CHARLES UNIVERSITY IN PRAGUE
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Department of Social and Clinical Pharmacy

MASTER IN PHARMACY

Diploma Thesis:

The analysis of pharmacotherapy by patients suffering with DM in Greece I.

Tutor

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January 2015 *Georgios Kalaitzidis*

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Hradec Kralove, 26/01/2014 Georgios Kalaitzidis

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Abstrakt

Analýza farmakoterapie od pacientů s DM v Řecku I

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Úvod: Diabetes mellitus v rozvinutých zemích postihuje asi 11% populace ve věku starším 70let a příčinou úmrtí v celé populace je asi ve 3%.

Cíl: Cílem bylo analyzovat farmakoterapii nemocných s diabetem mellitus II v malém řeckém městě Veria.

Metoda: Jde o retrospektivní průřezovou studii prováděnou v lékárně malého řeckého města Veria. Do studie bylo zahrnuto 60 pacientů, u kterých byl diagnostikován diabetes mellitus II. Data byla získána pomocí dotazníku, který respondenti vyplňovali sami.

Výsledky: Průměrný věk testovaných osob byl 56.5±17.5 let. Ženy byly v převaze (n=40). Většina respondentů znala svou hladinu glukózy v krvi (93.3%,n=56). Z pacientů, kteří znali svou hladinu glukózy, mělo 36 (64.3%) vysokou hladinu glukózy a 20 (35.7%) fyziologická hladina glukózy. Ze všech pacientů (n=60) navštěvovali někteří lékaře každých šest měsíců (n=24) nebo každé tři měsíce (n=20), zatímco někteří jej navštívili každý měsíc (n=8) a jiní po více než šesti měsících (n=8). Více než 50% pacientů si měřilo hladinu glukózy v krvi během minulého měsíce (n=36), někteří před třemi měsíci (n=20) a čtyři pacienti před šesti měsíci. Ze všech 60 osob si někteří měřili hodnotu glykémie sami (n=16), většina navštívila farmaceuta (n=28) a někteří lékaře (n=16). Pacienti byli nejčastěji léčeni monoterapi nebo kombinovane terapii spolu nebo s jinymi antidiabetiky inzulinem (52%) a metforminem (32%). Zhruba třetina (36.7%) pila každý den sklenici vína a 80% podpořilo léčbu dietním režimem. Pacienti, kteří užívali léky dle doporučení lékaře (p: 0.003, OR: 4.923, 95%CI: 0.978-24.789) měli 4.9 krát větší pravděpodobnost, že budou mít optimálnější glykémii než ti, kteří doporučení lékaře nerespektovali.

30% respondentů také trpělo dalšími potížemi, které zhoršily jejich diabetes mellitus.

Závěr: Jde o pilotní studii. V ní se ukázalo, že většina pacientů zná glykémii, glykémii si měří také v lékárně nebo sami doma. Asi třetina pacientů však přehlíží nezbytnost pravidelné léčby. Nutno též ověřit v terapii diabetu mellitus II celkem nedostatečné užívání metfominu a časté užívání inzulinem v monoterapii.

Abstract

The analysis of pharmacotherapy by patients suffering with DM in Greece I

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Introduction: The diabetes in developed countries concerns 11% of people over 70 years and is the cause of 3% of total deaths in general population.

Aim: The aim of the study was to assess the Pharmacotherapy of Diabetes mellitus type II in a pharmacy of a small town of Greece, Veria.

Methods: It is retrospective cross-sectional study, which was conducted in a pharmacy in a small town of Greece, Veria. The study population consists of 60 patients with known Type II diabetes Melitus. The data collection was performed by a self-reported questionnaire, which was created and developed by the researcher and filled by the respondents.

Results: The mean age of the sample was 56.5±17.5 years. Most of them were females (n=40). Most of the patients knew their fasting glucose level (93.3%,n=56).Of the patients who knew their fasting glucose level, 36 (64.3%) patients had high fasting glucose level and 20 (35.7%) had physiological fasting glucose level. From all the patiens(n=60), some of them visited their physician every 6 months (n=24), and every 3 months (n=20) while some others visited their physician every month(n=8) and some of them longer than 6 months(n=8). Also, above 50% of the patients measured their blood glucose level during the last month (n=36), few measured it 3 months before (n=20) and four patients 6 months before. From the 60 patients, some of them had their glycaemia measured by their selves (n=16), the majority of them by the pharmacist (n=28)

and some of them by the physician (n=16). Patients used mainly insulin (52%) and metformin (32%) as monotherapy or in combination therapy together or with other antidiabetic agents. About one third of patients (36.7%) drank a glass of wine every day and 80% support that food intake plays a role in treatment of the diabetes mellitus. Patients who use their drugs according advice of physician (p:0.003, OR:4.923, 95%CI:0.978-24.789) have 4.9 more chances to have optimum levels of glycaemia than patients who do not use their drugs according advice of physician.Also 30% of the patients suffered by comorbidities which increased the diabetes mellitus II complications.

Conclusions: With regard to the pilot study. It turned out that most of the patients knows the blood glucose, blood glucose is measured also in the pharmacy or by self-monitoring. About a third of the patients, however, overlook the need for regular treatment. Should also be verified in the therapy of diabetes mellitus II total insufficient use of metfomin and the frequent use of insulin in monotherapy

Introduction

The present dissertation tries to describe how the Greeks manage their type II diabetes mellitus and especially which are the drugs they consume in order to regulate their blood sugar levels. The present study consists of 5 chapters. The first chapter includes the theoretical framework of diabetes mellitus and begins with the definition and classification of diabetes mellitus. Moreover, the epidemiology, the pathogenesis and the clinical presentation of diabetes mellitus is presented. This chapter, also, makes particular reference to the treatment of diabetes, especially in drugs that are administered to these patients.

The second chapter describes the aim of the study. The third chapter analyzes the sample, the study design and the statistical methods that were used to analyze the data of patients. The fourth chapter outlines the results of the study, which are presented by figures and tables.

Finally, the fifth chapter explains the results of the study in relation to the culture of the Greek population and the politics of Greece. This chapter finishes with the conclusions of the dissertation.

1.1 Definition and classification

Diabetes mellitus (DM) is the most common metabolic disease in the world and one of the main causes of mortality and morbidity, not only in developed countries but also in developing countries. According to the World Health Organization (WHO), the DM is defined internationally as "a metabolic disorder of multiple etiology, characterized by chronic hyperglycemia due disturbances in the metabolism of carbohydrates, fats and proteins, as a result of inadequate secretion or insulin action or both of them. Chronic hyperglycemia leads to long-term damage, dysfunction and failure of various organs, especially the eyes, kidneys, nerves, blood vessels and heart (Alberti & Zimmet, 1998). Diabetes is a condition that is defined primarily by the level of hyperglycemia leading to increased risk of macrovascular and microvascular complications lesions. It is a strong risk factor for the occurrence of several chronic diseases, for early mortality, significant morbidity and deterioration of quality of life (WHO, 2006). Moreover, diabetes increases the risk of renal failure, cataracts, delayed blindness, amputations of the lower limbs, peripheral neuropathy and also leads to increased incidence of cardiovascular episodes of poor prognosis (Bloomgarden, 2002).

So, diabetes mellitus is a range of metabolic disorders characterized by chronic increase in blood glucose levels (hyperglycemia), which arises as a result of inadequate secretion and / or insulin action. This condition may be accompanied by various metabolic disorders of carbohydrates, proteins and fats. The severity of the various clinical manifestations of diabetes depends on the underlying cause, the extent of the deficit of insulin action, coexisting disease and the extent of tissue damage diabetic etiology. The morbidity and mortality of diabetic patients are due fortiori to vascular causes (Levene & Donnelly, 2011).

The classification of diabetes mellitus has been done by the World Health Organization. The American Diabetes Association has reviewed the diagnostic criteria for classification of diabetes mellitus and recommended changes in 1997, which were subsequently accepted by the World Health Organization (Report of the expert Committee, 2002, WHO, 1999).

The terms type 1 diabetes and type 2 diabetes, replaced the old categories of insulin (IDDM) and non- insulin dependent (NIDDM) diabetes. The old classification criterion was the treatment (many patients with non- insulin dependent diabetes treated with insulin, however), but did not indicate the nature of the underlying disorder (Wroe, 1997).

Diabetes Type 1 is characterized by destruction of the beta cells of the pancreas, which are responsible for insulin production, causing absolute or relative insulin poverty. The destruction of beta cells is autoimmune origin and greater percentage of patients with type 1 diabetes are detected in the circulation of one or more types of autoantibodies, and these patients have an increased susceptibility to other autoimmune diseases. But generally considered that there is a genetic substrate on which are interfered various environmental and immunological factors or even some viruses to manifest diabetes.

Diabetes mellitus type 2 is characterized by relative insulin deficiency and insulin resistance. Firstly, there are normal or elevated insulin levels.

Gestational diabetes concerns women during pregnancy who have high blood glucose levels. Gestational diabetes affects about 4% of all pregnant women.

Diabetes Type MODY (Maturity-Onset Diabetes of the Young) includes various forms of diabetes due to genetic abnormalities in the functioning of pancreatic beta - cells (decreased insulin secretion). Usually manifests as mild hyperglycemia at an early age, and usually inherited in an autosomal dominant manner (Giuffrida & Reis, 2005).
Secondary Diabetes: represents only 1-2 % of patients with diabetes and is caused by:

- Cystic fibrosis, chronic pancreatitis, pancreatectomized, pancreatic cancer.
- Syndrome Cushing, acromegaly, thyrotoxicosis, pheochromocytoma, glucagonoma.
- Medications that cause secondary diabetes, such as: theiaidika diuretics, corticosteroids, atypical antipsychotics, antiretroviral protease inhibitors.
- Congenital lipodystrophy

- Acanthosis nigricans and
- Genetic factors eg syndrome Wolfram (which is also known as DIDMOAD: diabetes insipidus, diabetes mellitus, optic atrophy and deafness), (Barrett et al., 1997), ataxia of Friedreich, myotonic dystrophy, hemochromatosis and glycogen storage diseases (Tidy, 2011).

The main clinical type is DM type II (non -insulin dependent) corresponding to about 80-90% of all cases (Kawano et al., 1999). This type is more common in middle-aged and elderly. The cause o DM II is a combination of resistance to insulin action and inadequate compensatory secretion of insulin from the beta cells of the pancreas (Ryden et al., 2007). In this category a degree of hyperglycemia which can cause pathologic and functional changes in various target tissues, but without clinical symptoms, may there be for a long time before diabetes is detected. During this asymptomatic period, it may be possible to be detected an abnormality in the metabolism of carbohydrates, measuring the plasma glucose levels in the fasting state or after challenge with oral glucose.

The criteria for the diagnosis of diabetes according to the ADA are the follows (ADA, 2007):

1. Symptoms of diabetes and a random measure of blood glucose levels ≥ 200mg/dl (≥11.1mmol/l). The term “random” is defined as any time of day, regardless of how much time has passed since the last meal. Symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.
2. or fasting blood glucose levels ≥ 126mg/dl (≥ 7mmol/l). “Fasting” is defined as non food intake for more than 8 hours.
3. or blood glucose levels at 2 hours≥200mg/dl (≥ 11.1mmol/l) during glucose tolerance test (Oral Glucose Tolerance Test, OGTT). The test must be performed as described by WHO, using anhydrous glucose dissolved in water (75gr).

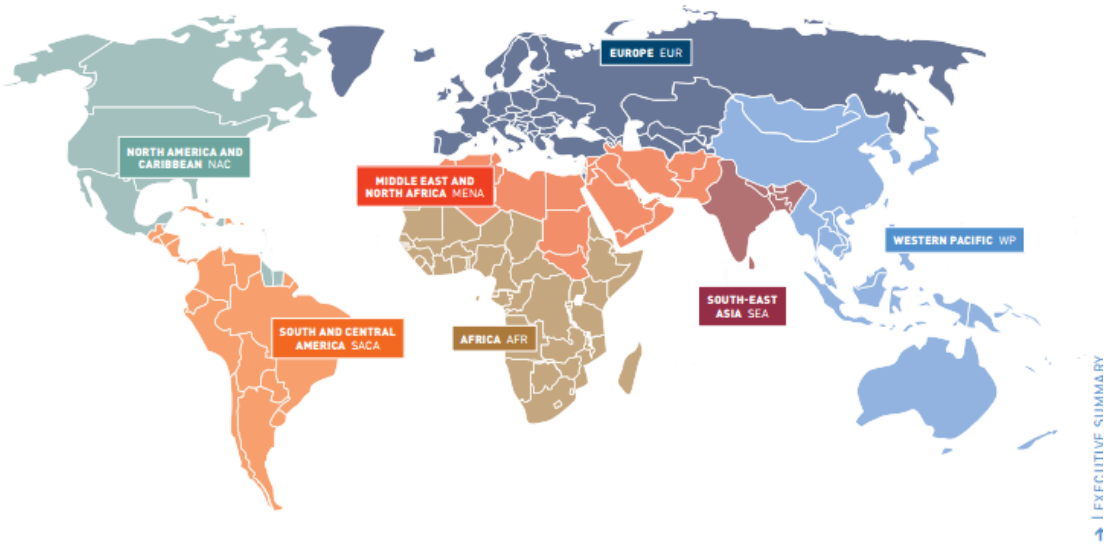
WHO and International Diabetes Federation (IDF) includes only 2 and 3 of the ADA`s diagnostic criteria (WHO, 2006).

1.2 Epidemiology

Although DM is found worldwide, it is more common in developed countries. The diabetes in developed countries concerns 11% of people over 70 years and is the cause of 3% of total deaths in general population. The rate of increase of diabetes is such that it is considered by many researchers and clinicians as pandemic. The greatest increase in prevalence of DM II is expected in Asia and Africa by 2030. The increasing incidence of diabetes in developing countries follows the trend of urbanization and migration lifestyle, and perhaps most importantly, the "western diet" pattern. This suggests that there is an environmental (dietary) effect on the pathogenesis of the disease, without the mechanism to be clear at present (Wild et al., 2004).

The WHO predicts a significant increase incidence of diabetes, especially type II, in all countries. The disease is more common in women than men, and this difference is most pronounced in developed countries. This was attributed to the fact that women have longer life expectancy than men. The IDF estimates that in the year 2007, 246 million people (the 6% of the world population) suffered from diabetes, while according to the WHO the year 2000 there were 171 million diabetics people worldwide, and the prospect was to reach 325 million by 2025 and 366 million by 2030 (Erkelens, 2001). However, according to the latest announcement of the IDF on the prevalence of DM in 2012, diabetic patients worldwide amounted to 371 million, with estimated global incidence of diabetes about 8.3% (see Figure 1) (IDF, 2012). The main reasons are the increase percentage of overweight and obesity people and the increasing trend of people to exercise less, over the years.

