The average price paid for certain group of antidiabetics verify in a wide range (Figure 24). The biggest expenses for one DDD belong to new agent Sitagliptin (7.27 LTL/DDD) and thiazolidinediones (5.01 LTL/DDD). The least ones are taken by biguanides 0.70 LTL/DDD and sulphonylureas 0.77 LTL/DDD in 2009.
According to the data given by „Systematic Review: Comparative Effectiveness and Safety of Oral Medications for Type 2 Diabetes Mellitus“ [78], which included 216 controlled trials and cohort studies and 2 systematic reviews, summarized all available head-to-head comparisons, compared with newer, more expensive agents (thiazolidinediones, α-glucosidase inhibitors, and meglitinides), older agents (second-generation sulfonylureas and metformin) have similar or superior effects on glycemic control (absolute decrease in hemoglobin A1c level of about 1 percentage point) and other cardiovascular risk factors (blood pressure, lipid levels, and body weight). Each oral diabetes agent is associated with adverse events that counterbalance its benefits. Overall, metformin seemed to have the best profile of benefit to risk. Large, long-term comparative
studies on major clinical end points, such as myocardial infarction, chronic kidney disease, and cardiovascular mortality, are needed to determine definitively the comparative effects of the oral diabetes agents. New agent Sitagliptin was not included into this systematic review.

According to review, metformin, which is the sheapest – 0.70Lt/DDD, have the best profile of benefit to risk, meanwhile thiazolidinediones, the one of the most expensive oral antidiabetics – 5.01 LTL/DDD have even more cautions for using them than others. In order to rationalize the expenses for oral antihyperglycemics, there should be considered to use reference pricing (Table 12).

Table 12. Pharmacoeconomic calculations based on consumption of oral antidiabetic agents in suggesting price of Metformin as the reference price in oral antidiabetics group (excl.Sitagliptin) in 2009

<table>
<thead>
<tr>
<th></th>
<th>Price For DDD</th>
<th>DDDs</th>
<th>Costs</th>
<th>Referenced Price/DDD</th>
<th>Cost Using Reference Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biguanides</td>
<td>0,70</td>
<td>9.652.079,50</td>
<td>6.756.455,65</td>
<td>0,70</td>
<td>6.756.455,65</td>
</tr>
<tr>
<td>Sulphonylueas</td>
<td>0,77</td>
<td>12.133.832,14</td>
<td>9.343.050,75</td>
<td>0,70</td>
<td>8.493.682,50</td>
</tr>
<tr>
<td>Glinides</td>
<td>2,47</td>
<td>77.985,00</td>
<td>192.622,95</td>
<td>0,70</td>
<td>54.589,50</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>5,01</td>
<td>906.000,67</td>
<td>4.539.063,34</td>
<td>0,70</td>
<td>634.200,47</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>22.769.897,31</td>
<td>20.831.192,69</td>
<td></td>
<td>15.938.928,12</td>
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<tr>
<td>Saved money</td>
<td></td>
<td></td>
<td>4.892.264,57</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 12 illustrates a hude money saving- LTL 4.892 million in 2009, if reference pricing would be adjusted to oral antidiabetic agents.

According to data available, there are seen sharp differences of one DDD price among medications in the group of sulphonylureas. It verify from 0.08 LTL/DDD for glibenclamide to 1.17 LTL/DDD for glipizide (Figure 25). According to NICE guidelines [51], therapeutic efficacy of these medications is almost equal, there can be prescribed to a patient any of sulthonylureas, but not glibenclamide. Glibenclamide, a long-acting sulphonylurea, is associated with a greater risk of hypoglycaemia, though according comparative trials all second- generation sulphonylureas had similar reduction in hemoglobin A1c [78,79,80]. Therefore it is possible to adjust a reference price (Table 13).
Figure 25. Dynamics of costs per DDD by Litas (LTL/DDD) for sulphonylureas by substances in Lithuania, 2009

