MASTER'S THESIS

TREATMENT LINES AND GLYCEMIC CONTROL AMONG PATIENTS WITH TYPE 2 DIABETES IN NORTH KARELIA, FINLAND

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Type 2 diabetes mellitus (T2DM) is one of the major concerns in health care due to the numerous complications and related increase in poor outcomes of patients and costs. To avoid or delay these complications it is important to choose a correct treatment and use it properly. The objectives of this research were to analyse the differences in glucose control of T2DM patients by treatment options such as insulin, non-insulin treatments and combination therapies and to examine the differences in treatment options and glycemic control by demographic factors using T2DM patient cohort in North Karelia, Finland from 2017.

This retrospective, cross-sectional study obtained data from an electronic patient database used in North Karelia, Finland. Patients selected were those diagnosed with type 2 diabetes and aged 20 years or older. The treatment lines of patients were defined using the prescriptions and by grouping the medications in non-insulin, insulin and combination treatments. The outcome evaluated was the achievement of the target level of HbA1c (<53 mmol/mol).

Metformin was the most used treatment line in diabetic patients and the second one of the non-insulin treatments was gliptins. Insulins in general were the second most common group. There was a statistically significant difference in HbA1c levels by treatment lines ($p<0.001$). Patients without medication had a lower mean HbA1c level (42.2 mmol/mol) than patients who were under any medication. Patients using metformin and gliptins had an average lower HbA1c level than the clinical recommendations (53 mmol/mol). Approximately 8% of patients taking only metformin had an HbA1c level ≥ 53 mmol/mol. Patients with short-term insulins had the highest mean HbA1c level of 64.2 mmol/mol. Only 21.4% of female patients under short term insulins and 29.6% under long-term insulins were reaching the glycemic targets. There was a statistically significant difference between treatment groups and the proportion of patients having HbA1c level ≥ 75 mmol/mol (p-value < 0.001). Highest proportions of patients with HbA1c level ≥ 75 mmol/mol (over 15%) were among those using insulins.

There was a statistically significant association between municipalities and HbA1c level ≥ 75 mmol/mol (p-value = 0.007). Municipalities like Ilomantsi and Juuka had a higher proportion of patients with HbA1c levels ≥ 75 mmol/mol (9.9% and 8.6% respectively) than the other municipalities. In contrast, most of the patients that lived in Kontiolahti had a good glycemic control with only 3% of patients with HbA1c level ≥ 75 mmol/mol. Binary logistic regression analysis showed that rurality (urban, semi-urban and rural) was not associated with high HbA1c levels (≥ 75 mmol/mol) (p-value = 0.161). Differences in HbA1c levels were observed between patients from different municipalities but under the same treatment.

This study identified differences in the used medications by age and gender as well as in glycemic control by age and treatment options. However, it seemed that the treatment lines assessed using prescriptions followed the guidelines and clinical indications. This study suggests that the variance in treatment options and glycemic control by demographic factors is most likely explained by differences in the age of the patient populations and other possible causes such as treatment adherence, training for self-care or cost preferences.

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CONTENTS

ABBREVIATIONS

ADA - American Diabetes Association
ANOVA - Analysis of Variance
ASCVD - Atherosclerotic Cardiovascular Disease
ATC - Anatomic Therapeutical Chemical
BMI - Body Mass Index
CKD – Chronic Kidney Disease
CVD - Cardiovascular Disease
GLP-1 - Glucagon-Like Peptide-1
HbA1c - Glycated Hemoglobin
ICD - International Classification of Diseases
IGT - Impaired Glucose Tolerance
LDL - Low Density Lipoproteins
OGTT - Oral Glucose Tolerance Test
SD - Standard Deviation
SGLT2 - Sodium-Glucose Cotransporter 2
T2DM - Type 2 Diabetes Mellitus
TZD - Thiazolidinediones

SYMBOLS

β: beta
X^2: chi-square test

1 INTRODUCTION

The number of people with type 2 diabetes (T2DM) was estimated to be 382 million by 2012 and the prediction of the number of people developing diabetes before 2030 is approximately 550 million (Rees et al. 2017). In Finland, the number of people with diabetes has risen quickly from the beginning of the 21st century. According to the Finnish Social Insurance Institution 368,900 people purchased antidiabetic medicines in 2016, but it is important to mention that not all diabetics are on medication and not all diabetics get their medication covered by the social insurance (Kansaneläkelaitos 2019).

Diabetes mellitus is a multisystem disease and its chronic macrovascular and microvascular complications lead to significant morbidity and mortality (Rees et al. 2017). In 2016, diabetes was one of the leading causes of death worldwide with 1.6 million people dying due to diabetes complications (World Health Organization 2018). The cost of diabetes care (treatment and management) in Europe was 89 billion euros in 2011 (Reini 2013). In Finland, the cost of diabetes care was about 9% of health care expenditure in 2007 and additional costs of diabetes care was approximately 833 million euros (National Institute for Health and Welfare 2016).

Evidence suggests that diabetes complications can be prevented, and costly services can be reduced by good care of diabetes (International Diabetes Federation 2011), including early diagnosis and appropriate treatment following the recommended treatment guidelines (Finnish Diabetes Association 2003).

A combination of lifestyle management and pharmacological treatment is necessary for the treatment of high blood glucose in patients with T2DM. In fact, the combination of diet and physical exercise have shown more improvement in hyperglycemia and cardiovascular risk factors reduction than each intervention alone (Franz et al. 2015). For this reason, both are recommended as first-line therapy with pharmacological treatment from the time of the diagnosis (Type 2 Diabetes: Current Care Guidelines 2018). There are different treatments available in Finland for management of T2DM, some of them are oral agents (metformin, gliptins, sulfonylureas, glinides, SGLT2 inhibitors and glitazones) and some others are injectable agents (GLP-1 analogues and insulins). The first choice of treatment is metformin (except when it is contraindicated or intolerable). Diabetes is likely to progress, and patients

eventually need to change from metformin to other pharmacological treatment or combination therapies. It is important to be familiar with the different treatment options for patients with T2DM and select the most effective ones to achieve and keep good glycemic control.

In Finland, a five-year study by Nazu et al (2019) reported the glycemic control in patients with T2DM and also examined certain demographic factors. This study showed that blood glucose management overtime is a difficult task for all diabetes patients, but female patients tended to have a poorer glycemic control than males. The study concluded that effectively tailored treatment strategies have the potential to improve the quality of care and blood glucose control.

However, information is limited on the use of different treatment options and their association with blood glucose control among patients with T2DM in Finland. Thus, the aim of this study is to investigate the differences in glucose control of T2DM patients by different treatment choices, such as insulin, non-insulin and combination therapies, and further to analyze the differences in treatment lines and glycemic control by demographic factors using the data from Finnish primary health care.

2 THEORETICAL BACKGROUND

2.1 Type 2 diabetes

2.1.1 Definition and pathophysiology

T2DM is a metabolic and heterogeneous disorder with insulin resistance and/or insulin deficiency (Sheehan & Ulchaker 2012) resulting in increased blood glucose concentration. To understand T2DM risk factors, development of complications and optimal treatment choices, we need to understand the main pathogenic mechanisms.

Insulin resistance means the inability of insulin to stimulate glucose uptake in tissues, and it mainly occurs in the liver, in the skeletal muscle and in the adipose tissue. Due to the insulin resistance, the release of the glucose is increased from the liver and the production of non-esterified fatty acids is raised in the adipose tissue. The free fatty acids induce insulin resistance, impair insulin secretion, and stimulate triglyceride synthesis and gluconeogenesis. (Rees et al. 2017).

During the insulin resistance, pancreatic β-cells attempt to maintain normal glucose levels increasing insulin output (Kahn et al. 2014). This dynamic interaction is essential to the maintenance of normal glucose tolerance (Carrera Boada & Martínez-Moreno 2013). However, the ability of β-cells to produce insulin is decreased, and constant elevation of blood glucose leads to progressive deterioration of β-cells and glucose homeostasis and then the development of T2DM (Kahn et al. 2014).

2.2 Risk factors

The management of risk factors is one of the most important ways to prevent the development of T2DM and to reduce the risk of cardiovascular diseases and other complications among people that are already diagnosed with diabetes (Reddy et al. 2013). The most important causes of insulin resistance and pancreatic β-cell deterioration are genes and environment. However, the genetic variation cannot explain the rapid increase in the prevalence of T2DM during the recent decades, indicating the importance of environmental changes in determining T2DM epidemic (Kahn et al. 2014).

Risk factors can be classified as nonmodifiable and modifiable. Figure 1 summarises non-modifiable and modifiable risk factors of T2DM. Nonmodifiable risk factors are those risks that cannot be modified or altered but some of these can be used to calculate the disease risk and serve also in guiding treatment or interventions (Lindström & Tuomilehto 2003 & Levene et al. 2008).

The strongest nonmodifiable risk factor is age (Reddy et al. 2013). Tuomilehto et al. (2003) reported that the prevalence of T2DM rises when age increases. Prevalence of diabetes was lower in subjects who were younger than 60 years old (<10%) than those who were 60-79 years old (10-20%) and mean 2-h plasma glucose (2hPG) concentration showed a linear increment with age. The same study found significant gender difference in the prevalence of T2DM, impaired fasting glycemia (IFG) defined by isolated fasting hyperglycemia and isolated post load hyperglycemia, specifically impaired glucose tolerance (IGT). Diabetes and IFG were more common in men than in women (30-69 years of age) although prevalence of IGT was higher in women than men particularly in the elderly (older than 70 years of age).