IDF Regions and global projections of the number of people with diabetes (20-79 years), 2013 and 2035



IDF REGION	2013 MILLIONS	2035 MILLIONS	INCREASE %
Africa	19.8	41.4	109%
Middle East and North Africa	34.6	67.9	96%
South-East Asia	72.1	123	71%
South and Central America	24.1	38.5	60%
Western Pacific	138.2	201.8	46%
North America and Caribbean	36.7	50.4	37%
Europe	56.3	68.9	22%
World	**381.8**	**591.9**	**55%**

Figure 1. World atlas for the prevalence of DM by IDF. http://www.idf.org/diabetesatlas/data-visualisations. Accessed February 2014.

In Greece about 6-7 % of the population suffers from known diabetes, while 5.4% have diabetes and they ignore it. According to WHO the number of diabetics patients in Greece in 2007 was 853.000 and is expected to reach 1.077.000 in 2025 (Alberti & Zimmet, 1998). About 20% of people over 60 years, mainly obese, suffer with diabetes type II, but 15-20% of them achieve the goal of glycemic control (Expert Committee on Diagnosis and Classification of Diabetes Mellitus, 2006) only. Also, in Greece about 400-500 young people annually under the age of 20 develops diabetes type I.

The prevalence of diabetes increases with age. The record of NHANES III (The Third National Health and Nutrition Examination Survey, 1988-1994)

showed that the 18-20% of the population over 65 years has diabetes and the 40% has either diabetes or impaired glucose tolerance (IGT) (Harris et al., 1998). It is very significant the fact that at least 50% of sufferers do not know that. In some countries this percentage reaches 80%. As the prevalence of diabetes is increasing, the morbidity and mortality due to diabetes are major issues of public health. The DM is one of the biggest modern medico-socio-economic problems.

1.3 Pathogenesis

The DM is considered as a multifactorial metabolic disease. Several pathogenetic mechanisms are responsible for DM. One of them is the genetically inherited autoimmune destruction of beta – cells pancreatic islets of Langerhans, leading to partial or total insulinopenia. This concerns mainly diabetes type I and exists until the inability of the body to properly use the insulin, which is produced endogenously due to insulin resistance, which after a long of time leads to insulinopenia and finally to diabetes type II (UKPDS group, 1998).

The main cause of diabetes is dysfunction of beta cells of the pancreas, which is a gland that produces and secretes insulin, a hormone important for the maintain of life. Secretion of insulin in healthy persons is regulated by levels of blood glucose and helps to entry, utilization and storage of glucose in cells and tissues. Deficiency of insulin and as a result hyperglycemia exists when 85-90% of beta - cells of the pancreas are destructed. Therefore, the time occurrence of diabetes depends on the size of the cell damage and the body's needs of insulin (Atkinson & Maclaren, 1994). Another mechanism that has been recognized in recent years is the role of alpha - cells of the pancreas and the weakness of diabetes type 2 patients inhibit postprandial glucagon secretion from alpha cells, which leads to increased glucose production by the liver and the occurrence of liver insulin resistance. As a result, the secretion of insulin is increased and the beta cells are depleted rapidly (Zoupas, 2007). Insulin secretion depends not only on the blood glucose levels, but also from a variety of gastrointestinal hormones, integrins, which discovered recently and are mainly represented by the GLP-1 (Glucagon-like peptide 1). The GLP-1 increases much more the postprandial insulin secretion compared with

intravenous administration of glucose. This phenomenon is clearly reduced in patients with diabetes type II. Genetic and acquired factors are involved in these complex disorders (20). Diabetes type II is a heterogeneous disease, the pathogenesis of which consist of the combination of impaired insulin action (insulin resistance) and disordered insulin secretion (progressive, loss of mass and function of beta cells). There is a hypothesis that supports the interaction between genetic predisposition and environmental trigger factors, associated with the change in lifestyle and behavior of individuals. These factors are age, obesity, excessive caloric intake and decreased physical activity. On the other hand, family history, twins, insulin resistance and disorders of insulin secretion in first degree relatives of patients with diabetes type II modulate the profile of genetic predisposition for DM type II. So, it can be said that the genes which influences the action and secretion of insulin are expressed in susceptible individuals (Florez, 2007).

In recent years efforts have been initiated to detect genes, which are responsible for DM type II. Despite several positive genetic combinations have been reported, few are those who have been copied steadily. The singleton nucleotide polymorphisms (single nucleotide polymorphisms, SNPs) in transcriptional gene TCF7L2 (transcription factor-7-like 2) have a close relationship with DM type 2 and with impaired secretion of insulin (Florez, 2007). In a multicenter study in Sweden (16,061 people) and Finland (2770 people) with 22 years of monitoring, Lyssenko et al (2007) identified three SPNs genotypes (rs7903146, rs12255372, rs10885406) in the gene TCF7L2. The genotypes CC/TT of SPN rs7903146 were potent factors for the onset of DM type II in two different groups. No correlation was found between these alleles genes and insulin sensitivity, but these carriers had significantly reduced secretion of insulin and activity of integrins and increased hepatic gluconeogenesis. The same study showed that the TCF7L2 gene is expressed in human pancreatic islets and that its expression is five times more in islets of patients with DM type II. Also, the degree of expression of TCF7L2 mRNA is proportional to the expression of insulin, but inversely proportional to the induced by glucose secretion of insulin. Finally, overexpression of the gene TCF7L2 in human islets decreases the glucose induced secretion insulin. This study showed also that 11 different genes (TCF7L2, PPARG, FTO, KCNJ11,

WFS1, CDKAL1, IGF2BP2, SLC30A8, JAZF1 and HHEX) had statistically significant association with the risk for diabetes type II independent of other risk factors (Lyssenko et al., 2008). However, the gene TCF7L2 is now considered as the most powerful genetic factor associated with DM type II (OR = 1.4). Also, there have been identified, some others SPNs by examining a large number of genomes (Lyssenko et al., 2008). By functional point of view, most of these genes (HHEX, CDKAL1, CDKN2A / B, TCF7L2, HHF1B) seems to be associated with the decrease in mass of beta- cells. It has, also, suggested the hypothesis that several genetic variables are associated with reduced insulin action (WFS1, PPARG) including those affecting insulin`s signaling. This is of special interest, because these variables can affect the function of beta – cells (Florez, 2008).

The Accili and colleagues showed that insulin signaling regulates the function and the survival of beta - cells through the activation of IRSs (insulin receptor substrates). More specifically, it was reported that activation of IRS-1 is involved in the synthesis and secretion of insulin, while the IRS-2 regulates the apoptosis, the neogenesis, multiplication, and the size of the beta - cells (beta-cell mass). Various studies have shown that polymorphisms of IRSs affect the function of beta - cells (Accili, 2001).

Factors that are associated with increased risk of DM type II are the following:

- Family history of diabetes
- Cardiovascular disease
- Obesity
- No exercise
- Arterial Hypertension
- History of gestational diabetes
- Polycystic Ovarian Syndrome
- Pre diagnosis of impaired glucose tolerance or impaired fasting glucose.

Obesity is now recognized as the most important modifiable risk factor for the occurrence of DM type II. Numerous studies (such as the Nurses' Health Study and the Physicians Health Study) have shown the correlation between duration and the degree of obesity with DM type II both in men and in Women

(Prenki & Nolan, 2006). Over 85% of people with DM type II are overweight or obese. Obesity is accompanied by increased volume of free fatty acids (FFA), which have harmful effects on insulin sensitivity and insulin signaling in the beta- cell. The infiltration of adipose tissue by macrophages increases the secretion of proinflammatory cytokines, chemokines and angiogenic factors, by stimulated abdominal adipocytes, which prospers the development of systemic and local insulin resistance. The stimulated adipocytes secrete adhesion molecules (MCP -1, CCL2), which attract monocytes – macrophages in the abdominal region. Thus, the cycle of inflammation - abdominal obesity - insulin resistance reproduced and maintained (Song et al. 2007).

Obesity and especially the abdominal obesity, reduce the sensitivity of the tissues in insulin, causing a compensatory increase of insulin secretion of beta - cell. This increased insulin secretion counter forces the existing insulin resistance unless coexists genetic disorder in beta- cell lacking allowing the necessary increase of insulin secretion and thus, leads to increase blood glucose and the appearance of DM type II. The fact that about half of obese people will develop diabetes or impaired tolerance glucose (Impaired Glucose Tolerance-IGT) confirms the scenario of genetic predisposition for the occurrence of diabetes. In addition to the risk of the occurrence of DM type II, insulin resistance is associated with major factors of cardiovascular risks, such as hypertension and dyslipidemia. There have been described several factors that when there is obesity contribute to increase the resistance of target tissues to insulin. Among these is the TNF -alpha, the IL-6, elevated free fatty acids (FFA), leptin, MCP-1 etc. (Chandalia & Abate, 2007).

The TNF- α (Tumour Necrosis Factor- α) is secreted by adipocytes, reduces tissue insulin sensitivity (via phosphorylation at sites of serine – threonine of the IRS-1 substrate, leading to decrease in the activity of PI-3 kinase), increases the secretion of FFA improving lipolysis in adipose cells and activates the important transcription factor NF-kB (regulates the expression of many inflammatory molecules). Finally, it stimulates the production other cytokines that directly increase the resistance in skeletal muscles.

The IL-6 (interleukin-6) increases lipolysis in adipocytes and increases insulin resistance in liver cells. The chemokine MCP-1 (Monocyte Chemoattractant Protein-1) affects the sensitivity of adipocytes to insulin and

promotes adhesion, transfer and infiltration of adipose tissue by macrophages. The latter increases the production of proinflammatory molecules from adipose tissue. Leptin is secreted from adipose tissue, is strongly associated with insulin levels in fasting and the percentage of body fat and contributes in adding and filtering of the adipose tissue by macrophages. Hyperinsulinemia also explain its down regulation insulin receptors and intracellular insulin resistance secondarily (Van Gaal et al., 2006).

The free fatty acids increase the insulin resistance in muscle and liver, decreases the uptake of glucose by muscles and increases hepatic gluconeogenesis. At the molecular level, the FFA increases the intramitochondrial levels of acetyl-CoA and NADPH and cause inactivation of pyruvate dehydrogenase, hexokinase and phosphofructokinase resulting reduction of the intracellular metabolism of glucose, i.e. glycolysis. Also, the FFA causes the down regulation of the insulin receptor in muscle cells, decrease tyrosine phosphorylation of IRS-1 and thus reduce PI3 kinase and increase of diacylglycerol and subsequent activation of Protein kinase C (PKC). The combined effect of cytokines and FFA significantly increases the intracellular concentration of triglycerides in muscle cells, and therefore significantly increases the resistance to insulin of adipose, muscle and liver cells (Wilding, 2007).

As mentioned above, insulin resistance and subsequent hyperinsulinemia are not sufficient to lead to the development of DM type II, if does not coexist inherited (gene identified) or acquired dysfunction of beta cells in the pancreas leading to reduced insulin secretion. Adoptive dysfunction in beta - cells are qualitatively and quantitative, since apart from disadvantaged function show and progressive reducing mass. In this complex dysfunction contributes the elevated FFA, chronic hyperglycemia in phase of dysglykaimia [impaired fasting glucose (IFG) and impaired glucose tolerance (IGT)], insulin resistance due to the presence of advanced levels of proinflammatory cytokines, which prevent the transmission of insulin signal in the beta - cell, and finally, the deposition of amyloid in the islets of Langerhans (Hajel et al., 2008). All these factors lead to increased free oxygen radicals and increased intracellular oxidative stress, which promote apoptosis of beta cells and finally

reduce their mass and functionality and the risk of occurrence of DM type II (Gopaul et al., 2001).

1.4 Clinical Presentation

Most patients with DM type II have primarily a symptom-free period (impaired glucose tolerance-IGT), which is characterized by an abnormal response to a glucose test but does not meet the criteria of diabetes (see table 1) (ADA, 2007, Kawano et al., 1999). Diabetes mellitus type 2 is the final stage of a syndrome which is developed gradually and is characterized by resistance of target tissues to the action of insulin, that cannot be compensated for by the hypersecretion of beta cells. Large studies have shown that the tissue sensitivity to insulin is disturbed 10-20 years before the appearance of real diabetes in populations with a predisposition (39). They also have shown that at the time of occurrence of DM type II, there is already 50% reduction in the function of B-cell, which is developed gradually as a result of fat toxicity and glucotoxicity in beta- cells (UKPDS group, 1998). In the primary stage, some people appear a set of powerful risk factors such as central obesity, hypertriglyceridemia, low HDL-cholesterol, high blood pressure and insulin resistance, which is associated with a pro-inflammatory condition. In these cases, the patients are advanced to change their lifestyles. However, most patients cannot lose weight and develop late complications of diabetes because of gradually established micro- and macro- vascular disease (Paniagua et al., 2002).

The three main symptoms of diabetes is polydipsia, polyuria and binging with accompanying weight loss, which help in diagnosis of the disease, but their appearance is usually very late (Cox & Elelman, 2009, WHO, 2006). It is necessity for health care professionals to find out sensitive groups population with increased susceptibility, and also hidden symptoms, such as recurrent vaginitis in women and balanopostidis in men, frequent furunculosis, delayed wound healing, postprandial drowsiness, unexplained refractive errors, morning fatigue and undue erectile dysfunction in middle age. These symptoms bring suspicion of impaired glucose tolerance or DM type II, and specific laboratory test is needed to confirm the diagnosis and prompt treatment in order to avoid chronic complications of the disease (Harris et al., 1992).

Table 1: Diagnostic criteria for diabetes mellitus and impaired glucose tolerance

	Glucose levels in fasting	2 hrs after intake of 75gr glucose	Increased risk for:
Diabetes	>7.0	> 11.1	Cardiovascular diseases, nephropathy, neuropathy, ocular diseases
Impaired glucose tolerance	< 7.0	7.8-11.0	Diabetes and cardiovascular diseases

Diabetic patients are prone to multiple and complex complications, due to the development and installation of a serious vascular disease, resulting in macro- and micro- angiopathy. Complications include cardiovascular disease-macrovascular disease (vascular stroke, peripheral vascular disease, coronary artery disease) and microvascular disease (retinopathy, neuropathy, microalbuminuria-nephropathy). Also, we must note the increased susceptibility of diabetic patients for the development of infections (e.g., diabetic foot), which is an important cause of morbidity. According to data from a large prospective study for DM type II in the UK (UKPDS), 50% of diabetics type II who discovered diabetes for the first time already had some of the chronic complications in their small or large vases (UKPDS group, 1998). This makes it even more imperative the need for timely search, diagnosis and treatment.