Table 13. Pharmacoeconomic calculations based on consumption of oral antidiabetic agents in suggesting the lowest price of sulphonylureas (Not Glibenclamide) as the reference price in 2008-2009

<table>
<thead>
<tr>
<th>2009</th>
<th>Price For</th>
<th>DDDs</th>
<th>Costs</th>
<th>Referenced</th>
<th>Cost Using</th>
<th>Cost Using</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DDD</td>
<td></td>
<td></td>
<td>Price/DDD</td>
<td>Referenced</td>
<td>Referenced</td>
</tr>
<tr>
<td>Glibenclamide</td>
<td>0,08</td>
<td>15.257,14</td>
<td>1.295,84</td>
<td>0,08</td>
<td>1.295,84</td>
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</tr>
<tr>
<td>Glimepiride</td>
<td>0,58</td>
<td>4.433.775,00</td>
<td>2.561.632,35</td>
<td>0,58</td>
<td>2.561.632,35</td>
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</tr>
<tr>
<td>Gliclazide</td>
<td>0,85</td>
<td>6.753.900,00</td>
<td>5.730.207,82</td>
<td>0,58</td>
<td>3.902.094,43</td>
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</tr>
<tr>
<td>Gliquidone</td>
<td>1,05</td>
<td>121.080,00</td>
<td>126.891,84</td>
<td>0,58</td>
<td>69.954,48</td>
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<tr>
<td>Glipizide</td>
<td>1,17</td>
<td>809.820,00</td>
<td>949.733,64</td>
<td>0,58</td>
<td>467.876,95</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>12.133.832,14</td>
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<td>7.002.854,05</td>
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<table>
<thead>
<tr>
<th>2008</th>
<th>Price For</th>
<th>DDDs</th>
<th>Costs</th>
<th>Referenced</th>
<th>Cost Using</th>
<th>Cost Using</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DDD</td>
<td></td>
<td></td>
<td>Price/DDD</td>
<td>Referenced</td>
<td>Referenced</td>
</tr>
<tr>
<td>Glibenclamide</td>
<td>0,08</td>
<td>82.457,14</td>
<td>7.003,36</td>
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<td>7.003,36</td>
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</tr>
<tr>
<td>Gliclazide</td>
<td>0,91</td>
<td>6.566.465,00</td>
<td>5.946.545,18</td>
<td>0,91</td>
<td>5.946.545,18</td>
<td></td>
</tr>
<tr>
<td>Glimepiride</td>
<td>0,97</td>
<td>4.541.700,00</td>
<td>4.382.926,11</td>
<td>0,91</td>
<td>4.112.932,03</td>
<td></td>
</tr>
<tr>
<td>Gliquidone</td>
<td>1,05</td>
<td>130.140,00</td>
<td>136.386,72</td>
<td>0,91</td>
<td>117.853,88</td>
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</tr>
<tr>
<td>Glipizide</td>
<td>1,18</td>
<td>804.600,00</td>
<td>948.102,74</td>
<td>0,91</td>
<td>728.640,18</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>12.125.362,14</td>
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<td></td>
<td></td>
<td>10.912.974,63</td>
</tr>
<tr>
<td>Saved Money</td>
<td></td>
<td>2.510.801,48</td>
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</tbody>
</table>

The assessment of reference price shows possible LTL 2.367 million saving in 2009, if the reference price would have been the lowest price of sulphonylureas but not glibenclamide.
6. DISCUSSION

High prevalence of diabetes and inadequate use of antidiabetics

Diabetes is one of the most common non-communicable diseases globally with high morbidity and co-morbidity and economic costs. According to Diabetes Atlas [1], it is estimated that the world prevalence of diabetes among adults (aged 20–79 years) is 6.6%, affecting 285 million adults, in 2010. In European Region prevalence of diabetes is much higher- 8.6% and there exists a great diversity of it among the 54 countries and territories. Moreover, it is disappointing that the morbidity of diabetes in Lithuania is one of the highest rates in Europe, as only ten countries (out of 54) had higher values. There are 239,800 people, who suffer from diabetes in Lithuania, it tally with 9.7% of all population. Diabetes prevalence is increasing for a number of reasons: a true increase in incidence (aging population, increased obesity and sedentary life style), increased diagnosis (case finding, better patient education) and increasing life expectancy after diagnosis [81].