Biological factors explain gender variances in risk and outcomes of T2DM. Sex hormones influence on energy metabolism, body composition, vascular function, and inflammatory responses. Endocrine disparities are associated with negative cardiometabolic characteristics for instance androgen excess in women or hypogonadism in men (Kautzky-Willer et al. 2016).

Differences in the risk of T2DM are partly explained by genetic factors. According to Villegas et al. (2012) fourteen Single Nucleotide Polymorphisms (SNPs) were significantly associated with T2DM in middle-aged Han Chinese population. This study was adjusted for age, sex and BMI. Predisposition to develop T2DM has also been explained by ethnicity. Ethnic groups involve individuals with close genetic inheritance. Investigations report that diabetes prevalence in Hispanics is 1.9 times higher than in Caucasian populations (Umpierrez et al. 2007) and, Asians, Hispanics and Asian–Indians have a very high risk of T2DM enhanced by the adoption of the United States lifestyle (Abate & Chandalia 2003). However, Reedy et al (2013) advise that genetic variants explicate less than 10% of the genetic basis of the risk of T2DM making it difficult to use just genetic data for preventive strategies.

Other studies confirm that patients with gestational diabetes have higher risk of T2DM than those who have a normoglycemic pregnancy (Bellamy et al. 2009). Also, women with polycystic ovary syndrome (PCOS), particularly older women, with abdominal obesity and a family history of diabetes, have high prevalence of T2DM and IGT (Dabadghao et al. 2007).

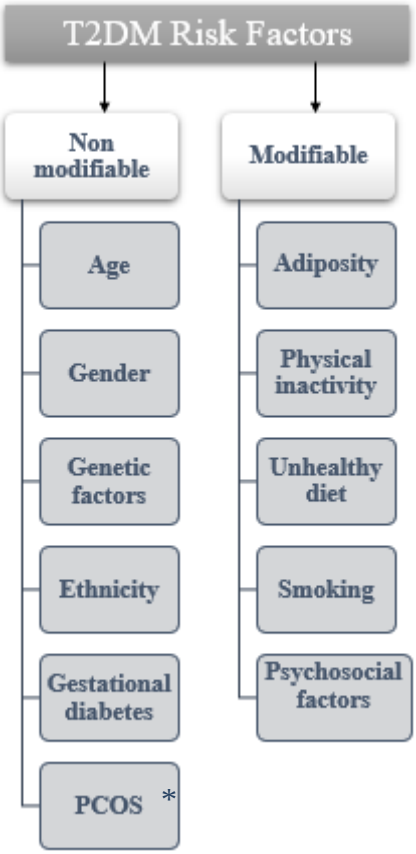

Figure 1. Nonmodifiable and modifiable risk factors for T2DM
*PCOS: Polycystic ovary syndrome

Conversely, modifiable risk factors are those risks that can respond to an intervention (Levene et al. 2008). The modifiable risk factors of T2DM are adiposity (high body mass index, waist circumference, waist to height ratio, waist to hip ratio and early/late weight gain), physical inactivity (decreased physical activity, high sedentary time), unhealthy diet (high consumption of saturated fatty acids and energy dense foods (including a lot of sugar and fat), low intake of fibre, and low adherence to otherwise healthy dietary pattern) and smoking (Reddy et al. 2013 & Bellou et al. 2018). Psychosocial risk factors consist of economic and behavioural components such as low educational level, occupation, low income and stress.

These may otherwise impact diabetes risk overall and between genders (Kautzky-Willer et al. 2016).

2.3 Complications of type 2 diabetes mellitus

Morbidity and mortality in T2DM arise from the progress of the chronic complications of the disease. Patient´s quality of life is seriously affected by the symptoms caused by many complications and psychological effects. Complications can be classified as acute and chronic. Examples of acute complications are hypoglycemia, diabetic ketoacidosis, and hyperosmolar hyperglycemic state. Chronic complications might be classified as microvascular complications, for instance, neuropathy, retinopathy, nephropathy and diabetic foot, and macrovascular complications such as hypertension, cardiovascular disease (CVD), cerebrovascular disease (CBD), peripheral vascular disease (PVD) and erectile dysfunction (Scobie et al. 2009).

Large multicenter studies demonstrated that microvascular outcomes improve with intensive glycemic control more than macrovascular outcomes (Turner et al. 1998). The most serious complications of T2DM are CVDs because the risk of death is three times higher compared with individuals who do not have CVD (Stamler et al. 1993). Several enhancements have occurred in preventing CVD in patients with T2DM such as declining smoking prevalence, managing total cholesterol and blood pressure levels, but CVD still persists among patients with T2DM (Chatterjee et al. 2017)

2.4 Criteria for diabetes diagnosis

The T2DM cannot always be recognized based on diabetes-related symptoms such as thirst, high urine volume and unexplained weight loss as it can be symptomless for a long time even the blood glucose levels are elevated. Some symptoms can exist already when patient has IGT but are usually milder (Valdés et al. 2008).

The criteria for the diagnosis of prediabetes in Finland are fasting plasma glucose (FPG) of 110 mg/dl (6.1 mmol/l) to 124 mg/dl (6.9 mmol/l) or 140 mg/dl (7.8 mmol/l) to 200 mg/dl

(11.0 mmol/l) at 2 hours on the oral glucose tolerance test (OGTT). If the patient does not present symptoms but has an increased FPG at least 126 mg/dl (7 mmol/l) or two-hour glucose stress test greater than 200 mg/dl (11 mmol/l) or measurement of glycosylated hemoglobin (HbA1c) ≥ 48 mmol/mol (≥ 6.5%) then the diagnosis can be confirmed. But if the diagnosis is based exclusively on FPG or 2 hours OGTT, the abnormal result should be checked on a different day. It is recommended to carry out the 2-hours OGTT for patients with high risk. The diagnosis of patients that experience classical symptoms may be based on random plasma glucose concentrations above 200 mg/dl (11 mmol/l). But the determination of venous blood glucose is more reliable than capillary glucose (fingertip measurement). Diagnosis cannot be done through tissue glucose monitors (sensors). HbA1c measurement is also recommended for guidance and follow-up as soon as the diagnosis is made (Type 2 Diabetes: Current Care Guidelines 2018). Above diagnosis criteria is described in table 1.

Table 1. Classification of diagnosis by glucose concentration in plasma

Measurement	Normal	Prediabetes		Diabetes
		*IGT**	*IFG**	
Fasting plasma glucose (mmol/l)	≤ 6.0		6.1 - 6.9	≥ 7.0
Glucose tolerance test for 2 hrs. (mmol/l)	< 7.8	7.8 – 11.0		> 11.0
HbA1c (mmol/mol, (%))	< 42 (6.0)			≥ 48 (6.5)
Random value in symptomatic patient (mmol/l)				> 11.0

*IGT: impaired glucose tolerance
*IFG: increased fasting glucose

2.5 Clinical targets in type 2 diabetes care

Treatment targets are set to avoid or prolong the onset of the complications and to continue with a good quality of life. Microvascular benefits can be obtained by reaching glycemic targets. These targets are glycosylated hemoglobin (HbA1c) less than 53 mmol/mol or 7%, pre-prandial blood glucose <7mmol/l and postprandial <10mmol/l (Type 2 Diabetes: Current Care Guidelines 2018). UK Prospective Diabetes Study (UKPDS) noticed that for each 1% point decrease in HbA1c levels, there is a 21% reduction in the risk of clinical complications associated with hyperglycemia (UK Prospective Diabetes Study Group 1998).

Another treatment target is that low density lipoproteins (LDL) should be lower than 2.5 mmol/l but if diabetic patient has also CVD or increased cardiovascular risk, LDL should be <1.8 mmol/l (Type 2 Diabetes: Current Care Guidelines 2018).

Blood pressure should be <140/80 mmHg for diabetic patients who experience also hypertension and a low risk for CVD (10-year atherosclerotic cardiovascular disease (ASCVD) risk <15%) and <130/80 mmHg for those with a high CVD risk (10-year ASCVD risk >15% or existing ASCVD), but only if it can be safely achieved (Type 2 Diabetes: Current Care Guidelines 2018 & Hypertension: Current Care Guidelines 2014).

Weight management is determined by body mass index (BMI). Diabetic patients should have and maintain a BMI <23 kg/m^2 in order to lessen the risk of CVD and all-cause mortality (American Diabetes Association 2019). Table 2 summarises all these treatment targets.

Table 2. General targets of Diabetes management

Meter	Target	Remarks
HbA1c (mmol/mol (%))	Less than 53 (7.0)	Unless of severe hypoglycemia
Pre-prandial blood glucose (mmol/l)	Less than 7	In self-measurement, the standard level
Postprandial glucose concentration (about 2 hours after a meal) (mmol/l)	Less than 10	In self-measurement, the standard level
LDL cholesterol (mmol/l)	Less than 2.5 Less than 1.8	All diabetics Diabetics with arterial disease, microvascular complications or other risk factors for arterial disease
Blood pressure (mmHg)	Less than 140/80 Less than 130/80	 Diabetics with higher cardiovascular risk
Body Mass Index (kg/m^2)	Less than 23	

The clinical targets in diabetes care could be achieved with non-pharmacological treatment (incl. physical activity, healthy diet, weight control/loss, non-smoking). However, many patients with diabetes are not able to follow neither a rigid diet nor an exercise regime and they will eventually require the drug treatment (Nguyen et al. 2008). Nowadays, the pharmacological treatment aims to impact not only the blood sugar levels, but also cholesterol, blood pressure and metabolic factors.