1.5 Treatment

In recent years various studies have been made to determine the ability and benefits of different strategies of prevention or delay of the onset of DM type II. The first step of the treatment is the intervention to diet and exercise, which has

been shown to be effective in improving glychaimias and reduce cardiovascular risk factors (studies DPS, DPP) (Knowler et al., 2002). As prediabetes progresses, pharmacological intervention management of hyperglycaemia and risk factors for coronary heart disease becomes necessary. Drugs used for this purpose are metformin (studies DPP, IDPP) (Knowler et al., 2002), acarbose (STOP-NIDDM) (Chiasson et al. 2002) and thiazolidinediones (DREAM, ACTNOW) (Defronzo et al., 2009). Large multicenter studies have shown that these drugs reduce the progression from prediabetes to diabetes.

In recent years, great improvement has been achieved in the quality and duration of life of diabetic patients, due to the understanding of the pathophysiological mechanism of DM type II and the discovery of new therapeutic agents for delaying the progression and the ideal setting of. However, the treatment of the disease remains inadequate, firstly because of the complexity of the pathophysiological mechanism of DM type II which requires the use of multiple drugs to achieve the therapeutic goal, and partly because of the failure of any medication in depth time. Thus, the limit of glycosylated hemoglobin (HbA1c) <6.5-7%, which is the level of protection of the chronic complications, is achieved only in 15-20% of patients (Turner et al., 1999). It is important to be noted that the treatment of the diabetic syndrome is not possible, if all parameters associated with increased morbidity and mortality in this multifactorial disease are not taken into account and not targeted properly. So, the treatment of diabetic patients is multilevel and as the glucose levels, all other risk factors such as hypertension, hyperlipidemia, obesity, and smoking have to be treated aggressively.

1.5.1. Hypoglycemic medication

The most important factor for the effective treatment of diabetes is changing lifestyle regarding physical activity and nutrition. Studies have shown that the maintenance of body mass index (BMI) lower than 25kg/m^2, food rich in fibers and unsaturated fat, diet low in saturated and trans fats and low GI (glycemic index), regular exercise, no smoking and limited alcohol consumption leads to a significant reduction in the incidence of diabetes and improves glycemic control in diabetic patients (Boffetta et al., 2011). Instructions for lifestyle change have to be individualized depending on the physical and functional condition of each patient (Chiniwala & Jabbour, 2011).

Until 1990 there were only 3 categories of hypoglycaemic agents: sulfonylureas, biguanides, and acarbose. About 20 years later, there are another 5 categories: thiazolidinediones, meglitinides, potassium chanels activators, GLP-1 *analogues*, and inhibitors *of* DPP-4. So, nowadays the total categories of drugs which are used for the treatment of hyperglycemia in DM type II are: insulin, sulfonylureas, biguanides, glucosidase inhibitors, thiazolidinediones, meglitinides and incretins (inkretinomimetics of GLP-1 receptors and inhibitors of DPP-4). The choice of the best and most effective treatment of hyperglycemia in DM type II should be considered taking into account the following factors: duration of diabetes, age and weight of the patient, presence or absence of residual secretion of insulin, the degree of hyperglycemia and the levels at which health care professionals want to regulate blood sugar, speed and mode of action of the drug, the degree of compliance of the patient, the effect of these drugs on lipids, contraindications and side effects of drugs (Zoupas, 2007).

1.5.1.1. Insulin

Insulin is the first therapeutic agent used for the treatment of diabetes. It is the most effective therapeutic intervention for the treatment of hyperglycemia, because the appropriate titration of insulin therapy can lead to the achievement of therapeutic targets regardless of the first levels of HbA1c.

Insulin has been widely used as monotherapy and in combination with antidiabetic tablets since the late '50s. Today, it is estimated that only one-third of DM type II is treated with insulin and 15% in combination of insulin and antidiabetic tablets (Mayfield & White, 2004).

A British prospective study - UKPDS 4 (Turner et al., 1999, UKPDS group, 1998) which concerns diabetes type II, showed that after the first year of treatment, blood sugar control with any treatment has a progressively deteriorating impact, which primarily is due to impaired function of beta-cells. As a result, each patient with DM type II, have to adjust his therapeutic treatment every 2-5 years. The most important finding of the study is the need to start insulin therapy as soon as possible. However, the majority of people with DM type II (80%) are unregulated, even after the insulin therapy.

Nowadays there is a wide range of insulins (slow insulin action, steady and 24-hour action with little risk of hypoglycaemia [Lantus, Levemir], ultrafast insulin action that is used to postprandial hyperglycemia [Novorapid, Apidra, Humalog], insulins of medium duration which are a mixture of rapid-and intermediate-acting insulins [Novomix 30, Humalog Mix 25/75, Humalog Mix 50/50]) that create new opportunities for best and ideal setting of diabetic patients. Modern insulinotherapy with basic and rapid-action insulins, offer improved glucose control in both assertive shapes, and in combination with a hypoglycemic agent and injection of basic insulin (Riddle et al., 2003).

1.5.1.2. Sulfonylureas

The sulfonylureas are drugs which cause the secretion of insulin and are effective since there are only alive β-cells and residual insulin secretion (UKPDS group, 1998). Their main effect is the stimulation of pancreatic beta cells to increase both basic and postprandial insulin secretion. In this manner, they drop the blood sugar. Also, they decrease the gluconeogenesis in the liver and improve partially reduced postsynaptic insulin action in muscle and fat tissue. The grade of insulin secretion depends on the secretory capacity of the beta cells, the secretory effect of administered sulfonylurea (stronger are the

first generation sulfonylureas and glibenclamide), the duration of action (glibenclamide and glimepiride have longer action of newer sulfonylureas), and the dosage, since insulin secretion is dose dependent. The sulfonylureas are quite frequent in the symptomatic treatment of diabetic patient. The limitation in their activities is that they do not improve the activity of the beta-cells (study ADOPT) (Kahn et al., 2006). The main undesirable effect is hypoglycemia, which occurs frequently in elderly patients. This fact is very frequent especially with sulphonylureas first generation and glibenclamide (Inzucchi, 2002). According to University Group Diabetes Program study (UGDP), treatment with sulfonylureas increases cardiovascular mortality (Meinert et al., 1970). This statement was not confirmed by the UKPDS (UKPDS group, 1998) and ADVANCE (2008) studies. Although, sulfonylureas are a reliable, economic and effective treatment, healthcare providers must pay attention to the risk of hypoglycaemia.

1.5.1.3. Biguanides

The main drug of biguanides is the metformin. Biguanides affect and improve the phenomenon of insulin resistance (UKPDS group, 1998). That is why their combination with other drugs is in many cases the most effective treatment. Metformin is old drug. It is used in clinical practice since the late '50s. Metformin affects mainly the metabolism of carbohydrates and lipoproteins. The main action is decrease of glucose production by the liver, since inhibits gluconeogenesis and suppresses endogenous glucose production, reducing the insulin resistance by hepatocytes and finally improves glychaimias during fasting (Defronzo & Goodman, 1995). At molecular level, metformin activates the AMP kinase leading to improved liver insulin sensitivity (Kim et al., 2008). Also, it slows the absorption of glucose from gastrointestinal tract and as a result reduces the postprandial hyperglycemia, the peak hyperinsulinemia and indirectly reduces the insulin resistance. The lowering effect of insulin resistance is through the action of the tyrosine kinase of the insulin receptor and its action on glucose transporters, which enhance the intracellular transmission of the message of insulin and increase glucose utilization in

peripheral tissues (Bosi, 2009). In vitro studies have shown that metformin protects B-cells by reducing oxidative stress (Hou et al., 2010). Moreover, metformin reduces the oxidation of FFA, improves the lipid profile and in many cases shows antiorexiogono activity contributing to weight loss (Scarpello & Howlett, 2008). There have been, also, report positive effects on diabetic cardiomyopathy, vasoprotective action and improve of endothelial function (Skrha et al., 2007).

Metformin is the drug of choice for obese diabetic type II patients and is associated with all anti diabetic tablets and insulin with very good results. Also, it is used for the prevention or the delay of the development of diabetes in people with impaired glucose tolerance (Scarpello & Howlett, 2008). Additionally, it has been shown that reduces the cardiovascular mortality (UKPDS group, 1998). For these reasons, metformin is placed by ADA and EASD (European Association for the Study of Diabetes) in the first step of the treatment algorithm (Nathan et al., 2008). The adverse effects of metformin include gastrointestinal disorders (mainly diarrhea and flatulence) and it is contraindicated in hepatic, renal and heart failure, pregnancy, alcoholism, serious infections, and should be interrupted temporarily when patient is going to do examinations with intravenous contrast (Scarpello & Howlett, 2008). So, the beneficial effects of metformin are the following:

- Reduces hepatic glucose production
- Rarely causes hypoglycemia-saving insulin action
- Documented positive safety profile
- High initial response rate
- Does not increase the body weight
- Promotes lipid profile
- Improves endothelial function
- Reduces macrovascular complications (UKPDS)
- Low cost

1.5.1.4. Inhibitors of a-glucosidase

Inhibitors of α-glucosidase slow the absorption of polysaccharides from the small intestine, reducing thereby the postprandial glucose levels without causing hypoglycemia. The only drug of this category that exists in Greece is acarbose. It has mild antidiabetic activity and can be used in diabetic type II patients with mild diabetes who are just diagnosed, or combined with insulin or other antidiabetics tablets in severe cases. The main limitations to the widespread use of these drugs are the need for frequent reception before each meal and gastrointestinal side effects (Chiasson et al., 2003).

1.5.1.5. Thiazolidinediones

Thiazolidinediones or glitazones (pioglitazone) are anti-diabetic agents which act by increasing the sensitivity of target tissues to insulin action. For this reason, they are called insulin “sensitizers”. Their action is achieved through the activation of specific nuclear receptors, which are called PPAR-gamma. These receptors are mainly expressed in fat tissue and secondarily in liver and skeletal muscle. They are both specific nuclear receptors and transcription factors and reprogram gene expression (Yki-Jarvinen, 2004). Thiazolidinediones are power and selective agonists of PPAR-g receptors, leading to increase expression of a gene sequence, such as lipoprotein lipase, glucokinase, GLUT-4, etc. Also, the activation of PPAR-c receptor differentiates the large insulin resistance abdominal adipocytes to small insulin resistance adipocytes of subcutaneous region, which secrete significantly smaller quantities FFA, leptin and TNF-α, and larger amounts of adiponectin, which improves insulin sensitivity. By this manner, the total insulin resistance in the liver and muscles is reduced leading to increased consumption glucose by muscles and adipose cells, and to decreased endogenous production of glucose from hepatocytes and indirectly improve the functioning of the b-cells due to the reduction of glucotoxicity and lipotoxicity (Krentz, 2009). At ADOPT study, rosiglitazone maintained glycemic control for significant longer time period compared with metformin and glibenclamide (Goldberg, 2007, Kahn et al., 2006). It seems that glitazones have other beneficial effects, such as the

lipid metabolism (study PROACTIVE) (Dormandy et al., 2005), reduce the levels of blood pressure (CHMP, 2014), improve endothelial function, blood clotting, reduce microalbuminuria, have antioxidant activity and decrease the thickness of the medial carotid (study CHICAGO) (Goldberg, 2007). But the most important side effect is that patients increase their weight due to the increased fat and the retention fluids, which causes edema at 4.5% of patients. For this reason, its administration in patients with heart failure is contraindicated (Duan et al., 2009). Because of the cardiovascular safety of the drug is debatable, the circulation of rosiglitazone has inhibited (2010) of the European Medicines Agency (Erdmann & Wilcox, 2008).

1.5.1.6. Glinides

The glinides (repaglinide and nateglinide) are insulin secretion drugs and have faster and shorter insulin secretion of sulfonylureas. Their action requires live beta cells. They are absorbed very quickly and cause rapid insulin secretion, restoring partially the abnormal first phase insulin secretion. So, they are used for the control of postprandial hyperglycemia. They should be taken 15 minutes before each meal. Their combination with metformin is interest for pathophysiological terms in order to address both postprandial (glinides), and fasting hyperglycemia (metformin). For this class of drugs there are no large studies with strong cardiovascular endpoints (Anselmino, 2009).

1.5.1.7. Incretins (inkretinomimitika of GLP-1 receptor and inhibitors of DPP-4)

The incretins are peptide hormones secreted by entero-endocrine cells of the gastrointestinal tract after consumption of a meal containing carbohydrates or fats and are essential for maintaining sugar metabolic homeostasis. They regulate the secretion of pancreatic cells as part of the “enteropancreas” axis. There are two major categories of incretin hormones involved in sugar metabolism: the peptide that mimes the action of glucagon (GLP-1, Glucagon-like peptide) and the peptide that affects insulin secretion via glucose (GIP,

Glucose-dependent insulinotropic polypeptide). The GLP-1 consists of 30 amino acids and is secreted from the L cells of the ileum and colon. The GIP consists of 42 amino acids and is secreted from endocrine K cells which are located mainly in duodenum and small intestine. Their actions are made through receptor activation (GLP-1R and GIP-R) located in various tissues (GLP-1R in A and B-cells, CNS, heart, kidney, lung, gastrointestinal system, GIP-R b- cells, CNS and adipose tissue). The insulinotropic action of GLP-1 is glucose dependent and is significantly reduced when glucose levels are closer to normal. So, the risk of hypoglycemia is minimized (Drucker, 2006). Studies have shown that persons with DM type II have significantly reduced secretion of GLP-1. The levels of GIP are normal but they are not capable of stimulating the secretion of the second phase insulin (Nauck et al., 1986). Animal experiments have shown that administration of GLP-1 inhibits apoptosis of beta cells, stimulate their proliferation and promotes islet neogenesis from other pancreatic progenitor cells (Drucker, 2003). Summary, the actions of GLP-1 are the following:

- Stimulates insulin secretion by glucose-dependent manner, restores the first phase insulin secretion and increases the postprandial insulin secretion in diabetic type II patients
- Reduces hyperglucagonemia that characterizes DM type II
- Reduces food intake and body weight
- If trophic actions of human pancreatic cells are confirmed, they can delay the progress of diabetes.

The half-life of GLP-1 is 1-2 minutes because it catabolized rapidly by the enzyme DPP-4 (dipeptilo peptidase 4), which makes it difficult to use in clinical practice. Thus, the pharmaceutical research and industry developed drugs that have activity to GLP-1 and are resistant to the action of DPP-4 and drugs that inhibit DPP-4. The first are agonists of GLP-1 receptors and are called GLP-1 analogs or incretinomimitika (Loveshin & Drucker, 2009), while the second are called DPP-4 inhibitors and are administered per os and inhibit the action of DPP-4 (Drucker, 2007).