Contrary, our study shows that the consumption of antidiabetic drugs in Lithuania has been very low compared to other countries, [82, 83, 84], see Figure 26. This is the first study providing information on antidiabetic drug consumption in Lithuania in a 4-year period (2006–2009). Since 2006, the total hyperglycemia lowering drug consumption increased by 33.33% reaching the value of 28.72 DDDs/1000 inhabitants/day. In fact, the results of the similar studies in other countries also indicate the increased use of antidiabetic agents. However, in comparison with these reports, despite the observed increase the consumption of antidiabetics in Lithuania is still low. It could be explained by the tendency towards diabetes, especially type 2, to be under-recognized and under-treated until the first evidence of complications occurs. Evidence supporting the benefit of tight control of blood glucose in reducing complications in type 1 and type 2 diabetes should lead to initiatives to improve the management of diabetes in Lithuania. Together with the increase in prevalence, these might increase the use of hypoglycaemic medicines.
Growing consumption of antidiabetic drugs

The estimations showed that consumptions of insulins have increased by 30% (2.18 DDD/TID) reaching the value of 9.43 DDD/TID, likewise the consumption of oral anti-diabetics have risen by 35.1% (5 DDD/TID) reaching the value of 19.29 DDD/TID (2009) (Figure 5). The total increase in oral antidiabetic agents was two times higher than insulins.

The key finding is the increase in the use of all agents but especially metformin. The utilization has almost doubled and reached 8.21 DDD/TID during the study period (Figure 13). While most of the increased use of oral hypoglycaemic agents is simply due to an increased prevalence of type 2 diabetes, much of the rise for metformin is due to an early addition of metformin to newly diagnosed patients, especially overweight, intensified treatment of diagnosed patients by early addition of metformin to a sulphonylurea as a combination treatment, that improves HbA1c significantly [81]. This is the result of clinical guidelines [51, 66] that prefer metformin, as a first choice therapy in T2DM treatment and suggest using either a sulfonylurea or thiazolidinedione if metformin is not tolerated. Thiazolidinediones have more cautions for using and much higher DDD price than others, therefore there are two predominant groups of oral antidiabetic drugs in Lithuanian market: biguanides (43%) and sulphonylureas (52%).

This study demonstrated that utilization of human insulin has a tendency to decline.
During the four-year study period, the consumption of human insulin has decreased five times reaching the value of 0.54 DDD/TID, while the utilization of insulin analogues has increased by two times reaching the value of 8.89 DDD/TID in 2009 (Figure 9). The use of human insulin analogues produced synthetically by recombinant DNA technology is increasing rapidly and replacing the cheaper isophane and soluble insulins. It is a consequence of clinical trials characterizing insulin analogues as more flexible in injection timing, lower risks of hypoglycemia, improving adherence, compliance and quality of life compared with human insulins, though according to latest meta analysis data [72, 73, 76], insulin analogues did not produce any significant improvement of HbA1c, in comparison with human insulin. Insulin analogues have similar bioactivities to human insulin, though they are different in pharmacokinetics.

**Growing expenditures for antidiabetic drugs**

Pharmacoeconomic side of the study shows that a large amount of money is spent every year for antidiabetic agents. Moreover, expenses are increasing continually due to increasing consumption of hypoglycaemic medicines. In 2009, the sum of expenditures reached the value of LTL 70.5 million, two thirds of total expenses were for insulin, despite the fact that utilization of insulin was two times lower than oral antidiabetic drugs. Expenses for insulin were extremely increasing all the study period because of using more expensive insulin analogues instead of cheaper human insulin.