Classification of glucose lowering medication can be done based on the mechanisms of action: 1) insulin secretion stimulation by pancreas, 2) insulin sensitivity increment in target organs, and 3) glucose absorption rate decrement from gastrointestinal (GI) tract. Treatment targets and medication should always be tailored individually to every patient's preferences, goals and patient characteristics (Davies et al. 2018). The use of glucose lowering medication is described more detailed in the chapter 2.8.

Statins are prescribed as first choice for patients with total cholesterol ≥5.0 mmol/l and LDL ≥2.5 mmol/l. Statins are LDL cholesterol reducers and cardio protectors. In case hypertriglyceridemia is predominant and lifestyle management has not normalized triglyceride levels, it is indicated to start fibrate therapy (Scobie et al. 2009).

Also, rapid initiation and timely titration of medications is recommended to patients with confirmed blood pressure ≥140/80 mmHg to achieve blood pressure goals. The first-line therapies for hypertension in patients with diabetes are angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (Hypertension: Current Care Guidelines 2014 & American Diabetes Association 2019).

Strong evidence has shown that weight management is also beneficial in the treatment of T2DM complications. Thus, diabetic patients with obesity (BMI ≥30 kg/m²) or overweight should achieve >5% weight loss with diet, physical activity and behavioural therapy, and physicians should minimize medications for comorbid conditions inducing weight gain (Type 2 Diabetes: Current Care Guidelines 2018 & American Diabetes Association 2019). Usually, about 60% of patients with type 2 diabetes suffer from obesity and insulin resistance and they might be treated with medications and bariatric surgery as well (Chatterjee et al. 2017).

In addition, psychological approaches and proper drug therapies have helped in the support for smoking cessation (Scobie et al. 2009) and it is advised to all diabetics avoid smoking cigarettes, e-cigarettes or other tobacco products.

2.6 Blood glucose monitoring

The most suitable way of assessing glycemic control is the measurement of HbA1c and self-monitoring of blood glucose (SMBG). The first one gives information about long-term control of blood glucose, but it does not take into account daily glycemic differences as the second one does (Mohan et al. 2014).

Patients who have stable glycemic control; HbA1c test should be performed once or twice a year. Patients whose therapy has changed or who are not meeting glycemic goals should perform the HbA1c test quarterly. Patients with several doses of insulin or insulin pumps should be tested 3 or more times daily using glucose meter. Patients with less intensive insulin regimens or oral antidiabetic drugs can also benefit from SMBG, but the frequency should be personalized (Mohan et al. 2014). Glycemic monitoring must be reviewed in each follow-up visit to health services. The interval of the follow-up visits should be 3-6 months and adapted annually for each patient according to the glycemic control (American Diabetes Association 2019).

2.7 Management of type 2 diabetes with lifestyle modifications

The most effective and safest treatment is lifestyle management which induces beneficial changes in weight and enhances glucose control in diabetic patients. It is recommended as first-line treatment after diagnosis and as part of treatment in patients that need glucose-lowering medications (Davies et al. 2018). Lifestyle management comprises diabetes self-management education and support (DSMES), recommended diet or medical nutrition therapy (MNT), physical activity, smoking cessation counseling, and psychosocial care (Type 2 Diabetes: Current Care Guidelines 2018 & American Diabetes Association 2019).

2.7.1 Diet

An unhealthy diet plays an important role in the development of type 2 diabetes and it´s complications. Dietary risk factors are often related to western diets. In particular, a high

intake of total and saturated fat and low fibre intake are associated with an increased type 2 diabetes risk (Villegas et al. 2009). In general, there are numerous suitable choices and eating patterns, which have demonstrated health benefits and low harm according to patient preferences and metabolic needs. For instance, the Mediterranean diet is rich in fruit and vegetables and has shown several benefits for people with type 2 diabetes (Davies et al. 2018) as well as the Nordic diet (Uusitupa et al. 2013).

In Finland, the recommended diet for patients with type 2 diabetes follows the general nutrition recommendations. Recommended diet is based on plant products, i.e. whole grains, vegetables, berries and fruit, and includes also fish, fish oils and other soft fats, as well as fat-free and low-fat dairy products. A balanced overall diet also encompasses a moderate amount of poultry and some read meat (National Nutrition Council 2019 & Type 2 Diabetes: Current Care Guidelines 2018).

Nutrition therapy is associated with weight management, but weight reduction and weight control maintenance are frequently challenging for diabetic patients. Weight management have notable long-term benefits like HbA1c enhancements and lipid concentration reductions. Weight loss can be achieved with 1200-1500 kcal/day for women and 1500-1800 kcal/day for men, adjusted for the individual´s baseline body weight. Health status, individual preferences and ability of the patient to follow the recommendations need to be considered in any meal plan (American Diabetes Association 2019).

2.7.2 Physical activity

Exercise or physical activity in diabetic patients promotes metabolic control and have a role in preventing complications. Regular moderate-intensity aerobic activity leads to a reduction in blood glucose levels with a slight risk of hypoglycemia (Mohan et al. 2014) and it is associated with a considerable reduction of cardiovascular and overall mortality risks in T2DM (American Diabetes Association 2019). Evidence describes that a combination of resistance training and aerobic exercise might be more effective in decreasing HbA1c than resistance training alone. In fact, there is a varied range of physical activity that can reduce considerably HbA1c and weight including leisure time activities (e.g. walking, swimming, jogging and so on) (Davies et al. 2018).

Adults should engage in 150 minutes or more weekly of moderate to vigorous intensity aerobic activity dispersed over as a minimum three days per week with no more than two consecutive days of inactivity (American Diabetes Association 2019). Nevertheless, physical activity may cause hypoglycemia to patients that are under insulins or secretagogues or both medications and the doses or carbohydrate consumptions are not adjusted. These patients may require consuming some additional carbohydrate if blood glucose levels before exercise are lower than 90 mg/dl (5.0 mmol/l). It, however, depends on whether they can reduce insulin dosages during the physical activity, the time of day exercise is performed and the intensity and duration of the activity (Colberg et al. 2016).

2.8 Pharmacological management of type 2 diabetes

2.8.1 Drug therapy

Finnish guidelines strongly underline the importance of individualized glycemic targets (Type 2 Diabetes: Current Care Guidelines 2018), and selection of drug therapy implicates numerous considerations such as the degree of HbA1c lowering needed, residual β-cell function, comorbidities (gastrointestinal disorders, congestive heart failure, renal insufficiency, etc), hypoglycemia risk, weight gain risk, costs of medications or co-pays, risk for side effects and patient preferences (Mohan et al. 2014). Organizations like the Finnish Medical Society Duodecim, the Finnish Society of Internal Medicine and the Finnish Diabetes Association (2018), the American Diabetes Association (ADA) (2019) and other European Associations have co-published an algorithm that help practitioners in the prescriptions of oral and/or parental antihyperglycemic agents available for the treatment of T2DM. Chapter 2.8.2 illustrates this algorithm.

In Finland, seven major classes of non-insulin antihyperglycemic drugs are available for management of T2DM (table 3). Most of them are oral agents except for glucagon-like peptide-1 analogues. Non-insulin antihyperglycemic drugs can be divided into three categories based on their mechanisms of action – secretagogues, insulin sensitizers and dipeptidyl peptidase-4 (DPP-4) inhibitors. (Type 2 Diabetes: Current Care Guidelines 2018).

Table 3. Characteristics of non-insulin antihyperglycemic agents

Class of medicine	Medicine	Daily dose (mg)	Indication	The most common side effects
Biguanides	Metformin	500-3,000	Primary drug for the treatment of hyperglycemia	Stomach upset Nausea
Gliptins	Sitagliptin	25-100	Hyperglycemia	Headache
	Vildagliptin	50-100	Hyperglycemia	Nausea
	Saxagliptin	2.5-5	Hyperglycemia	Nausea
	Linagliptin	5	Hyperglycemia	Nausea
	Alogliptin	6.25 to 25	Hyperglycemia	Nausea
Sulfonylureas	Glimepiride	1-6	Hyperglycemia	Hypoglycemia Weight gain
	Glipizide	2.5-20	Hyperglycemia	Hypoglycemia Weight gain
Glinides	Repaglinide	0.5 to 16	Postprandial hyperglycemia	Hypoglycemia Weight gain
GLP-1* analogues	Liraglutide	0.6 to 1.8	Hyperglycemia in overweight diabetics	Early nausea
	Exenatide	5-10 µg	Hyperglycemia in overweight diabetics	Early nausea
	Exenatide (long acting)	2	Hyperglycemia in overweight diabetics	Early nausea
	Dulaglutide	0.75-1.5	Hyperglycemia in overweight diabetics	Early nausea
	Lixisenatide	10-20 µg	Postprandial hyperglycemia	Early nausea
SGLT2* inhibitors	Dapagliflozin	10	Hyperglycemia	Genital and urinary tract infections
	Empagliflozin	10-25	Hyperglycemia	Genital and urinary tract infections
Glitazones	Pioglitazone	15-45	Hyperglycemia	Swelling, anemia

** SGLT2=SGLT2 inhibitors i.e. sodium-glucose cotransporter-2 inhibitors, GLP-1=GLP-1 agonists i.e. glucagon-like peptide 1*

2.8.2 Selection of the diabetes medication

As mentioned in chapters 2.3 and 2.5 the main target is to avoid hyperglycemia in order to prevent the development of acute and chronic complications. The cornerstone in the treatment of high blood glucose in patients with T2DM is lifestyle changes.