In 2005, the FDA (Food and Drug Adminitration) approved the first incretin that belongs to the category of GLP-1 and called exenatide (Kendall et al., 2005). It is administrated subcutaneously and has duration of action about 6 hours. The most frequent side effect is the nausea (Bunck et al.m 2009). Some studies have shown beneficial effect on the metabolism of lipids, reduction of blood pressure and cardioprotective effects (Van Gaal et al., 2008). In Greece, “circulate” the sitagliptin (approved by the FDA in 2006) (Aschner et al., 2006) and the vildagliptin (approved in 2008) (96). These drugs has been shown by studies and meta-analyzes that are mild antihyperglycemic drugs which are safe and have no significant side effects (Ahren, 2007).

1.5.2. Hypolipid medication

The increased incidence of cardiovascular morbidity in diabetic patients can partly be explained by disturbances of lipid metabolism, which observed in these patients (Syvanne & Taskinen, 1997). The detection and treatment of dyslipidemia of diabetes is an important part of their treatment. In diabetics patients compared with no-diabetics must annually assign total cholesterol, LDL-cholesterol, HDL-cholesterol and fasting triglycerides of blood (ADA, 2012). Also, it is necessary, before any hypolipid treatment to be checked and excluded the possibility of primary or other cause of secondary dyslipidemia (eg, hypothyroidism, nephritic syndrome, medicines, etc.).

Abnormalities in lipoproteins exist already from the long-term asymptomatic pre-diabetic stage and contribute substantially to the increase in risk for macrovascular disease (Syvanne & Taskinen, 1997). The proposal by Haffner et al. that "the clock for macrovascular disease in diabetes begins ticking long before the installation of hyperglycemia" seems to be confirmed (Kreisberg, 1998). Steiner, also, states that "strict control of blood glucose is essential to prevent the complications of the eyes, kidneys and central nervous system, and it has little effect on the frequency of cardiovascular events" (Spanheimer, 2001).

During the prediabetic stage, qualitative and quantitative abnormalities to lipoproteins contribute significantly to the development of macrovascular disease (Syvanne & Taskinen, 1997). Dyslipidemia associated with insulin resistance, known as diabetic dyslipidemia, is characterized by the following: increased levels of triglycerides, normal levels of total and LDL-cholesterol, decreased levels of HDL-cholesterol, increased levels of Apo-B and VLDL-cholesterol and predominance of small LDL particles. It is due to the resistance of adipose tissue to the insulin action (Steiner, 1997). The inability of the resistant fat cells to store triglycerides results in hydrolysis of triglycerides and release of FFA. The parallel reduced insulin-dependent FFA uptake by skeletal muscle results in increased bioavailability in the liver, leading to increased hepatic synthesis of cholesterol ester and release VLDL with Apo-B. The FFA is combined with a molecule of cholesterol and form a cholesterol ester. The enrichment of HDL and LDL triglycerides leads to decreased levels of HDL particles and small dense LDL, which is strongly atherogenic. The enrichment of HDL and LDL triglycerides made in exchange with cholesterol esters. Thus, VLDL is rich in cholesterol while HDL and LDL are triglyceride-rich. Then the hepatic lipase removes triglycerides from LDL and new small dense particles of LDL are created. The latter are not easily removed by normal LDL-receptors (impaired clearance of rich triglycerides lipoproteins by lipoprotein lipase), oxidized, and glycosylated faster than large LDL particles and are involved in athirogenetic process and the formation of atherosclerotic plaque (Ginsberg, 1996). While dyslipidemia is present in almost all diabetic patients, only 30-40% of these patients have triglycerides more than 200mg/dl and only 10% of them have more than 400mg/dl. The hypertriglyceridemia in DM type II almost always indicates the presence of other predisposing factors, such as obesity, sedentary lifestyle, age, pharmaceutical treatment for other concomitant diseases and / or delayed expression of genetic disorders involving lipids (Reusch, 2002).

The ADA has published recommendations in 2012 and targets for the therapeutic treatment of diabetic dyslipidemia. Thus, suggests to diabetic patients to change food habits in order to improve their lipid profile. The goal of the suggested diet is the reduced saturated fat, trans fat and cholesterol, and the increase of intake of omega-3 fatty acids, fiber, stanols and sterols, while

should be attempted weight loss, and where appropriate increase of physical activity (ADA, 2012). Treatment with statins should be added to every diabetic patient, regardless of baseline lipids, with known cardiovascular disease, or no history cardiovascular disease but with age over 40 years and has at least one more risk factor for cardiovascular disease (ADA, 2012). For patients with smaller risk (without known cardiovascular disease, and aged less than 40 years), treatment with statin should be given in addition to the instructions for changing the way of life, if LDL is more than 100mg/dl or if the patient has many cardiovascular risk factors (ADA, 2012). In patients without known cardiovascular disease, the initial target for LDL is less than 100mg/dL (2.6 mmol/L). In patients with known cardiovascular disease, the goal for LDL is less than 70 mg/dL (1.8 mmol/L), with high-dose of statin. If this target is not achieved by the maximum tolerated dose of a statin, then the alternative therapeutic target is the reduction of LDL levels by 30-40% from initial value. The desired levels of triglycerides have to be less than 150 mg/dL (1.7mmol/L) and HDL more than 40mg/dL (1.0 mmol/L) in men and more than 50mg/dL (1.3 mmol/L) in women. However, the preferred strategy for the reduction of LDL is the administration of statin. If the goals are not achieved with the maximum tolerated dose of a statin, then there can be used combinations of antilipidemic drugs, although such combinations have not been widely studied with regard to their effect on cardiovascular disease and their safety. Finally, treatment with statins is contraindicated in pregnancy (ADA, 2012).

As mentioned above, patients with DM type II have an increased frequency of lipid disorders that contribute to increased cardiovascular risk. In the last decade, many clinical studies have shown significant benefit from the use of hypolipid medication, mainly by administrating statins, on cardiovascular events in patients with chronic cardiac disease and primary prevention of cardiovascular disease (Baigent et al., 2005). As is shown in table 2, the reduction of cardiovascular deaths and no fatal myocardial infarction is more at diabetics patients with high risk of cardiovascular disease (known cardiovascular disease and/or very high LDL), and in general the therapy with statin protects more the diabetic patients with mild or high risk for cardiovascular disease. At the CARDS study (Collaborative Atorvastatin

Diabetes Study), which involved 2.838 people aged 40-75 years who had diabetes and at least one other risk factor, with no history of cardiovascular disease, atorvastatin 10 mg was administered for 3.9 years. The study was stopped 2 years earlier due to the apparent positive results in the intervention group, where there was a reduction of serious cardiovascular incidents by 37% and reduction to stroke by 48% (Colhoun et al., 2004).

Table 2. Studies of primary and secondary prevention: reduction of cardiovascular events by the use of statin in diabetic patients (n=16.032).

Study	**CVD Prevention**	**Type of statin and dose**	**Risk reduction (%)**	**Relevant risk reduction (%)**	**Absolute risk reduction (%)**	**LDL reduction**
4S-DM (Pyorala et al., 1997)	2	Simvastatin 20-40mg vs. placebo	85.7 to 43.2	50	42.5	186 to 119 mg/dl (36%)
ASPEN 2 (Knopp et al., 2006)	2	Atorvastatin 10mg vs. placebo	39.5 to 24.5	34	12.7	112 to 79 mg/dl (29%)
HPS-DM (Collins et al., 2003)	2	Simvastatin 40mg vs. placebo	43.8 to 36.3	17	7.5	123 to 84 mg/dl (31%)
CARE-DM (Goldberg et al., 1998)	2	Prabastatin 40mg vs. placebo	40.8 to 35.4	13	5.4	136 to 99 mg/dl (27%)
TNT-DM (Shepherd et al., 2006)	2	Atorvastatin 80mg vs. placebo	26.3 to 21.6	18	4.7	99 to 77 mg/dl (22%)
CARDS (Colhoun et al., 2004)	1	Atorvastatin 10mg vs. placebo	11.5 to 7.5	35	4.0	118 to 71 mg/dl (40%)

ASPEN (Knopp et al., 2006)	1	Atorvastatin 10mg vs. placebo	9.8 to 7.9	19	1.9	114 to 80 mg/dl (30%)
ASCOT-DM (Sever et al., 2005)	1	Atorvastatin 10mg vs. placebo	11.1 to 10.2	8	0.9	125 to 82 mg/dl (34%)

LDL: Low-density lipoprotein, CVD: cardiovascular disease

Low HDL-cholesterol levels in combination with high triglycerides levels are the most common disorders of lipids that are observed in diabetic patients type II. However, drugs that are used for these lipid disorders do not have the same impact on the reduction of cardiovascular risk compared with statins (Singh et al., 2007). Nicotinic acid appears to reduce cardiovascular events, although the study was conducted in no-diabetic population (Canner et al., 1986). Gemfibrozil is shown to reduce cardiovascular events both in non-diabetic patients (Rubins et al., 1999) and in a sub-group of diabetic patients of a large study (Canner et al., 1986). However, in a large study specially designed for diabetics, fenofibrate failed to reduce the total cardiovascular events (Keech et al., 2005).

For most diabetic patients, immediate priority for hypolipid treatment is the reduction of LDL levels lower than 100mg/dL (2.60 mmol/L) (NCEP, 2001), unless there is hypertriglyceridemia that require immediate treatment. The change of lifestyle with diet, exercise, weight loss and quitting smoking can help some patients achieve their lipid goals. Changes in the diet of each patient should always be made in accordance with the age, type of diabetes, the antidiabetic drug therapy, lipid levels and concomitant diseases and aim to reduce the saturated fat, cholesterol and trans unsaturated fats in the diet (ADA, 2012).

All studies done with statins and their effect on cardiovascular events, concern the action of statins versus placebo drugs, different doses of statins or different statins without focus on the target levels of LDL (Hayward et al., 2006). As been shown in Table 2, various studies with placebo found that statins

achieved reduction of LDL levels by 30-40%. Such reductions should be satisfactory for patients who cannot achieve their targets due to high initial level or intolerance to a maximum dose of statins. Recent studies in high risk patients (acute coronary syndrome, previous cardiovascular disease) (Cannon et al., 2004), have shown that aggressive treatment with high doses of statins and reduction of LDL level lower than 70 mg/dL resulted in a significant reduction of new episodes. So, in high-risk diabetic patients with known cardiovascular disease, the goal for LDL levels are less than 70 mg/dL (Grundy et al., 2004).

Each patient has a different response to the action of statins without it can be fully understood (Chasman et al., 2004). However, the reduction of cardiovascular events is associated very closely with the effect of statins and the reduction of LDL (Baigent et al., 2005). When the maximum dose of statin failes to reach the target and achieve reduction to LDL levels by 30-40%, should be done efforts for drug combinations. The ezetimibe, fenofibrate and resins (binders of bile acids) are drugs that offer additional reduction of LDL. However, it is not clear yet whether the combination of hypolipid drugs for the reduction of LDL would reduce cardiovascular events versus monotherapy with statins (Brunzell et al., 2008).

Severe hypertriglyceridemia should also be treated directly with change of lifestyle and pharmaceutical (fibrates and fish oil), in order to reduce the risk of acute pancreatitis. If there is no serious hypertriglyceridemia, therapy which is aimed at reducing triglycerides or increasing HDL is not the same beneficial as is the statin therapy (Grundy et al., 2002). The combination of statins with fibrates have positive effects in three fractions of lipids, but significantly increases the risk of liver damage, myositis, and rhabdomyolysis. In the ACCORD study, the combination of fenofibrate and simvastatin did not reduce the incidence of fatal cardiovascular events, of no-fatal myocardial infarction or no-fatal strokes compared with monotherapy with simvastatin in patients with DM type II at high cardiovascular risk (Ginsberg et al., 2010).

2.1. Aim

The aim of the study was to assess the Pharmacotherapy of Diabetes mellitus type II in a pharmacy of a small town of Greece, Veria. Especially, this is an effort to create the profile of diabetic patients in Greece and to assess the drugs that diabetic patients use in their daily.

2.2. Material and Methods

It is a cross-sectional study and includes data collection by questionnaires.

2.3. Study Population

This study was conducted in a pharmacy in a small town of Greece, Veria. The study population consists of 60 patients with known Type II diabetes Melitus.

The study did not include patients who:

1. had no diabetes
2. had other type of diabetes mellitus except type II.
3. did not agree to participate.

2.4. Data Collection

The data collection was performed by a self-reported questionnaire, which was created and developed by the researcher. The questionnaire included the following data:

1. Demographic (age and gender)
2. The time that type II diabetes mellitus was first diagnosed (Childhood, Adulthood, Elderly)
3. The knowledge of blood glucose level fasting of patients (yes or no)
4. The level of the glycaemia of patients (High or low)
5. The frequency to physicians` visit (every month, every 3 months, every 6 months, longer)

6. The time that patients last measured their glycaemia (1 month before, 3 months before, 6 months before, I do not remember)
7. Who measure their blood glucose level (By myself, By the physician)
8. The drugs for diabetes mellitus that patients use (metformin, Thiazolidinediones, Insulin Secretagogues, sulfonylureas, a-Glucosidase Inhibitors, DIpeptidyl-peptidase-4 Inhibitors, Incretin Mimetics, and Insulin)
9. If patients use drug according advice of physician (yes, no, I forget sometimes to take them)
10. If patients suffer from any comorbidities (yes, no)
11. The comorbidities that patients suffer from (Hypertension, Angina Pectoris, Myocardial Infarction, Dyslipidemia, Chronic kidney disease, Non-alcoholic fatty liver disease)
12. Other drugs patients use
13. The dosage of the other drugs
14. If patients drink a glass of wine every day (yes, no)
15. Their opinion whether the composition of food intake plays a role in treatment of the diabetes mellitus (yes, no, I do not know)
16. If patients follow the diet questionnaire (yes, no)

The questionnaire is shown in Appendix

2.5. Method

The questionnaires were delivered to the patients by a local pharmacist. First of all, the pharmacist explained patients the questions and the way they complete this. Then, patients answered the questions in the pharmacy and gave them back to the pharmacist.

2.6. Ethic Issues

I have to refer that every patient has confirmed that they are very willing to take part in the project and answer the questionnaire and their answers to be used for the purpose of the research.

Except of the demographic data of the patients who took part in the study, no personal data will be published in order to ensure the secret of personal data. For this reason, the name and the surname of the patients was not recorded.

2.7. Statistical Analysis

The statistical analysis of data was made by the statistical package SPSS for Windows (version 21) statistical software (SPSS Inc., Chicago, IL).