However, expenses for oral antidiabetic drugs did not show huge increase, conversely expenses declined by 6.4% during the last year. It was influenced by new generic agents with lower retail prices introduction to the market.

**Differences among costs per DDD**

Comparing the prices per DDD, extremely big differences are seen among costs per DDD for certain insulin group (Figure 19), price per DDD varied from 2.97 LTL/DDD to 5.67 LTL/DDD in 2009. Moreover there exists sharp discrepancy among costs per DDD for certain substance inside the insulin groups (Figure 20, Figure 21). The same observation was done among prices per DDD for oral antidiabetic agents (Figure 24), costs per DDD ranged from 0.70 LTL/DDD to 7.27 LTL/DDD.

The estimations also show that costs per DDD in Lithuania are higher compared to other countries, e.g. United Kingdom (Table 14). Key finding is that insulin analogues and new oral antidiabetic agents (thiazolidinediones, glinides and sitagliptin) have significantly lower retail prices in UK that in Lithuania. The price per DDD of the most expensive insulin analogues in Lithuania
insulin aspart is lesser by 19-23% (almost 1 LTL/DDD) in UK, moreover cost per DDD of new oral hypoglycemic agent Sitagliptin differs by 36% between these countries.

The high cost implication of hyperglycaemia lowering drugs leads to consider the cost-effectiveness of hypoglycaemic agent prescribing patterns. Especially that agents in different insulin and oral antidiabetic agent groups according to meta analysis and reviews [73, 76, 78, 79] data show the similar effectiveness and safety in therapy.

Table 14. Comparison of costs per DDD comparison between Lithuania and United Kingdom

<table>
<thead>
<tr>
<th>Insulins</th>
<th>LT/DDD (Lithuania)</th>
<th>LT/DDD (United Kingdom)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-acting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human</td>
<td>2,63</td>
<td>2,78</td>
</tr>
<tr>
<td>Aspart</td>
<td>4,09</td>
<td>3,15</td>
</tr>
<tr>
<td>Glulisine</td>
<td>3,61</td>
<td>2,75</td>
</tr>
<tr>
<td>Lispro</td>
<td>3,60</td>
<td>3,01</td>
</tr>
<tr>
<td>Intermediate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human</td>
<td>2,97</td>
<td>2,87</td>
</tr>
<tr>
<td>Biphasic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human</td>
<td>2,90</td>
<td>1,99</td>
</tr>
<tr>
<td>Aspart</td>
<td>4,09</td>
<td>3,33</td>
</tr>
<tr>
<td>Lispro</td>
<td>3,51</td>
<td>3,12</td>
</tr>
<tr>
<td>Long-acting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Detemir</td>
<td>5,69</td>
<td>4,38</td>
</tr>
<tr>
<td>Glargine</td>
<td>5,67</td>
<td>4,13</td>
</tr>
<tr>
<td>Oral agents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>5,23</td>
<td>4,01</td>
</tr>
<tr>
<td>Repaglinide</td>
<td>2,47</td>
<td>1,50</td>
</tr>
<tr>
<td>Rosiglitazone</td>
<td>4,50</td>
<td>3,66</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>7,27</td>
<td>4,64</td>
</tr>
</tbody>
</table>

^ Data available from British National Formulary [30].

The effect of reference-based pricing

Nowadays expenditures for reimbursement of medicines increase remarkably in Lithuania and other countries. Reference-based pricing limits reimbursement for a group of drugs with similar therapeutic application but different active ingredients to the price of the lowest-cost drug within the group (the reference standard). The goal of reference price seems to be the control of third-party expenditure on prescription drugs, not the limitation of overall pharmaceutical expenditure. The schemes of reference price were introduced in many European countries and well assessed [85].