After diagnosis, Finnish Current Care Guidelines (2018) recommend lifestyle changes and the initiation of metformin (unless it is not contraindicated or not tolerated). This intervention

should last from 3 to 6 months and then the effectiveness of the treatment should be evaluated.

If HbA1c is lower or equal than 48 mmol/mol (6.5%) lifestyle intervention and metformin should continue. T2DM is a progressive disease and metformin monotherapy is unlikely to maintain good glucose control for several years. HbA1c will eventually be higher than 48 mmol/mol (6.5%). The degree of hyperglycemia can be mild or asymptomatic, but in this case, patients require dual combination therapy to achieve the treatment target. There is not a recommendation for the order in selecting the second pharmacological therapy: glinides, gliptins, GLP-1 analogues, pioglitazone, SGLT2 inhibitors or sulfonylurea.

The next medication should be selected taking into account contraindications, possible side effects and existing comorbidity. Particularly attention should be paid when considering hypoglycemic treatments such as sulfonylureas or glinides in the elderly. These conventional ones and TZD are not much addressed anymore for the reasons explained in the chapters 2.8.7, 2.8.8 and 2.8.9 although these are still listed in the Finnish Current Care guidelines as possible options.

In case that the glycemic targets are not achieved, the second line therapy can be replaced by another pharmacological choice, or a third agent or insulin therapy might be required. If the patient needs more effective glucose-lowering medication than oral agents, GLP-1 receptors agonists are preferred instead of insulin when possible. But, if HbA1c is > 53 mmol/mol (7%) patient should start insulin with other therapy.

If the degree of hyperglycemia is significant or symptomatic especially with catabolic features like weight loss, hypertriglyceridemia or ketosis, the patient should start insulin.

Special consideration should be paid to diabetics with a high risk of major adverse cardiovascular events (MACE), hospitalization for heart failure (hHF), cardiovascular death, or chronic kidney disease (CKD) progression. The medications for these patients are preferably GLP-1 analogues and SGLT2 inhibitors but the selection should be considered according to baseline HbA1c or individual glycemic target (Buse et al. 2020).

The figure 2 illustrates the selection of medicines. It is advised that for each intervention a continuous evaluation for efficacy, side effects, and the patient's burden should be performed.

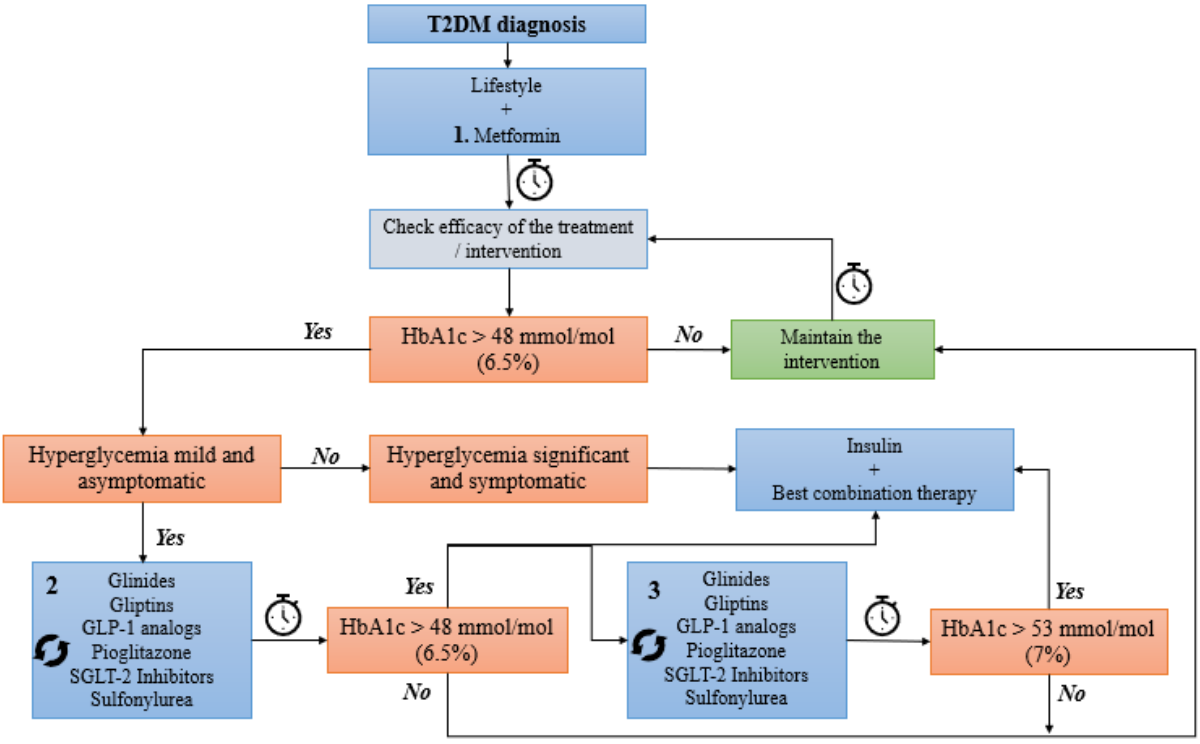

Figure 2. Selection of the appropriate diabetic medication (newly diagnosed) according to the Finnish Current Care guidelines.

Finnish Current Care Guidelines (2018) also provide recommendations about insulin selection. The first insulin choice to start is a basal insulin (long-term insulin analogs) or NPH insulin. The classification of the insulins is described in the chapter 2.8.10. Basal insulin should be administered once a day and NPH insulin should be given in the evening at bedtime. The insulin dose is increased 1 to 2 times a week based on the morning blood glucose value until the target is reached.

Prandial insulin or fast-acting insulin analogue should be started in addition to basal insulin if glycemic targets are not reached (strong increase in blood glucose after meals and overnight levels remain under control) despite proper titration of basal insulin or bedtime NPH insulin. One dose of prandial insulin should be administered with the largest meal according to carbohydrates intake. But it is highly important to mention that a combination of a fast-acting and long-acting insulin analogue is used if the daily rhythm and food intake are relatively

constant from day to day. Thus, home monitoring of glucose or HbA1c levels are needed for the titration.

Alternatively, the regimen of basal and prandial insulin can be switched to 2-3 doses of a premixed insulin or combination products. These products are for example Insulin Lispro 25/75 which is a product that contains 25% of fast-acting insulin lispro and the remainder of insulin lispro long-acting protamine. These mixed insulins can be used only with the largest meal of the day or with the meal that increases blood glucose the most.

2.8.3 Metformin

The main action of metformin is to lower hepatic glucose production and it is recommended as the first line therapy in type 2 diabetes for the following reasons: there is robust evidence that metformin decrease efficiently blood glucose, it does not produce hypoglycemia, it helps with weight management, it is safe to use for a long term, there are not many drug interactions and it has a reasonable cost (Type 2 Diabetes: Current Care Guidelines 2018).

A double-blinded, placebo-controlled, multicentre clinical trial that involved obese subjects diagnosed with type 2 diabetes demonstrated by week 29 that patients treated with metformin (up to 2550 mg/day) had a reduction in the fasting plasma glucose levels by an average of 53 mg/dL from baseline and placebo group showed an average increment of 6.3 mg/dL from baseline. Additionally, HbA1c was reduced around 1.4% points in subjects treated with metformin and HbA1c was increased by 0.4% points in subjects receiving placebo (DeFronzo & Goodman 1995).

However, one disadvantage is that vitamin B12 deficiency may occur due to prolonged use of metformin. To monitor above side effects, periodic measurement (every 3 to 5 years) of vitamin B12 should be performed particularly for those patients with anemia or peripheral neuropathy. Another disadvantage is that metformin dose should be quickly reduced for patients with moderate renal insufficiency because metformin is mainly excreted by kidneys (Type 2 Diabetes: Current Care Guidelines 2018). The creatinine level of patients using metformin should thus be controlled regularly.

2.8.4 Gliptins

Gliptins or dipeptidyl peptidase-4 inhibitors is a new class of oral antihyperglycemic drugs that inhibits the breakdown of endogenous glucagon-like peptide-1 controlling or even reversing some of the metabolic disorders observed in T2DM. These are shown to lower HbA1c by 0.5% to 0.8% points. The most important advantage is that it only works when blood glucose is high reducing the risk of hypoglycemia (Nguyen et al. 2008). Nevertheless, patients with renal impairment should reduce dose of saxagliptin, sitagliptin, vildagliptin and alogliptin (Type 2 Diabetes: Current Care Guidelines 2018).