The first part of the analysis included the frequencies and the percentages of each quality variable. In particularly, the rate of gender, the rate of the time that diabetes mellitus was first diagnosed, the rate of the knowledge of blood glucose level fasting of patients, the rate of the level of the glycaemia of patients, the rate of the frequency to physicians` visit, the rate of the time that patients last measured their glycaemia, the rate of the person who measured their blood glucose level, the rate of the drugs for diabetes mellitus that patients use, the rate of whether patients use drug according advice of physician, the rate of whether patients suffer from any comorbidities, the rate of the comorbidities that patients suffer from, the rate of other drugs patients use, the rate of the dosage of the other drugs, the rate of whether patients drink a glass of wine every day, the rate of the opinion of patients whether the composition of food intake plays a role in treatment of the diabetes mellitus and the rate whether the patients follow the diet questionnaire, were calculated. Moreover, the mean and the standard deviations of the quantity variables were calculated, such as the age (Chatterjee& Price, 1980).

The second part of the analysis included the results of the simple correlations (bivariate analysis). Firstly, all variables were examined for their normality by Kolmogorov-Smirnov test. Between two variables that had normality was done t-test, while two variables had no normality was done Man

Whitney test. One way ANOVA analysis was done when compared three or more normal variables, and Kruskal Wallis test was performed when the variables had no normality. The statistical level (p) was defined at 0.05. So, all values smaller or equal than 0.05 ($P \leq 0.05$) were statistical significant (Chatterjee& Price, 1980).

It was done correlation coefficient with Pearson/Spearman, depending on the normality of variables (Pearson, 1895). The third part of the analysis included the multiple regression analysis. The dependent variables were the glucose level of patients (high versus low) and the person who measure the glycaemia of patients (myself versus pharmacist or physician). For this purpose, it was done univariate regression analysis and excluded all factors had $P>0.1$. The rest of factors ($P<0.1$) it was done multivariate regression analysis. The results that were significant were those with $P<0.05$ (Chatterjee& Price, 1980).

3. Results

The sample consists of 60 diabetic II patients. The mean age of the sample was 56.5±17.5 years with a minimum rate of 25 years and a maximum of 75 years. Most of them were females (n=40) aged years and the rest were males (n=20). The percentage of gender is shown in figure 1.

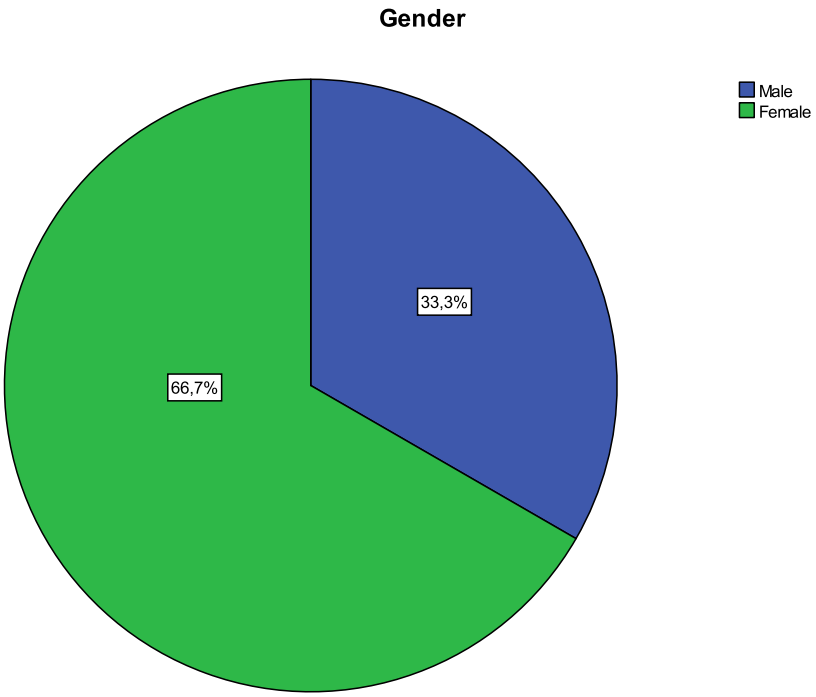


Figure 1. Gender of patients. Denominator 100% is the total amount of patients.

Most of the patients, diagnosed type II diabetes mellitus for first time in the elderly (n=40). The percentages of the first time that patients diagnosed diabetes are shown in figure 2.

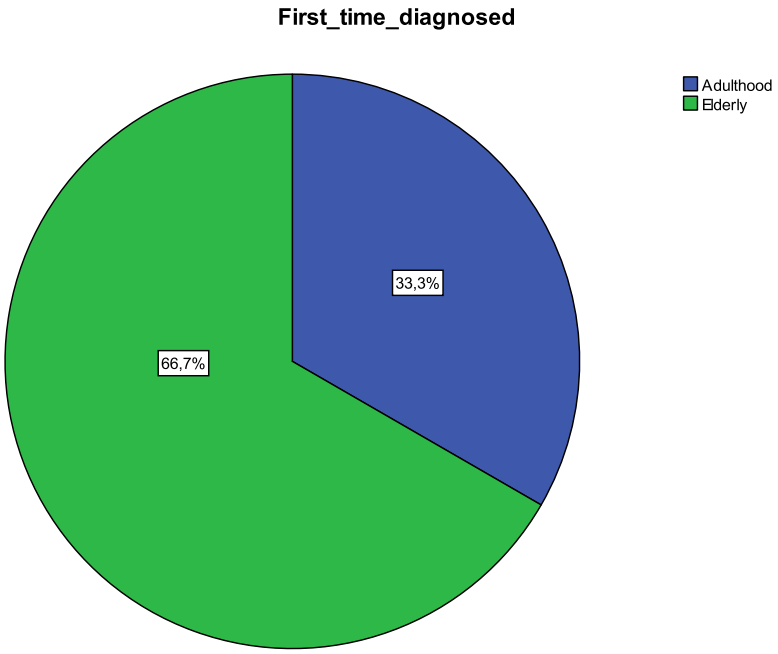


Figure 2. First time diagnosed diabetes. Denominator 100% is the total amount of patients.

Most of the patients(N=56) knew their fasting glucose level. Four of them did not know their glucose level (see figure 3).The four patients who did not know their glucose level had their last glycemia measured longer than 6 months ago therefore therefore they do not know their fasting glucose level.

Figure 3. Patients who knew their glucose level fasting. Denominator 100% is the total amount of patients.

Of the patients who knew their fasting glucose level, 36 (64.3%) patients had high fasting glucose level and 20 (35.7%) patients had physiological fasting glucose level . The patients were questioned how frequently did they visit their physician (see figure 4). Some of them visited their physician every 6 months (n=24), and some patients every 3 months (n=20). From all of patients, 8 patients visited their physician every month and 8 patients visited longer than six months.

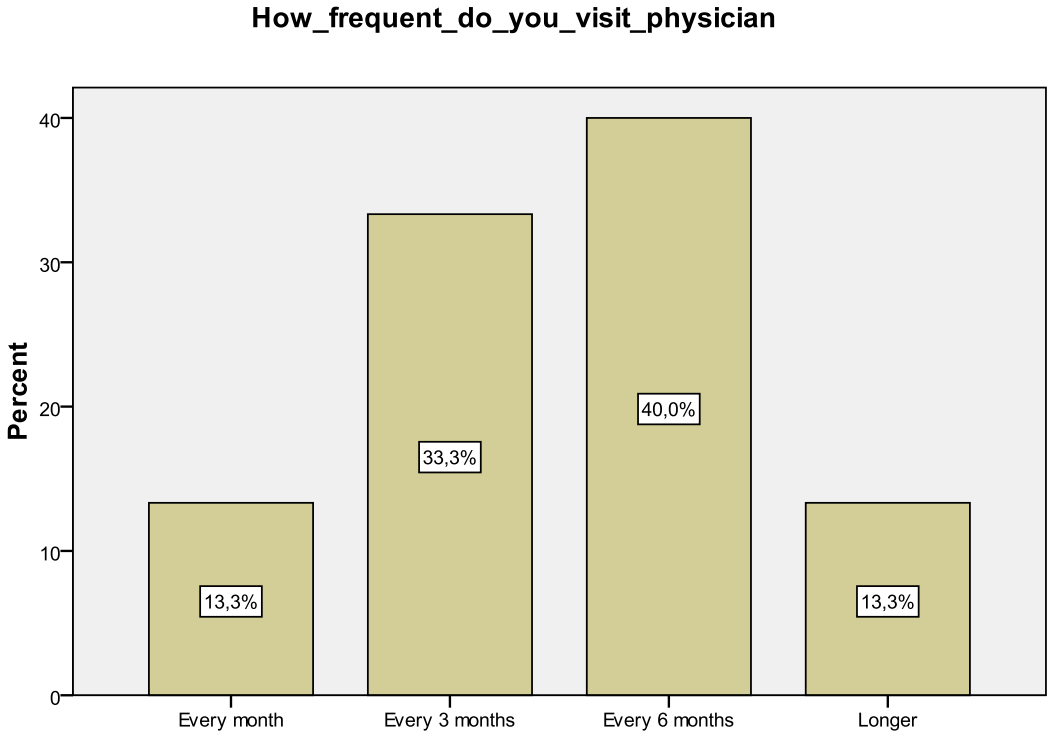


Figure 4. Frequency that patients visit their physician. Denominator 100% is the total amount of patients months.

Above 50% of the patients measured their blood glucose level during the last month (n=36); few measured it 3 months before (n=20) and four patients 6 months before (see figure 5). The patients had their glycaemia measured by their selves (n=16), by the pharmacist (n=28) and by the physician (n=16). The way that patients measured their glycaemia is shown in figure 6.

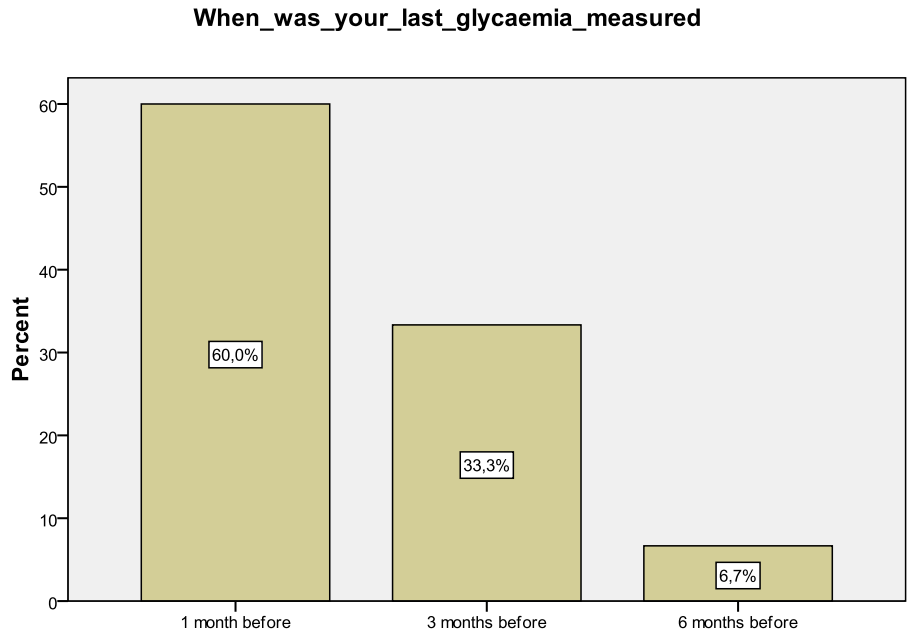


Figure 6. Last glycaemia measured. Denominator 100% is the total amount of human months.

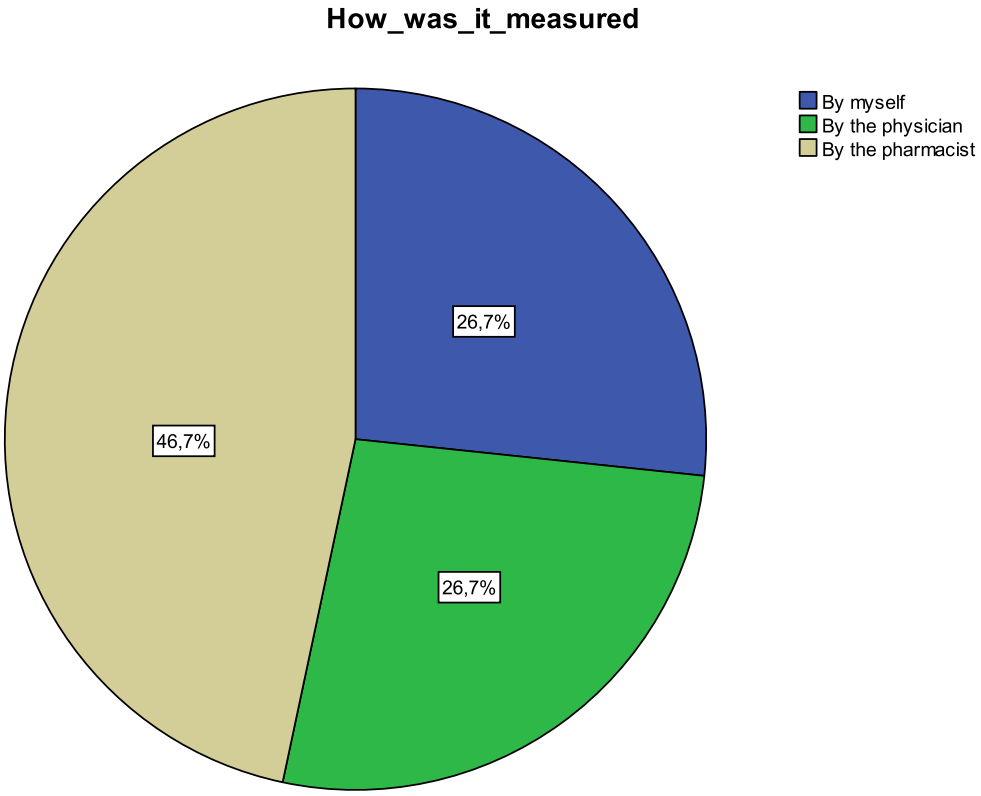


Figure 6. How was measured the blood glucose level of patients. Denominator 100% is the total amount of patients.

The medications that patients administered for the treatment of type 2 diabetes were metformin (32%), Insulin Secretagogues and sulfonylureas (4%), Dipeptidyl-peptidase-4 Inhibitors (8%), Sitagliptin (4%) and Insulin (52%) (See figure 7).