Pharmaceutical reference prices are reimbursement ceilings set by payers that fully cover drugs up to the reference price. Above that level, patients or supplementary private insurance pays the difference between the reference price and the actual price. While most direct price-control
systems regulate selling prices product by product, reference pricing is based on the assumption that medications within a specific class are interchangeable and that a common reimbursement level can be established.

In the case of different co-payment, there is a discussion between doctor and patient, which medicine should be prescribed. During discussion patients often select a product which does not include co-payment unless they have a particular one that wants to use. Since doctors dislike discussing this, they frequently choose a product at or below the fixed level. This reimbursement mechanism is intended to make patients more aware of costs and to promote the rational use of ‘similar’ or interchangeable medicines [71].

Therefore, the cost-minimization analysis performed estimating the effect of reference-based pricing, accounting the reference price as the highest price to be spent for the particular drug in every class, allows more rational use of financial resources of national health system for diabetes treatment.

According to the data of this paper, the biggest savings could be made using the lowest price of the certain substance for insulins and oral antidiabetic agents as the reference price. Setting human insulin price for biphasic and short-acting insulin groups and intermediate-acting insulin price for long-acting insulins as a reference prices, it would be possible to reduce the total cost of insulins by 30% saving LTL 14 million (Table 10, Table 15). Choosing biguanides price as a reference price for oral antidiabetic drugs, it would be possible to decline the expenses for oral hypoglycaemic agents by 21% saving almost LTL 5 million (Table 12, Table 15). Consequently, it is estimated the possible total savings of LTL 19 million is lowering the total expenses by 27% (Table 15).

Table 15. Total expenses and possible money saving in Lithuania in 2009

<table>
<thead>
<tr>
<th></th>
<th>Total expenses in 2009 (Lt)</th>
<th>Expenses with reference price (Lt)</th>
<th>Money saving (Lt)</th>
<th>Money saving (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulins</td>
<td>47.415.488,65</td>
<td>33.290.853,94</td>
<td>14.124.634,71</td>
<td>29,79</td>
</tr>
<tr>
<td>Oral antidiabetics</td>
<td>23.115.382,61</td>
<td>18.223.118,04</td>
<td>4.892.264,57</td>
<td>21,16</td>
</tr>
<tr>
<td>Total</td>
<td>70.530.871,26</td>
<td>51.513.971,97</td>
<td>19.016.899,29</td>
<td>26,96</td>
</tr>
</tbody>
</table>

Considering reference-based pricing, it is possible to lower the treatment costs maintaining similar therapeutic effect of the drug. These results of cost-minimization analysis based on antidiabetic drug reference price limitation may have important implications for the cost effectiveness of the treatment of diabetes.
7. CONCLUSIONS

1. Total consumption of hypoglycaemic drugs (including insulins) increased by 33.33% from 21.54 DDD/TID in 2006 to 28.72 DDD/TID in 2009 over the four-year period.

2. Increase of utilization of oral antidiabetic drugs was higher in comparison with increase of insulins’ 35% versus 30%, accordingly from 14.29 DDD/TID in 2006 till 19.29 DDD/TID in 2009 versus 7.25 DDD/TID in 2006 to 9.43 DDDD/TID in 2009.

3. Consumption of antidiabetic drugs in Lithuania is low, despite the fact that the prevalence of Diabetes Mellitus is high comparing to other EU countries.

4. Total expenditures for hypoglycaemic drugs (including insulins) increased by 23.4% from LTL 57.138 million in 2006 to LTL 70.531 million in 2009. Expenses for insulin increased by 32% from LTL 35.931 million in 2006 to LTL 47.415 million in 2009 and took two thirds of total expenditures. Expenses for oral antidiabetic drugs increased by 16.5% from LTL 21.208 million in 2006 to LTL 24.698 million in 2008 and declined by 6.4% to LTL 23.115 million in 2009.