2.8.5 Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitors

SGLT2 inhibitors or gliflozins are oral medications that increase urinary excretion of glucose being highly effective in the reduction of blood glucose (Davies et al. 2018). Studies have shown that SGLT2 inhibitors considerably lower fasting and postprandial glucose levels leading to HbA1c reductions of 0.5-1.0% points (Cefalu et al. 2014). When gliflozins are used alone, they do not cause hypoglycemia (Type 2 Diabetes: Current Care Guidelines 2018).

SGLT2 inhibitors are linked with the reduction of weight and blood pressure (Kario et al. 2019). SGLT2 inhibitors require continuous monitoring of renal function since the beginning of the treatment and physicians should pay special attention when these inhibitors are used with diuretics and/or ACE inhibitors and angiotensin receptor blockers (Davies et al. 2018).

2.8.6 Glucagon Like Peptide (GLP-1) Analogues

GLP-1 analogues are proteins that imitate native GLP-1 being able to stimulate insulin secretion and decrease glucagon secretion in a glucose-dependent manner and to reduce gastric emptying as well as appetite leading to moderated food consumption and weight loss. GLP-1 analogues may expand β-cell mass causing satiety and promoting weight loss. GLP-1 analogues efficacy may be affected by the formulation and dosing, modifying glucose and weight decrease as well as side effect profile and cardiovascular effects (Cefalu et al. 2014 & Davies et al. 2018). GLP-1 analogues are classified as long acting drugs (dulaglutide, albiglutide, liraglutide) administered once per week or short acting drugs (exenatide, lixisenatide) administered once or twice daily (Chatterjee et al. 2017).

Garber et al (2009) report that this class of diabetic treatment is safe with a low risk of hypoglycemia unless combined with sulfonylureas or insulin, and effective indicating a reduction in HbA1c of around 1% point and in weight of about 4 kg. However, the contraindications for GLP-1 receptor agonists are medical history of chronic pancreatitis or pancreatic cancer even though the safety signal for pancreatic cancer is not amplified (Butler et al. 2013).

2.8.7 Thiazolidinediones (TZD)

Thiazolidinediones are also known as peroxisome proliferator activated receptors-γ (PPAR γ) agonists because this diabetic therapy improves insulin resistance by binding to PPAR-γ in the peripheral muscles, liver and adipose tissues leading to an alteration of the genes transcription that regulate glucose uptake in a positive way (Nguyen et al. 2008). Yakarylmaz & Öztürkv (2017) suggest that thiazolidinediones can be preferred in patients with impaired renal function, and the elderly who are not using insulins, because it is well tolerated and there is no risk of hypoglycemia. However, it is strictly contraindicated with sulfonylureas. The medication should be started with the lowest dose, and the duration of treatment should be short.

The drawbacks of this treatment are ophthalmopathy aggravation, risk of bone fracture, weight increment in combination with insulin therapy, cardiovascular events and bladder cancer risk (Kung & Henry 2012). By 2014 pioglitazone remained the most widely used TZD because some studies proposed that pioglitaz,one has a better safety profile and it is less controversial than other thiazolidinediones (Cefalu et al 2014). Shi et al. (2011) recommend that patients and physicians should discuss the risk vs. benefit issues of this therapy with the aim of improved glycemic control.

2.8.8 Glinides

The mechanism of glinides is similar to the sulfonylureas stimulating insulin secretion from the β cell. The advantages of these antidiabetics are the fast onset and very short duration of action. Therefore, they have lower frequency of hypoglycemic events compared with sulfonylureas (Germino 2011). The risk of hypoglycemia is more common in older adults

when they skip meals (Yakarylmaz & Öztürkv, 2017). Repaglinide is also a good option for elderly patients with renal impairment (or more severe degrees of impairment) and who cannot tolerate metformin and sulfonylureas (Christoph Hasslacher 2003).

2.8.9 Sulfonylureas

The target of these agents is the adenosine triphosphate (ATP)-sensitive potassium channels found in the pancreatic β-cells. Sulfonylureas obstruct these channels stimulating the release of insulin in a nonglucose-mediate manner into the bloodstream. Consequently, glucose lowering effects occur quickly even on the day of initiation (Bryan et al. 2005). Since sulfonylureas cause insulin secretion irrespective of blood glucose levels, hypoglycemia and weight gain are the most important side effects. The advantage of this treatment is the price, because it is the least expensive of all antihyperglycemic medications in many countries. Therefore, these are the drugs of choice for patients with financial considerations (Nguyen et al. 2008).

2.8.10 Insulin therapy

Several insulin formulations are available with different duration of action (table 4). Insulin treatment is indicated as the first line treatment in patients with evidence of insulin deficiency or if hyperglycemia causes significant symptoms (i.e., polyuria or polydipsia) among patient with type 2 diabetes at time of diagnosis or early during treatment. Insulin therapy is also initiated when other agents have not been effective and HbA1c ≥ 7.0-8.5 % (53-69 mmol/mol) (Type 2 Diabetes: Current Care Guidelines 2018).

The most common side effects of insulins are hypoglycemia and weight gain. And the disadvantages in the use of insulins are that it requires training for the drug administration, there is a frequent dose adjustment, it is often given twice daily or it may require multiple doses, and insulins may be more expensive than non-insulin agents (Davies et al. 2018).

Table 4. Characteristics of Insulins

Class of medicine	Medicine	Start of effect	Peak effect	Duration
Instant-acting analogues	Aspart	10-20 minutes	1-2 hours	3-5 hours
	Lispro			
	Glulisine			
Human fast-acting	Insulin Human	30 minutes	2-4 hours	5-8 hours
Intermediate-acting	Neutral Protamin Hagedorn (NPH)	0.5 to 1 hour	4-12 hours	12-20 hours
Long acting	Detemir	2-4 hours	8-12 hours	12-24 hours
	Glargine (U100)	2-4 hours	8-12 hours	20-30 hours
	Glargine (U300)	6 hours	12-16 hours	>24 hours
	Degludec (U100, U200)	0.5-1.5 hours	N/P*	>33-42 hours

*N/P no peak in activity due to the slow release

2.8.11 Future pharmacological therapies

The development of new pharmacological therapies is based on the identification of new therapeutic targets or "non-traditional" targets involving the intestine, kidney, brain, macrophage and adrenal gland. Also, plenty of central targets in the brain emerge, because of knowledge of its role in regulating metabolism broadens. However, work continues by additional approaches with existing molecules such as triple oral glucose-lowering medications and a "polypill" not only designed to decrease glucose. A greater focus is the development of personalized medicine that seems certain in the next 50 years due to the fast advances in genetics, epigenetics and metabolomics proposing additional targets and tailoring opportunities for therapeutic interventions (Kahn & Buse 2015).

In fact, a noninvasive alternative to subcutaneous insulin analogs through a new dry powder/inhaler system has been approved for the delivery of insulin with Technosphere. However, it is contraindicated in patients with chronic lung diseases and since it is a new alternative there is still a concern about the pulmonary function issues that could emerge (Goldberg & Wong 2015).

2.9 Barriers for treatment

Some physicians are not confident in prescribing for example insulins to patients due to lack of knowledge or experience in the use of them. They are also concerned about the risks such as hypoglycemia. These two limitations are considered as the key clinical barriers in the initiation and in the intensification of pharmacological therapy (Edelman & Pettus 2014).

The social determinants of health that influence negatively or positively in patients and families living with T2DM are income, education, housing, neighbourhood and employment, which for example can limit the use of certain treatments due to the costs or availability (Nadeau et al. 2016). In Finnish population, Toivakka et al. (2018) demonstrated that patients with low education level and those living in low-educated areas have poorer treatment outcomes than those with higher education level.

Other treatment limitations are negative attitudes toward some therapies, negative patient adherence to treatments (omitting doses or not fulfilling treatment regimens) and lack of confidence in the process of adjusting doses (Edelman & Pettus 2014).

3 AIMS

The aim of this study is to analyse the differences in glucose control of T2DM patients by treatment options such as insulin, non-insulin and combination therapies among T2DM patients in North Karelia, Finland in 2017.

Furthermore, the differences in treatment options and glycemic control are also examined by demographic factors and by area of living.

4 SUBJECTS AND METHODS

The hospital district in eastern Finland, Siun sote, includes 14 municipalities. All local primary health centers and central hospital have used a common electronic patient database system called Mediatri since early 2011. Mediatri database provides the data used in this study for the year 2017. This database contains information from both primary and

specialized health care. Data on all patients that were diagnosed with type 2 diabetes based on ICD-10 code E11 who were alive at the end of 2017 and aged 20 years or more were included in the study. Patients with no information about glycemic control (HbA1c measurement) were excluded.

There was a total of 12800 individuals with type 2 diabetes (based on ICD-10 code E11) in the North Karelia region at the end of 2017. After excluding those who did not have information on HbA1c level the number of patients in the analyses was 9746. The information from these patients included place of domicile (municipality), age at 2017, gender, laboratory data (value of HbA1c measurement in mmol/mol units) and drug prescriptions.

The 14 municipalities were classified as urban, semi-urban and rural based on the municipality code and the statistics Finland classification of municipalities (Tilastokeskus 2020).

The Finnish Current Care Guidelines recommend that HbA1c levels for T2DM patients should be monitored every 6-12 months. The HbA1c measurement used in the analyses was the last one for the year 2017. The measurements included in the analyses had to be at least three months after diabetes diagnosis to observe the treatment effect properly. All HbA1c samples were analyzed by the turbidimetric inhibition immunoassay method (TINIA) in the Eastern Finland Laboratory Centre Joint Authority Enterprise (ISLAB), which is an accredited laboratory and participates in external quality surveys. The glycosylated hemoglobin units have been standardized to International Federation of Clinical Chemistry (IFCC) units.