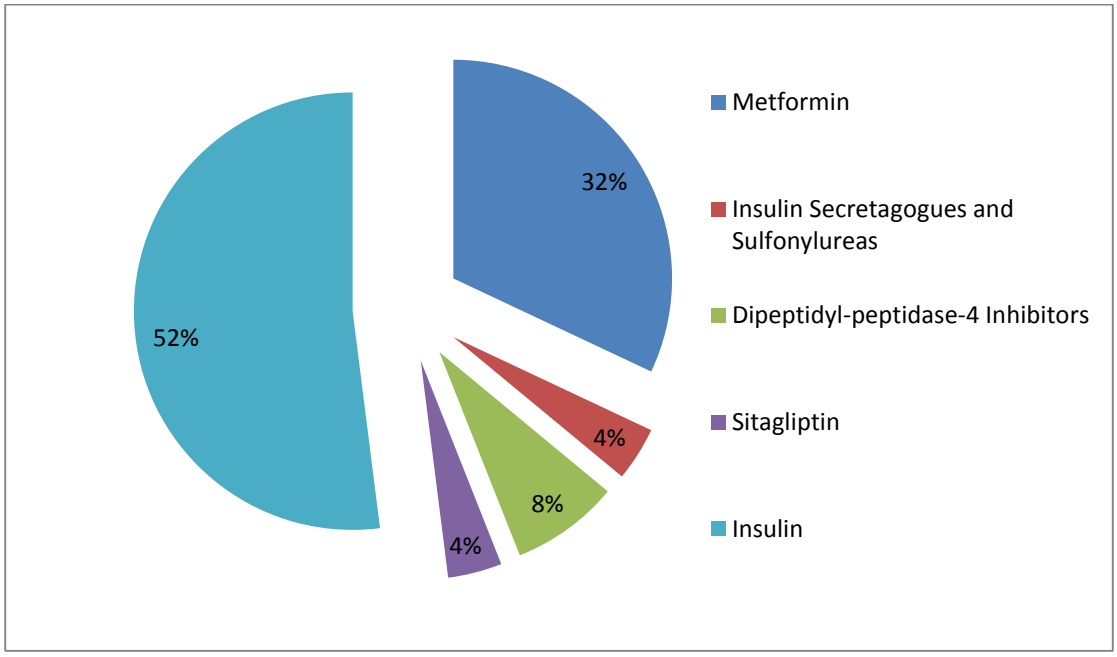


Figure 7. Drugs which were used for the treatment of type 2 diabetes, at the total. Denominator 100% is the total amount of antidiabetic drugs.

Patients used mainly insulin (52%) and metformin (32%) as monotherapy or in combination therapy together or with other antidiabetic drugs.Especially, metformin was administered in combination with Dipeptidyl-peptidase-4 Inhibitors or Insulin. Moreover, Insulin was taken in combination with Sitagliptin or sulfonylureas. Especially, 24 patients took insulin, 16 patients metformin, 4 patients metformin and Dipeptidyl-peptidase-4, 8 patients metformin and insulin, 4 patient insulin secretagogues in combination with sulfonylureas and 4 patient insulin and sitagliptine together. The majority of the patients(66,7%) follow monotherapy while other patients(33,3%) follow combination therapy. The results are shown in figure 8.

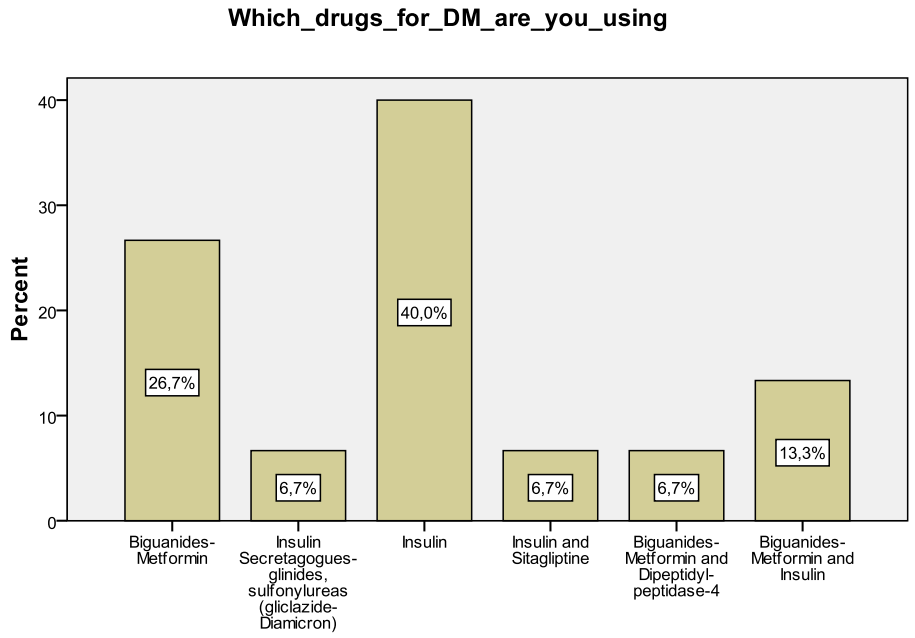


Figure 8. Drugs which were used for the treatment of type 2 diabetes, as they were prescribed by the physicians to the patients. Denominator 100% is the total amount of patients.

At the question, if they use their drugs according advice of physician, 40 (66.7%) patients answered positive, 4 (6.7%) patients answered negative and 16 (26.7%) patients answered that forget sometimes to take them. The answers of this question are shown in figure 9.

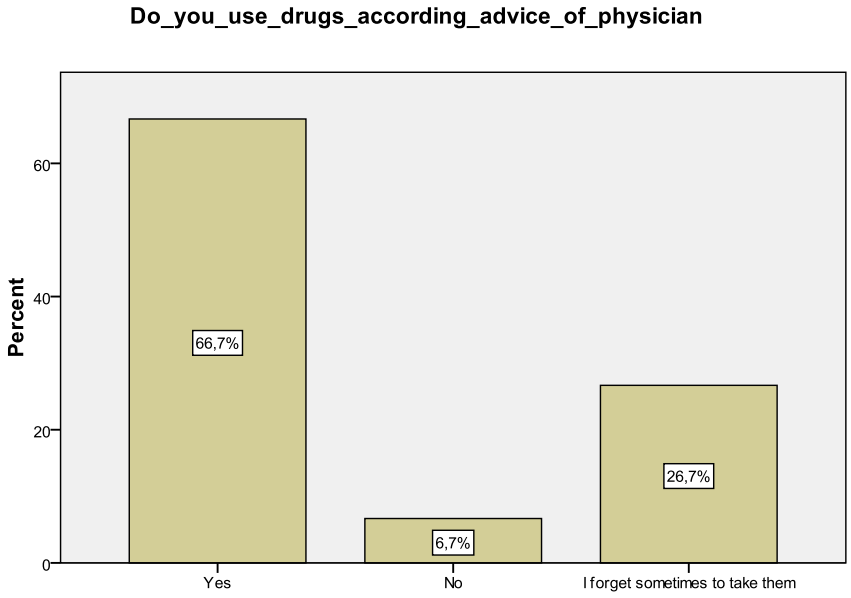


Figure 9. Do you use your drugs, according advice of a physician? Denominator 100% is the total amount of patients.

From all of patients, 52 (86.7%) of them suffered from other comorbidities which were hypertension (20 patients), Myocardial Infarction (4 patients), Dyslipidemia (8 patients), Hypertension and Dyslipidemia (12 patients), Hypertension and Myocardial Infarction (4 patient) and all of them together (4 patients). The comorbidities are shown in figure 10.

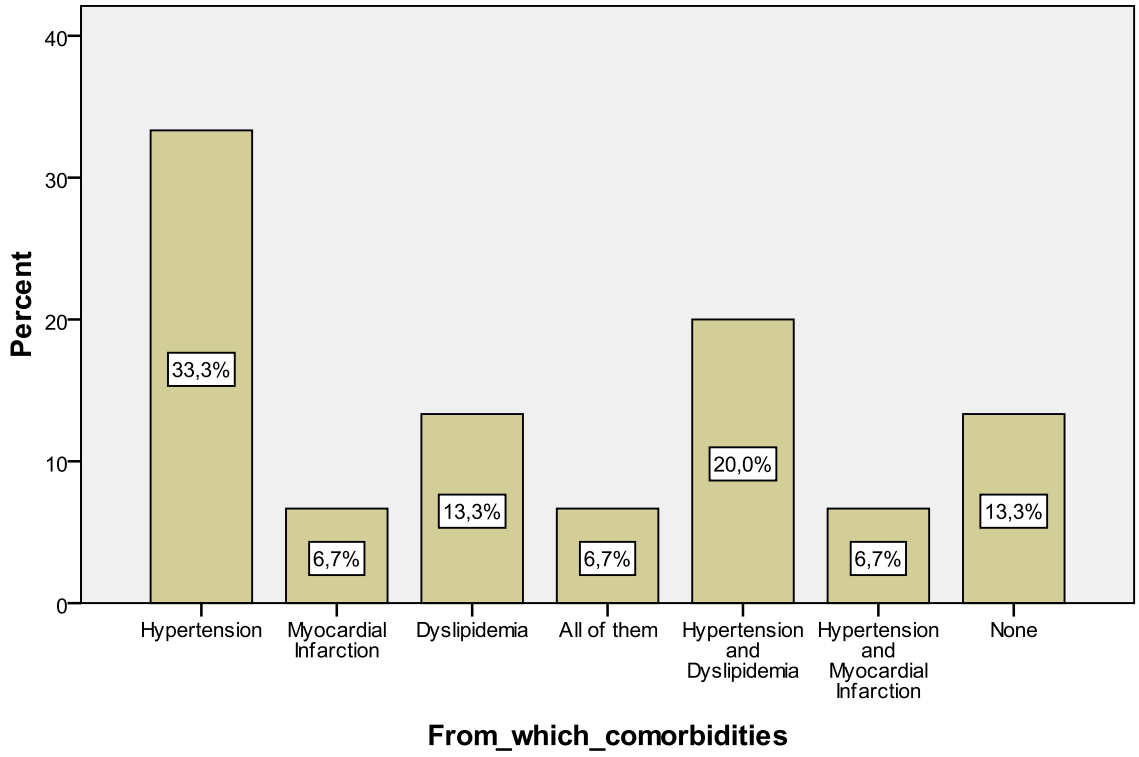


Figure 10. Comorbidities of patients. Denominator 100% is the total amount of diseases.

Over half of the total of the sample (48 patients) used another drugs. Four patients used Simvastatin, Valsarfan and Diltiazem together, 4 patients used Hydroxyzine dihydrochloride, Amlodipine, Acetylsalicylic acid, Allopurinol, and Bromazepam together, 4 patients used Clopidogrel, Valsartan, and Atorvastatin together, 4 patients used Amilodipine, 4 patients used Amilodipine and Symvastatine together, 4 patients used Symvastatin, Lercadipine, Isosorbide Mononitrate and Hydroxyzine dihydrochloride together, 4 patients

used Hydrochlorothiaside and Atenolol together, 4 patients used Losartan Potassium, 4 patients used Atorvastatin and Irbesartan together, 4 patients used Simastatin, 4 patients used Simastatin, Tamsulosine, Irbesartan, Isosorbide Monomitrate, Acetylsalicylic acid, and Clopidogrel together, 4 patients used Amlodipine, Atorvastatin Calcium Trihydrate, and Venlafaxine together and finally 4 patients used Enalapril. The results of the drugs that patients used parallel to the drugs for type 2 diabetes are illustrated in figure 11. The table 1 shows the drugs in total with their dosages that patients used for other diseases except type 2 diabetes mellitus.

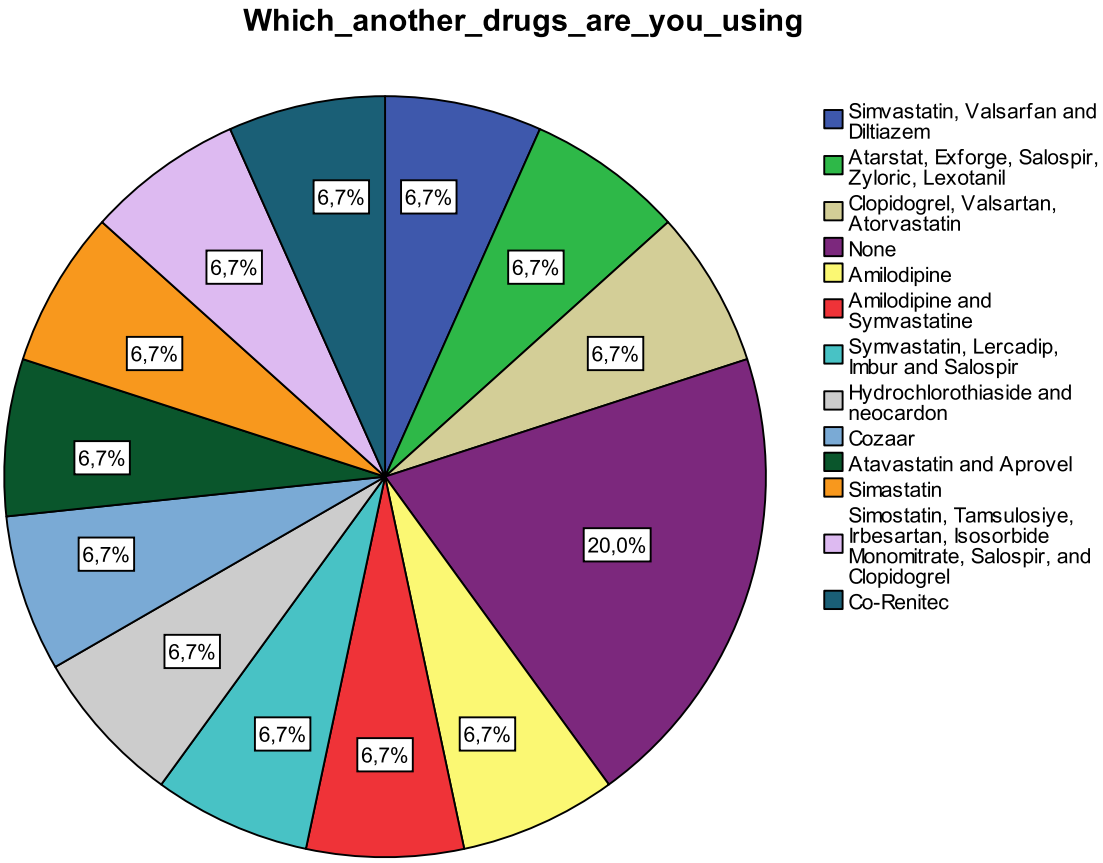


Figure 11. Drugs patients used parallel to the drugs for type 2 diabetes. Denominator 100% is the total amount of drugs.

Table 1. Drugs and dosages used by patients except drugs for type 2 diabetes.