5. Performed cost-minimization analysis using the reference-based pricing estimated the possible reduction of total antidiabetic drug expenditures by 27% (saving LTL 19 million), whereas the possible reduction of insulin and oral antidiabetic drugs expenses was estimated to be LTL 14 million and almost LTL 5 million, respectively.
8. SUMMARY

Pharmacoepidemiological study and costs analysis of oral antidiabetic drugs and insulins in Lithuania on 2006-2009 year

Objective: To perform pharmacoepidemiological study of the use of oral antidiabetic drugs and insulins in Lithuania on 2006-2009 year and cost-minimization and reference price analysis enabling more rational use of financial resources of national health system.

Material ans methods: The search for all literature relating to pharmacokinetic and pharmacodynamic characteristics of drugs for diabetes mellitus was done in MEDLINE database. The data on total sales of oral antidiabetic drugs and insulins in Lithuania over a four-year period (2006-2009) were obtained from Sofdent, Lithuania data base. Drugs were classified according to the Anatomic Therapeutic Chemical system. Data were calculated by DDD methodology and expressed in DDDs per 1000 inhabitants per day (DDD/TID). Calculations of drug prices and total expenditures for antidiabetic drugs were made by using retail prices from the National Patient Funds Price List on 2006-2009 years. Pharmacoeconomic calculations were done according to cost minimization and reference price methodologies.

Results: The total consumption of hypoglycaemic drugs (incl. insulins) increased by 33.33% from 21.54 DDD/TID in 2006 to 28.72 DDD/TID in 2009. The utilization of insulin increased by 30% reaching the value of 9.43 DDD/TID, similarly the utilization of oral antidiabetic drugs increased by 35% reaching the value of 19.29 DDD/TID in 2009. In comparison with antidiabetic drug consumption in other countries, this meaning was about two-three times lower in Lithuania, despite the fact that the prevalence of diabetes is one of the highest rates in European region. The total expenditures for hypoglycaemic drugs (incl. insulins) increased by 23.4% reaching the value of LTL 70.531 million in 2009. Performed cost-minimization analysis using the reference-based pricing estimated the possible reduction of total antidiabetic drug expenditures by 27% (saving LTL 19 million), whereas the possible reduction of insulin and oral antidiabetic drugs expenses was estimated to be LTL 14 million and almost LTL 5 million, respectively.

Conclusions: The findings suggest that the utilization of oral antidiabetic drugs and insulins is likely to increase in Lithuania. In comparison with the data in other countries, the consumption of these drugs in Lithuania is low and prices per DDD are high. Considering the similar efficacy and safety within drug classes, new prices for antidiabetic drugs should be discussed that could help to rationalize financial resources of national health system.
9. SANTRAUKA

Geriamųjų antidiabetinių vaistų ir insulinų farmakoepidemiologinis tyrimas ir farmakoekonominė analizė Lietuvoje 2006-2009 metais

Tikslai: Įvertinti geriamųjų antidiabetinių vaistų ir insulinų suvartojimo tendencijas Lietuvoje 2006–2009 m. ir atlikti farmakoekonominę analizę kaštų mažinimo ir referentinės kainos metodu siekiant racionaliai panaudoti sveikatos apsaugos lėšas cukriniam diabetui gydyti.


Išvados: Skaičiavimai leidžia teigti, jog geriamųjų antidiabetinių vaistų ir insulinų suvartojimas nuolat didėja. Lyginant su kitų šalių duomenimis, antidiabetinių vaistų suvartojimas Lietuvoje yra mažas, o DDD kainos yra aukštos. Atsižvelgiant į panašų antidiabetinių vaistų farmakoterapiinių grupių efektyvumą ir saugumą, remiantis farmakoekonominiais paskaičiavimais galėtų būti nustatytos naujos antidiabetinių vaistų kainos, o tai leistų racionaliau panaudoti sveikatos apsaugai skiriamas lėšas.
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