The treatment lines of patients were defined using the prescriptions and by grouping the medications based on ATC (Anatomic Therapeutical Chemical) classifications. The first group was patients having no prescribed medication. The second group was patients taking only metformin (ATC code: A10BA02). The third group included patients taking gliptins or dipeptidyl peptidase 4 inhibitors (ATC code: A10BH) as monotherapy or with metformin. These gliptins were sitagliptin, vildagliptin, saxagliptin, alogliptin and linagliptin. The fourth group involved patients taking sodium-glucose co-transporter 2 inhibitors (ATC code: A10BK) as monotherapy or with other tablet medication (metformin and/or gliptins). These SGLT2 inhibitors were dapagliflozin, canagliflozin, empagliflozin and ertugliflozin. The fifth

group comprised those patients taking glucagon-like peptide-1 analogues (ATC code: A10BJ) as monotherapy or with any tablet medication. These GLP-1 analogues included exenatide, liraglutide, lixisenatide, albiglutide, dulaglutide and semaglutide.

Groups 6 and 7 contained patients that administer insulin therapy with or without other diabetic treatment. Group 6 included patients taking short-term insulins such as fast-acting insulins and analogues (ATC code: A10AB or A10AD) with or without intermediate- or long-acting insulins and analogues. Group 7 contained patients under intermediate- or long-acting insulin (ATC code: A10AC or A10AE) with no fast-acting insulins in use.

An additional group consisted of other diabetic treatments such as sulfonylureas (ATC code: A10BB12), thiazolidinediones (ATC code: A10BG) and other blood-glucose-lowering medications for instance repaglinide (ATC code: A10BX02). Patients who belonged to this group were excluded from the outcome comparisons and statistics because of the small number of observations in this group (n=96) and because the treatment selections were very heterogeneous. After this exclusion, 9650 patients were available for the final statistics and analyses comparing the glycemic control between treatment lines.

The outcome of treatment was evaluated by the achievement of the target level of HbA1c (<7% or 53 mmol/mol). Also, glycosylated hemoglobin was classified in three groups for descriptive analysis: HbA1c < 53 mmol/mol (< 7%), HbA1c 53-74.9 mmol/mol (7-8.9%) and HbA1c ≥ 75 mmol/mol (≥ 9%). The last group indicated a very poor glycemic control.

Treatment outcomes were also presented by age categorized into five groups: <50, 50-59, 60-69, 70-79 and >79 years. The youngest age group was larger than others ranging from 20 to 49 years, because the number of type 2 diabetes patients was relatively small in this age group.

Data analysis was done using the IBM SPSS statistics program (Statistical Package for the Social Sciences) for Windows version 25. Chi-square test (X^2) was performed to observe the differences in the patient distribution per treatment group by gender and age categories or by municipalities. ANOVA or Student´s t-test was used for HbA1c mean values to estimate the significance of differences between gender, age groups and treatment groups. Log_{10}(HbA1c) was used as a response variable, because of the skewed distribution. ANOVA was also used

for HbA1c to assess differences between treatment groups and municipalities. A post hoc analysis tests were performed to those variables that presented a statistically significant interaction in the univariate analysis. A binary logistic regression was used to analyze the differences in the risk of patients having HbA1c ≥ 75 mmol/mol between gender, age categories, treatment groups, municipality and urban-rural classification. The level of statistical significance was set to $P < 0.05$ for all statistical analysis.

The ethical approval to study the treatment outcomes of patients with diabetes in North Karelia was achieved on November 13rd 2012, from the ethics committee of the Hospital District in Northern Savonia. The permission to use data from the electronic patient records of the region was achieved from Siun sote administering the database. Personal identity numbers were not included in the data to preserve the anonymity of the patients.

5 RESULTS

5.1 Glycemic control by gender, age and treatment lines

The study population includes a total of 9746 patients with type 2 diabetes mellitus. In the study population, 46.6% (n=4540) were women and 53.4% (n=5206) men. As shown in table 5, most of the women (32.1% n=1459) were within the age group of 70-79 years and most of the men (34.7% n=1807) were within the age group of 60-69 years. The lowest proportion of patients was found in the age category lower than 50 years being 4.6% (n=208) of women and 4.8% (n=251) of men.

Table 5. Distribution of study population by gender and age categories

	Age categories (years)					
	<50	**50-59**	**60-69**	**70-79**	**>79**	**Total**
	% (n)	% (n)	% (n)	% (n)	% (n)	n
Women	4.6 (208)	11.1 (505)	26.3 (1195)	32.1 (1459)	25.8 (1173)	4540
Men	4.8 (251)	14.0 (731)	34.7 (1807)	32.7 (1701)	13.8 (716)	5206
Total	4.7 (459)	12.7 (1236)	30.8 (3002)	32.4 (3160)	19.4 (1889)	9746

Table 6 compares the distribution of study population between gender and age categories by treatment lines. There were statistically significant differences between genders in treatment lines (χ2-test: p-value < 0.001), between women age categories and treatment lines (χ2-test: p-value < 0.001) and between men age categories and treatment lines (χ2-test: p-value < 0.001).

The proportion of subjects without treatment was 9.3%. This proportion was bigger than users of SGLT2 inhibitors (6.1%), GLP-1 analogs (1.7%) or other treatments (1.0%). From women under 50 years of age, only 10.1 % were totally without medication, but those who were 80 years or more already 16.5 % were without medication. The proportions of men in the same age groups without diabetic medication were 5.2% and 13.0%, respectively. Therefore, bigger proportion of females was without medication (10.4%) than males (8.4%). The highest percentage (15.2%) of subjects for both genders without diabetic treatment was found in the age category over 79 years.

Table 6. Distribution of study population by age categories, gender and treatment lines

Use of treatment		No medication	Only metformin	Gliptin (no SGLT2*, GLP-1* or insulin)	SGLT2* (no GLP-1* or insulin)	GLP-1* (no insulin)	Short-term insulin	Long-term insulin	Other
		% (n)	*% (n)*	*% (n)*	*% (n)*	*% (n)*	*% (n)*	*% (n)*	*% (n)*
Women	*<50*	10.1 (21)	38.9 (81)	10.6 (22)	10.1 (21)	2.4 (5)	11.1 (23)	16.3 (34)	0.5 (1)
	50-59	6.3 (32)	42.0 (212)	15.8 (80)	10.1 (51)	4.8 (24)	10.1 (51)	10.5 (53)	0.4 (2)
	60-69	7.6 (91)	42.8 (511)	16.3 (195)	6.9 (82)	2.2 (26)	9.5 (114)	14.2 (170)	0.5 (6)
	70-79	9.0 (132)	40.9 (597)	17.1 (249)	4.2 (62)	1.0 (15)	11.0 (161)	15.7 (229)	1.0 (14)
	> 79	16.5 (194)	28.0 (328)	20.6 (242)	1.9 (22)	0 (0)	14.0 (164)	17.4 (204)	1.6 (19)
	Total	10.4 (470)	38.1 (1729)	17.4 (788)	5.2 (238)	1.5 (70)	11.3 (513)	15.2 (690)	0.9 (42)
Men	*<50*	5.2 (13)	28.3 (71)	13.1 (33)	18.7 (47)	5.2 (13)	11.6 (29)	17.1 (43)	0.8 (2)
	50-59	6.4 (47)	32.3 (236)	17.0 (124)	10.3 (75)	3.6 (26)	10.7 (78)	19.0 (139)	0.8 (6)
	60-69	7.4 (133)	32.7 (590)	17.7 (320)	8.6 (156)	2.3 (41)	11.5 (208)	18.9 (341)	1.0 (18)
	70-79	9.0 (153)	33.6 (571)	19.0 (324)	4.4 (75)	1.1 (19)	14.2 (241)	17.6 (299)	1.1 (19)
	> 79	13.0 (93)	26.4 (189)	22.3 (160)	1.1 (8)	0.1 (1)	18.4 (132)	17.3 (124)	1.3 (9)
	Total	8.4 (439)	31.8 (1657)	18.5 (961)	6.9 (361)	1.9 (100)	13.2 (688)	18.2 (946)	1.0 (54)
All	*<50*	7.4 (34)	33.1 (152)	12.0 (55)	14.8 (68)	3.9 (18)	11.3 (52)	16.8 (77)	0.7 (3)
	50-59	6.4 (79)	36.2 (448)	16.5 (204)	10.2 (126)	4.0 (50)	10.4 (129)	15.5 (192)	0.6 (8)
	60-69	7.5 (224)	36.7 (1101)	17.2 (515)	7.9 (238)	2.2 (67)	10.7 (322)	17.0 (511)	0.8 (24)
	70-79	9.0 (285)	37.0 (1168)	18.1 (573)	4.3 (137)	1.1 (34)	12.7 (402)	16.7 (528)	1.0 (33)
	> 79	15.2 (287)	27.4 (517)	21.3 (402)	1.6 (30)	0.1 (1)	15.7 (296)	17.4 (328)	1.5 (28)
Total		9.3 (909)	34.7 (3386)	17.9 (1749)	6.1 (599)	1.7 (170)	12.3 (1201)	16.8 (1636)	1.0 (96)

**** SGLT2=SGLT2 inhibitors i.e. sodium-glucose cotransporter-2 inhibitors, GLP-1=GLP-1 agonists i.e. glucagon-like peptide 1***

P-value < 0.001 for gender differences in the use of treatment (χ^2-test)

P-value < 0.001 for women, age category differences in the use of treatment (χ^2-test)

P-value < 0.001 for men, age category differences in the use of treatment (χ^2-test)

Metformin monotherapy was the most used treatment line in diabetic patients with a total percentage of 34.7% users. The second most common was gliptins (monotherapy or with metformin) with 17.9% users and then long-term insulins with 16.8% users. Metformin use was most common among 70-79 years old (37.0%). In contrast, the lowest percentage of patients taking metformin for both women (28.0%) and men (26.4%) was in the age group of over 79 years. Comparing genders, female patients were more under metformin therapy (38.1%) than males (31.8%).