Drugs	n	Dosage
Amilodipine	8	1x1 and 1x2
Irbesartan	4	1x1
Hydroxyzine dihydrochloride	4	1x1
Atorvastatin	8	1x1
Clopidogrel	8	1x1
Enalapril	4	1x1
Losartan Potassium	4	1x1
Diltiazem	4	1x1
Venlafaxine	4	1x1
Hydrochlorothiaside	4	1x2
Isosorbide Mononitrate	8	1x1
Lercanidipine	4	1x2
Bromazepam	4	1x2
Atenolol	4	1x1
Acetylsalicylic acid	12	1x1
Simvastatin	20	1x1
Tamsulosin	4	1x1
Valsarfan	8	1x1 and 1x2
Allopurinol	4	1x2

Demnominator: total number of patients with DMII (n=60).

Only 20 (36.7%) patients drank a glass of wine every day (see figure 12). At the question if “you think that composition of food intake plays a role in treatment of your diabetes mellitus?”, 48 (80%) patients answered positive and 12 (20%) patients answered negative. The results of this question are shown in figure 13.

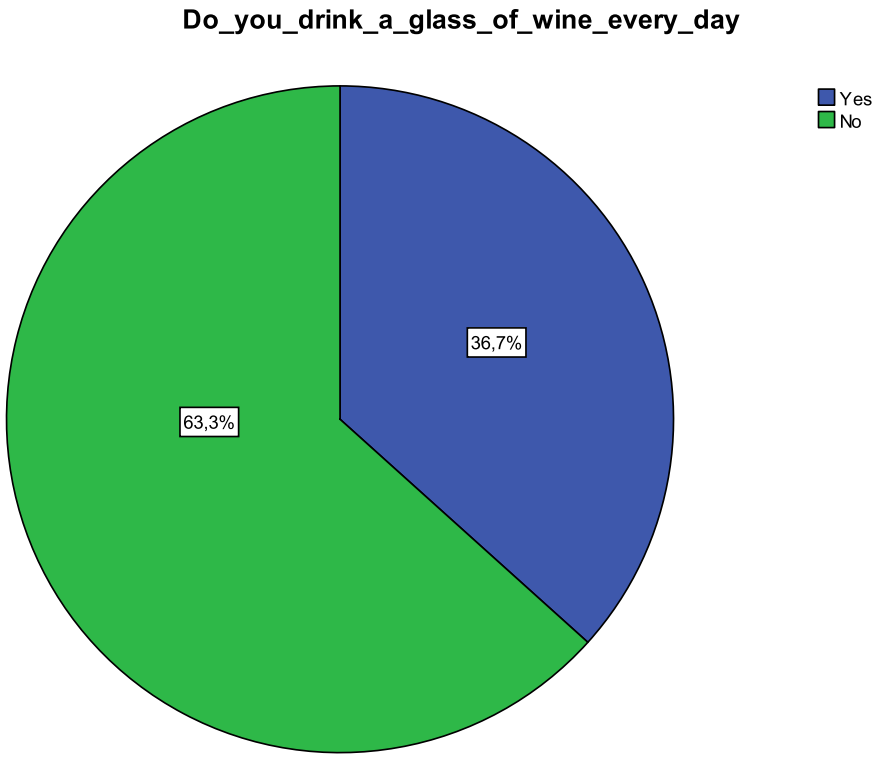


Figure 12. Do you drink a glass of wine every day? Denominator 100% is the total amount of patients.

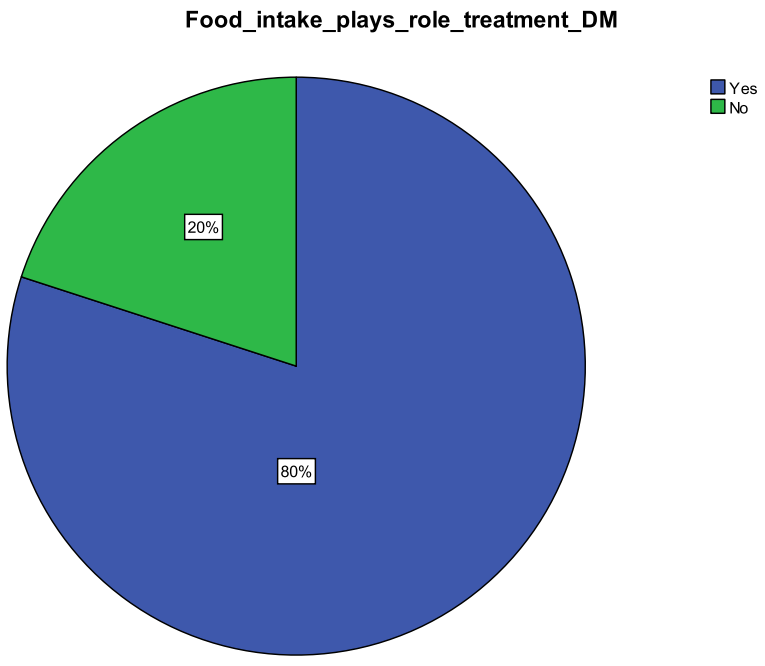


Figure 13. Do you think that composition of food intake plays a role in treatment of your diabetes mellitus? Denominator 100% is the total amount of patients.

The last question of the questionnaire was if patients follow the diet questionnaire. This question was answered only by 20 (33.3%) patients. That's why this result is not reliable. Most of patients (n=12) answered negative and 8 patients answered positive (see figure 14).

Figure 14. Do you follow the diet questionnaire? Denominator 100% is the total amount of patients.

According to Pearson correlation, the age of patients was positive weak linear correlated by the frequency of physician`s visit (r=0.412), by the way patients measured their glucose level (r=0.496), negative weak linear correlated by the drugs that patients were using for the diabetes mellitus (r=-0.445), negative middle linear correlated by the cormobidities patients suffered (r=0.600), the food intake (r=-0.544) and the diet questionnaire they follow (r=-0.542). The results of Pearson correlation according to age are shown in Table 2.

Table 2. Pearson correlation according to age.

Variables	Age		
	Pearson, r	**P**	**N**
When were you first time diagnosed?	0.837	0	60
How frequent do you visit physician?	0.412	0.001	60
How was it measured?	0.496	0	60
Which drugs for diabetes mellitus are you using?	-0.445	0	60
Are you suffering from any comorbidities?	-0.600	0	60
Does the food intake play role in treatment of Diabetes Mellitus?	-0.544	0	60
Follows the diet questionnaire?	-0.542	0.014	20

Denominator is the total amount of age.

The gender of patients was negative weak linear correlated by whether the food intake plays role in the treatment of type 2 diabetes mellitus (r=-0.354), and the dosage that patients use other drugs (r=-0.408) and positive middle linear correlated by the daily consumption of a glass of water (r=0.636), and the the whether they follow the diet questionnaire (r=0.612). The results of Pearson correlation according to gender are shown in Table 3.

Table 3. Pearson correlation according to gender.

Variables	Gender		
	Pearson, r	**P**	**N**
In which dosage are you using other drugs?	-0.408	0.004	48
Do you drink a glass of wine every day?	0.636	0	60
Do you think that composition of food intake plays a role in treatment of your DM?	-0.354	0.006	60
Follows the diet questionnaire?	0.612	0.004	20

Denominator is the total amount of gender.

The first time that patients diagnosed diabetes mellitus was positive middle linear correlated by the frequency patients visit the physician (r=0.586), positive weak linear correlated by the time patients last measured their glycaemia (r=0.305), by whom measured patients glycaemia (r=0.340), negative middle linear correlated by whether patients suffered from any comorbidities (r=-0.555), negative middle linear correlated by the fact if patients follows the diet questionnaire (r=-0.667), and negative weak linear correlated by whether the food intake plays role in treatment od diabetes mellitus (r=-0.354). The results of Pearson correlation according to the first time that patient diagnosed diabetes mellitus are shown in Table 4.

Table 4. Pearson correlation according to the first time that patient diagnosed diabetes mellitus.

Variables	**First time patient diagnosed diabetes Mellitus**		
	Pearson, r	**P**	**N**
How frequent do you visit physician?	0.586	0	60
When was your last glycaemia measured?	0.305	0.018	60
How was it measured?	0.340	0.008	60
Which drugs for diabetes mellitus are you using?	-0.492	0	60
Are you suffering from any comorbidities?	-0.555	0	60
Does food intake play role in treatment of diabetes mellitus?	-0.354	0.006	60
Follows the dietary questionnaire?	-0.667	0.001	20

Denominator is the total amount of month.

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The knowledge of the glucose level fasting of patients was positive weak linear correlated by the frequency of physicians visit (r=0.443), and the fact that patients use drugs according to advice of a physician (r=0.425), and negative

weak linear correlated by the drugs of diabetes mellitus patients were using (r=-0.389) and by the other drugs they were using (r=-0.403). The results of Pearson correlation according to the knowledge of the glucose level fasting of patients are shown in Table 5.

Table 5. Pearson correlation according to the knowledge of the glucose level fasting of patients.

Variables	**Knowledge of the glucose level fasting of patients**		
	Pearson, r	**P**	**N**
How frequent do you visit physician?	0.443	0	60
Which drugs for diabetes mellitus are you using?	-0.389	0.002	60
Do you use drugs according advice of a physician?	0.425	0.001	60
Which another drugs are you using?	-0.403	0.001	60

Denominator is the total amount of patients.

The glucose level of patients (high or low) was positive weak linear correlated by the frequency of the physician`s visit (r=0.337), and by the way patients measure their glucose blood level (r=0.409), negative weak linear correlated by the fact whether patients suffer from any comorbidities (r=-0.304), and by the fact whether patients think that composition of food intake plays a role in treatment of their diabetes mellitus (r=-0.389), positive middle linear correlated by the last time patients measured their glycaemia (r=0.595), negatine middle linear correlated by the type of drugs for diabetes mellitus patients used (r=-0.545), and by the fact whether they follow the diet questionnaire (r=-0.612) and negative strong linear correlated by the comorbidities patients are suffering from (r=-0.732). The results of Pearson correlation according to the glucose level fasting of patients are shown in Table 6.

Table 6. Pearson correlation according to the glucose level of patients (high or low).

Variables	Glucose level of patients (high or low)		
	Pearson, r	P	N
How frequent do you visit physician?	0.337	0.011	56
When was your last glycaemia measured?	0.595	0	56
How was it measured?	0.409	0.002	56
Which drugs for diabetes mellitus are you using?	-0.545	0	56
Are you suffering from any comorbidities?	-0.304	0.023	56
From which comorbidities are you suffering from?	-0.732	0	56
Do you think that composition of food intake plays a role in treatment of your diabetes mellitus?	-0.389	0.003	56
Do you follow the diet questionnaire?	-0.612	0.004	20

Denominator is the total amount of glucose level.

Furthermore, the frequency of physicians` visit of the patient was positive weak linear correlated by the last time patients measured their glycaemia (r=0.398), negative weak linear correlated by the dosage patients use their drugs for diabetes mellitus (r=-0.453), and whether patients think that composition of food intake plays a role in treatment of their diabetes mellitus (r=-0.490), negative middle linear correlated by the drugs for diabetes mellitus patients use (r=-0.506) and by the fact whether they follow the dietary questionnaire (r=-0.645). The results of Pearson correlation according to the frequency of physicians` visit of the patient are shown in Table 7.

Table 7. Pearson correlation according to the frequency of physicians` visit of the patient.

Variables	Frequency of physicians` visit of the patient		
	Pearson, r	P	N
When was your last glycaemia measured?	0.398	0.002	60
Which drugs for diabetes mellitus are you using?	-0.506	0	60
In which dosage form are you using them?	-0.453	0.001	48
Do you think that composition of food intake plays a role in treatment of your diabetes mellitus?	-0.490	0	60
Follow the diet questionnaire	-0.645	0.002	20

Denominator is the total amount of visits.

The last time glycaemia measured by patients was negative weak linear correlated by the comorbidities patients were suffering from (r=-0.478), and was negative middle linear correlated by the drugs for diabetes mellitus patients were using (r=-0.568), and by the fact whether patients follows the diet questionnaire (r=-0.612). The results of Pearson correlation according to the last time glycaemia measured by patients are shown in Table 8.

Table 8. Pearson correlation according to the last time glycaemia measured by patient

Variables	Last time glycaemia measured by patients		
	Pearson, r	P	N
Which drugs for diabetes mellitus are you using?	-0.568	0	60
From which comorbidities are you suffering from?	-0.478	0	60
Follows the diet questionnaire	-0.612	0.004	20

Denominator is the total amount of time.

The person that patients` glycaemia measured was negative weak linear correlated by the fact whether patients suffered from any comorbidities (r=-0.330), by the comorbidities patients were suffering from (r=-0.303) and by the fact whether food intake play role in treatment of diabetes mellitus (r=-0.320) and was negative middle correlated by the drugs patients were using for diabetes mellitus (r=-0.571). The results of Pearson correlation according to the person that patients` glycaemia measured are shown in Table 9.

Table 9. Pearson correlation according to the person that patients` glycaemia measured.

Variables	**Person that patients` glycaemia measured**		
	Pearson, r	**P**	**N**
Which drugs for diabetes mellitus are you using?	-0.571	0	60
Are you suffering from any comorbidity?	-0.330	0.010	60
From which comorbidities are you suffering from?	-0.303	0.019	60
Does food intake play role in treatment of diabetes mellitus?	-0.320	0.013	60
Follows the dietary questionnaire	-0.919	0	20

Denominator is the total amount of caregiver.

All males knew their glucose level fasting, while the percentage of females was 90% ($p<0.05$). Males visit their physician more often than females do (2.2±0.8 vs 2.7±0.9, $p<0.05$). Also, males drink a glass of wine every day significantly more than females (80% vs. 15%, $p<0.05$). But females support significant more that food intake plays role in treatment of diabetes mellitus than males (90% vs 60%, $p<0.05$).

Patients who measure their glycaemia by themselves measured their glycaemia significantly more in the last month (100% vs. 45.5%, $p<0.05$) and had significantly more chance to have high glucose blood level (100% vs. 45.5%, $p<0.05$), than the other patients.

The factors which were examined whether they affect the glucose level (low or high) according to the logistic regression are the following:

- Age
- Gender
- Type of DM
- First time diagnosed of DM
- Do you know your blood glucose level fasting?
- How frequent do you visit physician?
- When was your last glycaemia measured?
- How was it measured?
- Which drugs for DM are you using?
- Do you use your drugs according advice of physician?
- Are you suffering from any comorbidities?
- From which comorbidities
- Which other drugs are you using?
- In which dosage form are you using them?
- Do you drink a glass of wine every day?
- Do you think that composition of food intake plays a role in the treatment of your DM?
- Follows the diet questionnaire

The results of the univariate logistic regression analysis are shown in table 10.