Contrary to the group of patients taking metformin and similar to patients without diabetic treatment, use of gliptins (monotherapy or with metformin) was most common in over 79 years old patients (21.3%). Use of SGLT2 inhibitors (monotherapy or with metformin or gliptins) was the highest in patients in the age group under 50 years for both sexes (14.8%). Use of GLP-1 analogs (monotherapy or with metformin, gliptin, or SGLT2 inhibitors) was the highest in the age group 50-59 years for women (4.8%) and those under 50 years for men (5.2%).

Use of insulins was very common in this study population. Of women 26,5% and of men 31,4% were either on short-term or long-term insulin. The highest use of insulin was observed in the oldest age groups. Among those over 79 years already 31.4% of women and 33.1% of men were on insulin treatment.

A minor proportion of patients (1%) were using other diabetic treatments such as sulfonylureas, thiazolidinediones (pioglitazones) and other blood-glucose-lowering medications (repaglinide).

Table 7. Mean of HbA1c by treatment group, age categories and gender

		HbA1c mmol/mol (±SD)							
	Age categories	**No medication**	**Only metformin**	**Gliptin (no SGLT2*, GLP-1* or insulin)**	**SGLT2* (no GLP-1* or insulin)**	**GLP-1* (no insulin)**	**Short-term insulin**	**Long-term insulin**	**Total**
Women	**<50**	39.2 (4.9)	45.9 (11.7)	47.2 (10.3)	49.7 (10.7)	47.4 (12.0)	60.0 (18.0)	59.0 (16.1)	49.5 (14.1)
	50-59	40.3 (6.5)	43.3 (5.6)	48.2 (12.6)	55.8 (13.0)	55.7 (17.5)	70.6 (18.4)	64.6 (17.3)	50.8 (15.2)
	60-69	41.4 (6.7)	43.6 (6.6)	47.7 (9.5)	53.2 (10.5)	54.6 (15.0)	64.8 (16.3)	62.2 (15.3)	49.7 (13.2)
	70-79	42.0 (4.9)	43.9 (5.6)	48.5 (8.5)	52.8 (10.4)	53.0 (11.4)	65.5 (16.9)	60.4 (14.0)	50.0 (12.7)
	> 79	43.9 (6.3)	45.5 (6.1)	51.0 (10.9)	60.0 (12.4)	-**	66.6 (15.9)	60.6 (14.6)	52.3 (13.6)
	All	42.4 (6.1)	44.2 (6.5)	49.0 (10.1)	54.0 (11.4)	54.1 (14.9)	66.0 (16.7)	61.1 (14.9)	50.6 (13.5)
Men	**<50**	36.4 (7.4)	43.0 (10.4)	53.9 (17.3)	56.5 (15.4)	61.2 (13.1)	62.3 (20.2)	61.8 (16.9)	53.1 (17.0)
	50-59	43.2 (11.8)	43.5 (7.4)	51.6 (13.8)	52.4 (11.8)	58.6 (13.3)	67.5 (16.4)	62.1 (16.1)	52.5 (15.2)
	60-69	41.7 (7.3)	44.1 (6.8)	48.4 (10.6)	53.2 (11.6)	54.2 (9.7)	61.0 (13.8)	58.4 (14.2)	50.4 (12.6)
	70-79	41.4 (4.9)	44.0 (5.8)	48.4 (9.0)	54.6 (8.0)	50.1 (9.9)	61.5 (13.7)	57.9 (13.1)	50.1 (11.8)
	> 79	43.2 (7.2)	44.5 (6.5)	50.5 (10.7)	60.2 (7.1)	-**	65.7 (14.5)	59.8 (13.8)	52.5 (13.7)
	All	41.9 (7.3)	44.0 (6.7)	49.3 (11.0)	53.9 (11.6)	55.4 (11.6)	62.9 (14.7)	59.1 (14.3)	51.0 (13.2)
Total		42.2 (6.7)	44.1 (6.6)	49.2 (10.6)	54.0 (11.5)	54.9 (13.0)	64.2 (15.6)	60.0 (14.6)	50.8 (13.3)

** SGLT2=SGLT2 inhibitors i.e. sodium-glucose cotransporter-2 inhibitors, GLP-1=GLP-1 agonists i.e. glucagon-like peptide 1*

***no observations or only one observation*

ANOVA with log_{10} (HbA1c) as a response and sex, age group and treatment group (explanatory variables) gives following p-values for them: Gender p-value = 0.335, age categories p-value < 0.001, treatment groups p-value < 0.001

The mean HbA1c values classified by the above age categories, gender and treatment groups are described in table 7. The mean HbA1c value for all women was 50.6 mmol/mol (SD ± 13.49) and for all men 51.0 mmol/mol (SD ± 13.22) with no statistically significant difference between women and men (3-way ANOVA, p=0.335). There was a statistically significant difference between age categories in HbA1c levels ($p < 0.001$) and also between treatment lines in HbA1c levels ($p < 0.001$).

Female patients who were below 50 years had the lowest mean HbA1c level (49.5 mmol/mol SD ± 14.1) compared with the other age groups. In contrast, men in the same age group had the highest mean HbA1c level (53.1 mmol/mol SD ± 17.0) compared with the other age groups.

Moreover, patients without medication had a lower mean HbA1c level (42.2 mmol/mol SD ± 6.7) than patients who were under any medication. Patients using metformin and gliptins had an average lower HbA1c level than the clinical recommendations (53 mmol/mol or 7%), 44.1 mmol/mol and 49.2 mmol/mol, respectively. In those using SGLT2 inhibitors and GLP-1 analogs the mean HbA1c levels were quite similar (54.0 mmol/mol vs. 54.9 mmol/mol) and slightly over the recommendations.

As depicted in Figure 3, patients on insulins had higher HbA1c mean level than patients on other diabetic therapy. Those using short-term insulins had the highest mean HbA1c level of 64.2 mmol/mol (SD ± 15.6) followed with those using long term insulin (60.0 mmol/mol SD ± 14.6). Figure 3 also illustrates that there was a clear gender difference in mean HbA1c in those using insulins, which was not observed in the other treatment groups. Females seemed to have higher HbA1c mean levels than males. In fact, from the whole study population, the highest HbA1c mean level is found in 50-59-year-old women using short-term insulins (70.6 mmol/mol SD ± 18.4).