Table 10. Factors that influence the knowledge of glucose level fasting (univariate logistic regression analysis)

Factor	P	B	OR	95% CI
Age	0.521	0.011	1.011	0.978-1.044
Gender	0.074	1.163	3.200	0.892-11.483
First time diagnosed of DM	0.043	1.042	1.882	0.886-2.776
How frequent do you visit physician?	0.017	0.975	2.652	1.190-5.907
When was your last glycaemia measured?	0	2.490	12.056	3.330-43.639
How was it measured?	0.004	1.204	3.333	1.460-7.610
Which drugs for DM are you using?	0	-0.416	0.659	0.527-0.825
Do you use your drugs, according advice of a physician?	0.049	0.668	1.951	1.004-3.791
Are you suffering from any comorbidity?	0.114	4.119	2.110	1.416-4.781
From which comorbidities are you suffering from?	0.001	-1.063	0.345	0.188-0.635
Which other drugs are you using?	0.043	0.168	1.182	1.005-1.391
In which dosage form are you using them?	0.798	-0.182	0.833	0.206-3.371
Do you drink a glass of wine every day?	0.618	-0.288	0.750	0.242-2.325
Do you think that composition of food intake plays a role in the treatment of your DM?	0.442	2.838	1.774	0.815-3.146
Follows the dietary questionnaire	0.336	1.976	1.615	0.747-2.477

DM: diabetes mellitus

The table 10 shows that the glycaemia level of patients is related to ($P<0.1$):

- ✓ Gender

- ✓ First time diagnosed of diabetes mellitus
- ✓ How frequent do you visit youw physician?
- ✓ When was your last glycaemia measured?
- ✓ How was it measured?
- ✓ Which drugs for DM are you using?
- ✓ Do you use your drugs, according advice of a physician?
- ✓ From which comorbidities are you suffering from?
- ✓ Which other drugs are you using?

After that, it was done the multinomial logistic regression analysis, and found that no one factor has important statistical difference ($P<0.05$).

The factors which were examined whether they affect the person who measure the glucose level of patients, according to the logistic regression are the following:

- Age
- Gender
- Type of DM
- First time diagnosed of DM
- Do you know your blood glucose level fasting?
- How much is it?
- How frequent do you visit physician?
- When was your last glycaemia measured?
- Which drugs for DM are you using?
- Do you use your drugs according advice of physician?
- Are you suffering from any comorbidities?
- From which comorbidities
- Which another drugs are you using?
- In which dosage form are you using them?

- Do you drink a glass of wine every day?
- Do you think that composition of food intake plays a role in treatment of your DM?

The results of the univariate logistic regression analysis are shown in table 11.

Table 11. Factors that influence who measure the glucose level of patients (univariate logistic regression analysis)

Factor	P	B	OR	95% CI
Age	0.142	0.024	1.024	0.992-1.058
Gender	0.412	-0.539	0.583	0.161-2.114
First time diagnosed of DM	0.104	0.981	2.667	0.817-8.708
Do you know the glucose level fasting?	0.199	2.287	2.462	1.014-4.228
How much is it?	0.214	2.980	1.292	0.667-2.007
How frequent do you visit physician?	0.860	0.058	1.060	0.555-2.023
When was your last glycaemia measured?	0.157	2.491	3.225	1.879-4.774
Which drugs for DM are you using?	0.003	-0.760	0.468	0.283-0.774
Do you use your drugs according advice of physician?	0.079	0.763	2.146	0.916-5.026
Are you suffering from any comorbidity?	0.123	-1.204	0.300	0.065-1.384
From which comorbidities?	0.006	-0.274	0.761	0.625-0.926
Factor	**P**	**B**	**OR**	**95% CI**
Which another drugs are you using?	0.917	-0.008	0.992	0.852-1.155
In which dosage form are you using them?	0.445	-0.560	0.571	0.136-2.399

Do you drink a glass of wine every day?	0.264	-0.731	0.481	0.134-1.734
Do you think that composition of food intake plays a role in treatment of your DM?	0.561	-0.405	0.667	0.170-2.614

The table 11 shows that the person who measure the glycaemia level of patients is related to the following significant variables (P<0.1):

- ✓ Which drugs for DM are you using?
- ✓ Do you use your drugs according advice of physician?
- ✓ From which comorbidities?

Table 11. Factors that influence who measure the glucose level of patients (univariate logistic regression analysis)

Factor	P	B	OR	95% CI
Which drugs for DM are you using?	0.056	-0.557	0.573	0.385-0.853
Do you use your drugs according advice of physician?	0.003	1.594	4.923	0.978-24.789
From which comorbidities?	0.057	-0.466	0.628	0.446-0.883

After that, it was done multinomial logistic regression analysis, and found that only the patients who used their drugs according advice of physician has important statistical difference (B:1.594, p:0.003, OR:4.923, 95%CI:0.978-24.789). According to this result (table 11), patients who use their drugs according advice of physician have 4.923 more chances to have high levels of glycaemia than patients who do not use their drugs according advice of physician.

4. Discussion

This study included 60 diabetic patients of a pharmacy in Greece, with mean age 56.5±17.5 years.The pharmacy is located in a city Veroia, which accounts 60.000 inhabitants and its 90km away from Thessaloniki.The diabetic patients of this pharmacy in Veria appear to be sensitive to their disease, because 93.3% of the sample knew the glucose levels in their blood. Even patients who had low levels of glucose in their blood, knew their glucose levels.

Most patients visit their doctor every 3 and every 6 months. This may be justified by the fact that diabetes is not diagnosed for the first time recently. So, the blood glucose levels may be adjusted. Important role in the treatment and monitoring of type 2 diabetes in the town of Veria in Greece plays the pharmacist, since most patients had their blood glucose measured by pharmacist and not by the doctor.

In recent years there have been various trials to determine the ability and benefits of different strategies for prevention or delay the onset of diabetes mellitus type 2. The first goal of the proposed treatment is the interventions in the daily life (diet and exercise) of patients, which has been shown to be effectiveness and improve the glychaimia reducing the cardiovascular risk factors (DPS studies, DPP) (Lindstron et al., 2003, Knowler et al., 2002). As the pre-diabetes progresses, the pharmaceutical intervention for the management of hyperglycaemia and the risk factors for coronary heart disease is necessary. For this purpose, the medication includes metformin (DPP studies, IDPP) (Ramachandran et al., 2006, Knowler et al., 2002), acarbose (STOP-NIDDM) (Chiasson et al., 2002) and Thiazolidinediones (DREAM, ACTNOW) (Defronzo et al., 2009, DREAM, 2006). These medications an seems by large multicenter studies, reduce the progression from prediabetes to diabetes.

Since 1990 there were only three types of antidiabetic tablets: sulfonylureas, biguanides, and acarbose. Approximately 20 years after, another 5 categories have been added: thiazolidinediones, meglitinides, activators GLP-1, analogues GLP-1, and inhibitors of DPP-4. So, the total of categories of drugs used for the treatment of hyperglycemia in type 2 diabetes are: insulins, sulfonylureas, biguanides, glucosidase inhibitors, thiazolidinediones, meglitinides and incretins. The choice of the best and most effective treatment

for the management of hyperglycemia in type 2 diabetes mellitus should be considered in the light of the following factors: duration of diabetes mellitus, age and weight of patient, presence or absence of the residual secretion of insulin, the degree of hyperglycemia, the levels at which the health care professionals want to regulate sugar, speed and the medicament action mode, the degree of compliance of patients, the effect of these drugs on lipids, contraindications and the side-effects of drugs (Zoupas, 2007).

There is a tendency for the treatment of type 2 diabetes with insulin mainly, and with metformin. Other medicines used to treat type 2 diabetes, such as Insulin Secretagogues-glinides and sulfonylureas, Dipeptidyl-peptidase-4 Inhibitors, and Sitagliptin, are not used (prescribed) widely. This happens because of the policies of the doctors in Greece, although these drugs which are used to regulate the blood glucose levels are not used alone but in combination with metformin and insulin. Thus, somebody could claim that these drugs are used as auxiliary and not as main drugs for the treatment of diabetes mellitus.

Insulin has been widely used as monotherapy and in combination with antidiabetic tablets since the late 50s. Nowadays, it is estimated that only a third of diabetic type 2 is treated with insulin and a further 15% in combination of insulin and antidiabetic tablets (Mayfield & White, 2004). These statements does not agree with the results of this study, because 40% of patients used inslulin and 26,7% metformin as monotherapy. From the other hand, the rest patients were treated with combination of insulin and antidiabetic tablets as it is referred to the literature (Mayfield & White, 2004).

Our study showed that about one of three patients did not follow the advice of a physician for the use of their drugs. The Pharmaceutical Group of the European Union (PGEU) reported in May 2008 moderate and poor compliance of patients in antidiabetic treatment, and underline that health care professionals usually overestimate the degree of compliance (Pharmaceutical Group of the European Union Targeting adherence, 2008). In various studies compliance to anti-diabetic tablets ranges between 36-93% (Wong et al., 2011, Odegard & Capoccia, 2007, Cramer, 2004) to first 6-24 months of treatment, while the compliance to the treatment to Insulin is about 62-64% (Odegard &

Capoccia, 2007, Cramer, 2004). Our results are in agreement with the results of these studies, because about 35% of patients in this pharmacy in the city of Veria are not compliance with the treatment which is given by doctors.

In Greece, due to the lack of primary health care, access to doctors is difficult, takes a lot of time and often too expensive. This is the reason why Greek patients consider the local pharmacist as their “doctor”. Thus, patients most often seek advice from friends, the local pharmacist and others in order to change a medication or change the dose of the medication they use.

Most diabetic patients suffer parallel from other comorbidities. So, our study showed that Greek type 2 diabetic patients of this pharmacy in Veroia suffered from hypertension, myocardial infarction, and dyslipidemia. This is the reason why patients with type 2 diabetes mellitus use drugs that are not useful for the treatment of diabetes. These drugs are used for the treatment of the diseases that are caused due to diabetes or are independed with diabetes.

Furthermore, most patients do not drink a glass of wine every day, as it is recommended and their opinion about the fact whether the composition of food intake plays a role in the treatment of the diabetes mellitus is positive. As it was mentioned in the section of results the last question of the questionnaire, which was whether patients follow the diet questionnaire, only 40% of correspondence answer the question patients. The small response rate makes this result unreliable and non-evaluable.

The analysis of our study showed that the type of diabetes mellitus is correlated with the age of patients. It is reasonable, because younger patients suffer from type I diabetes and older patients suffer from type II diabetes. Also, patients with type I diabetes mellitus knew more their blood glucose level and measured their glycaemia more often. This is due to fact that these patients are younger in age and are more interest and coherence than older people. Moreover, patients with type II diabetes mellitus suffer from other comorbidities, because these patients are older and as it is known older people in the elderly usually have a lot of problems with their health. Diabetic type II patients, usually have increased blood glucose levels, which cause a lot of problems to those people.

Finally, this study showed that younger patients measure their blood glucose level by themselves, since older patients measure their glycaemia by the physician or by the pharmacist. Also, males drink a glass of wine every day significantly more than females.

5. Conclusions

Most of the diabetic patients of this pharmacy in the city of Veroia know the glucose levels in their blood and visit their doctor every 3 and every 6 months. The local pharmacist plays important role in the monitoring of the glucose level, probably because the access to the physicians is difficult and costs. The drugs that are used in the town of Greece, Veria, for the treatment of diabetes mellitus are insulin and metformin. Patients with type II diabetes are more possible to suffer from comorbidities. Also, younger patients are more cohesive and measure their blood glucose level by themselves more often than older patients.

It is very important for Greece to develop primary health care services in order patients to access physicians and regulate their glycaemia. Also, patients must be educated to measure their blood glucose level alone and learn other ways to treat their diabetes, such as exercise and diet.

Abbreviation

ADA: American Diabetes Association

BMI: body mass index

CVD: cardiovascular disease

DM: diabetes mellitus

DPP-4: dipeptilo peptidase 4

FDA: Food and Drug Adminitration

FFA: free fatty acids

GI: glycemic index

GIP: Glucose-dependent insulinotropic polypeptide

HDL: High-density lipoprotein

IDDM: insulin dependent diabetes mellitus

IDF: International Diabetes Federation

IFG: impaired fasting glucose

IGT: impaired glucose tolerance

IL-6: interleukin-6

LDL: Low-density lipoprotein

MODY: Maturity-Onset Diabetes of the Young

NHANES: National Health and Nutrition Examination Survey

NIDDM: non- insulin dependent diabetes mellitus

OGTT: Oral Glucose Tolerance Test

TCF: transcription factor

TNF- α: Tumour Necrosis Factor- α

WHO: World Health Organization

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Appendix

Questionnaire

The analysis of pharmacotherapy by patients suffering with Diabetes Mellitus type 2 in Greece

Please mark off your answer.

1. **What is your age?**

2. **What is your gender?**
   - ☐ Male
   - ☐ Female
3. **From which DM type are you suffering from?**
   - ☐ Type 1
   - ☐ Type 2
   - ☐ I do not know
4. **When were you first time diagnosed?**
   - ☐ Childhood
   - ☐ Adulthood
   - ☐ Elderly
5. **Do you know your blood glucose level fasting?**
   - ☐ Yes(if yes, go to question 6)
   - ☐ No(if no, go to question 7)
6. **How much is it?**
   - ☐ High
   - ☐ Low
7. **How frequent do you visit physician?**
   - ☐ Every month
   - ☐ Every 3 months
   - ☐ Every 6 months
   - ☐ Longer

8. **When was your last glycaemia measured?**

- ☐ 1 month before
- ☐ 3 months before
- ☐ 6 months before
- ☐ I do not remember

9. **How was it measured?**

- ☐ By myself
- ☐ By the physician

10. **Which drugs for DM are you using?**

- ☐ Metformin
- ☐ Thiazolidinediones
- ☐ Insulin Secretagogues- glinides,sulfonylureas
- ☐ A-Glucosidase Inhibitors
- ☐ DIpeptidyl-peptidase-4 Inhibitors
- ☐ Incretin Mimetics
- ☐ Insulin

11. **Do you use your drugs according advice of physician?**

- ☐ Yes
- ☐ No
- ☐ I forget sometimes to take them

12. **Are you suffering from any comorbidities?**

- ☐ Yes(if yes, go to question 13)
- ☐ No(if no, go to question 14)

13. **From which comorbidities:**

- ☐ Hypertension
- ☐ Angina Pectoris
- ☐ Myocardial Infarction
- ☐ Dyslipidemia
- ☐ Chronic kidney disease

☐ Non-alcoholic fatty liver disease

14. **Which another drugs are you using?**

15. **In which dosage form are you using them?**

16. **Do you drink a glass of wine every day?**

☐ Yes

☐ No

17. **Do you think that composition of food intake plays a role in treatment of your DM?**

☐ Yes

☐ No

☐ I do not know

18. **Follows the diet questionnaire**