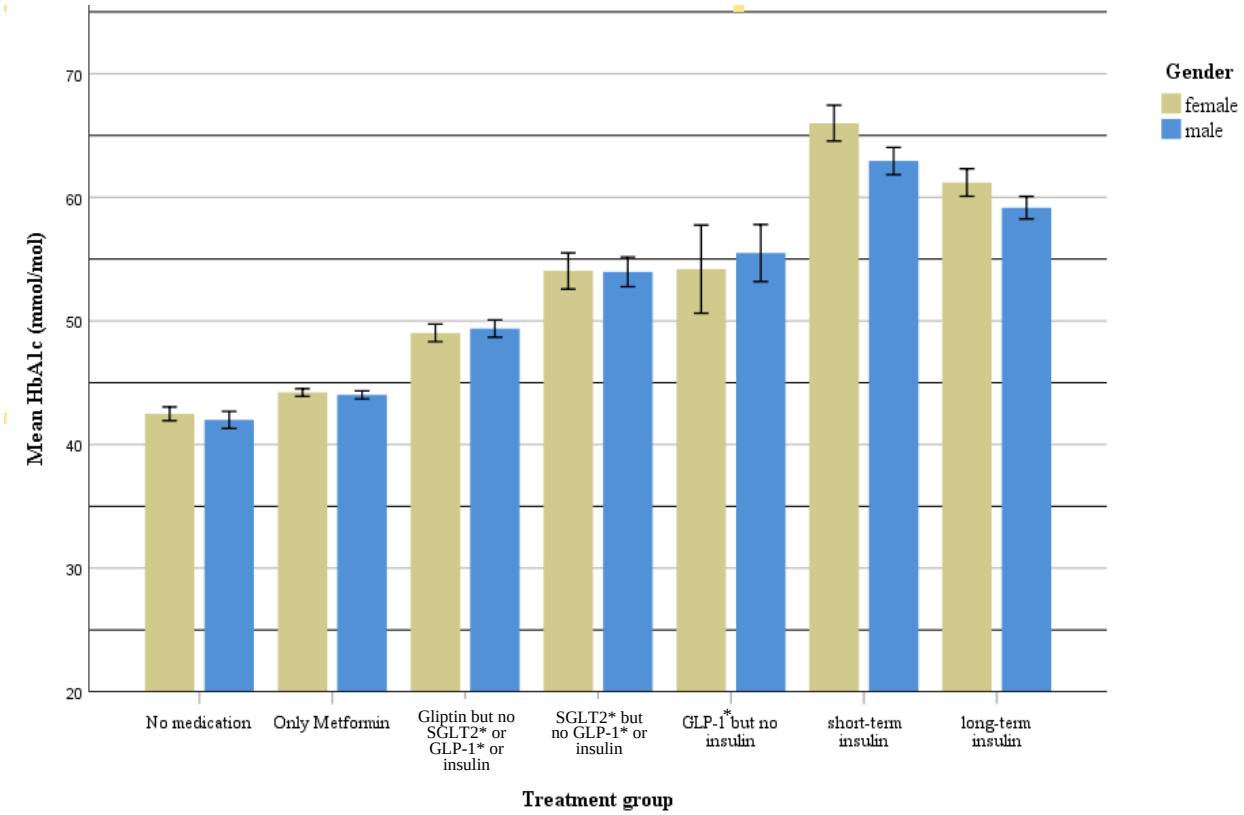

Figure 3. Mean HbA1c by treatment group and gender (95% CI)
** SGLT2=SGLT2 inhibitors i.e. sodium-glucose cotransporter-2 inhibitors, GLP-1=GLP-1 agonists i.e. glucagon-like peptide 1*

When observing HbA1c categories (<53 mmol/mol or <7%, 53-74.9 mmol/mol or 7-8.9% and ≥75 mmol/mol or ≥9%) of patients by gender, age categories and treatment groups it was noticed that only some patients under no treatment or metformin were not achieving the clinical glycemic recommendations (Table 8). Around 5.1% of diabetic patients under no medications had glycosylated hemoglobin higher than 53 mmol/mol and just 0.7% of them had higher or equal levels than 75 mmol/mol. Those percentages were still lower than those found in the patients under diabetic treatments. For instance, approximately 8% of the patients taking only metformin had an HbA1c level ≥ 53 mmol/mol.

Furthermore, there was a high proportion of patients that had an HbA1c level ≥ 53 mmol/mol in the other diabetic treatment groups such as gliptins (26.3%), SGLT2 inhibitors (47.7%), GLP-1 analogs (50.6%), short-term insulins (77.4%) and long-term insulins (66.9%). From all these patients under diabetic treatments, those that were under short-term insulins and long-term insulins had the highest percentage of patients within HbA1c level ≥ 75 mmol/mol being 21.6% and 15.0%, respectively.

Table 8a. Distribution of study population by treatment group, HbA1c categories, gender and age categories

Treatment groups	**No medication**			**Only metformin**		
HbA1c categories	**<53**	**53-74.9**	**≥ 75**	**<53**	**53-74.9**	**≥ 75**
Women	*% (n)*	*% (n)*	*% (n)*	*% (n)*	*% (n)*	*% (n)*
<50	100 (21)	0	0	86.4 (70)	8.6 (7)	4.9 (4)
50-59	93.8 (30)	6.3 (2)	0	93.9 (199)	6.1 (13)	0
60-69	96.7 (88)	2.2 (2)	1.1 (1)	94.1 (481)	5.3 (27)	0.6 (3)
70-79	97.7 (129)	2.3 (3)	0	93.5 (558)	6.5 (39)	0
> 79	90.7 (176)	9.3 (18)	0	87.8 (288)	12.2 (40)	0
All	94.5 (444)	5.3 (25)	0.2 (1)	92.3 (1596)	7.3 (126)	0.4 (7)
Men						
<50	92.3 (12)	7.7 (1)	0	87.3 (62)	11.3 (8)	1.4 (1)
50-59	91.5 (43)	4.3 (2)	4.3 (2)	93.6 (221)	5.1 (12)	1.3 (3)
60-69	94.7 (126)	3.8 (5)	1.5 (2)	91.7 (541)	7.8 (46)	0.5 (3)
70-79	98.0 (150)	2.0 (3)	0	91.4 (522)	8.4 (48)	0.2 (1)
> 79	94.6 (88)	4.3 (4)	1.1 (1)	92.1 (174)	7.4 (14)	0.5 (1)
All	95.4 (419)	3.4 (15)	1.1 (5)	91.7 (1520)	7.7 (128)	0.5 (9)
Total	94.9 (863)	4.4 (40)	0.7 (6)	92.0 (3116)	7.5 (254)	0.5 (16)
Treatment groups	**Gliptin but no SGLT2* or GLP-1* or Insulin**			**SGLT2* but no GLP-1* or insulin**		
HbA1c categories	**<53**	**53-74.9**	**≥ 75**	**<53**	**53-74.9**	**≥ 75**
Women	*% (n)*	*% (n)*	*% (n)*	*% (n)*	*% (n)*	*% (n)*
<50	77.3 (17)	22.7 (5)	0	66.7 (14)	28.6 (6)	4.8 (1)
50-59	78.8 (63)	17.5 (14)	3.8 (3)	45.1 (23)	45.1 (23)	9.8 (5)
60-69	81.0 (158)	16.4 (32)	2.6 (5)	59.8 (49)	35.4 (29)	4.9 (4)
70-79	77.5 (193)	20.9 (52)	1.6 (4)	61.3 (38)	33.9 (21)	4.8 (3)
> 79	64.9 (157)	31.4 (76)	3.7 (9)	18.2 (4)	77.3 (17)	4.5 (1)
All	74.6 (588)	22.7 (179)	2.7 (21)	53.8 (128)	40.3 (96)	5.9 (14)
Men						
<50	57.6 (19)	27.3 (9)	15.2 (5)	51.1 (24)	36.2 (17)	12.8 (6)
50-59	64.5 (80)	26.6 (33)	8.9 (11)	61.3 (46)	33.3 (25)	5.3 (4)
60-69	77.5 (248)	19.7 (63)	2.8 (9)	53.2 (83)	42.3 (66)	4.5 (7)
70-79	76.5 (248)	21.0 (68)	2.5 (8)	44.0 (33)	54.7 (41)	1.3 (1)
> 79	65.6 (105)	29.4 (47)	5.0 (8)	12.5 (1)	87.5 (7)	0
All	72.8 (700)	22.9 (220)	4.3 (41)	51.8 (187)	43.2 (156)	5.0 (18)
Total	73.6 (1288)	22.8 (399)	3.5 (62)	52.6 (315)	42.1 (252)	5.3 (32)

** SGLT2=SGLT2 inhibitors i.e. sodium-glucose cotransporter-2 inhibitors, GLP-1=GLP-1 agonists i.e. glucagon-like peptide 1*

Table 8b. Distribution of study population by treatment group, HbA1c categories, gender and age categories (continue)

Treatment groups		**GLP-1* but no insulin**			**short-term insulin**		
HbA1c categories		**<53**	**53-74.9**	**≥ 75**	**<53**	**53-74.9**	**≥ 75**
Women		*% (n)*	*% (n)*	*% (n)*	*% (n)*	*% (n)*	*% (n)*
	<50	80 (4)	20 (1)	0	43.5 (10)	30.4 (7)	26.1 (6)
	50-59	62.5 (15)	25.0 (6)	12.5 (3)	15.7 (8)	45.1 (23)	39.2 (20)
	60-69	50 (13)	42.3 (11)	7.7 (2)	26.3 (30)	53.5 (61)	20.2 (23)
	70-79	60.0 (9)	33.3 (5)	6.7 (1)	19.9 (32)	57.8 (93)	22.4 (36)
	> 79	0	0	0	18.3 (30)	54.3 (89)	27.4 (45)
	All	58.6 (41)	32.9 (23)	8.6 (6)	21.4 (110)	53.2 (273)	25.3 (130)
Men							
	<50	21.3 (3)	61.5 (8)	15.4 (2)	37.9 (11)	34.5 (10)	27.6 (8)
	50-59	30.8 (8)	61.5 (16)	7.7 (2)	16.7 (13)	56.4 (44)	26.9 (21)
	60-69	39.0 (16)	53.7 (22)	7.3 (3)	25.5 (53)	60.1 (125)	14.4 (30)
	70-79	78.9 (15)	15.8 (3)	5.3 (1)	24.9 (60)	59.3 (143)	15.8 (38)
	> 79	100 (1)	0	0	18.2 (24)	56.8 (75)	25.0 (33)
	All	43.0 (43)	49.0 (49)	8.0 (8)	23.4 (161)	57.7 (397)	18.9 (130)
Total		49.4 (84)	42.4 (72)	8.2 (14)	22.6 (271)	55.8 (670)	21.6 (260)
Treatment groups		**Long-term insulin**			**All patients****		
HbA1c categories		**<53**	**53-74.9**	**≥ 75**	**<53**	**53-74.9**	**≥ 75**
Women		*% (n)*	*% (n)*	*% (n)*	*% (n)*	*% (n)*	*% (n)*
	<50	38.2 (13)	47.1 (16)	14.7 (5)	72.0 (149)	20.3 (42)	7.7 (16)
	50-59	26.4 (14)	49.1 (26)	24.5 (13)	70.0 (352)	21.3 (107)	8.7 (44)
	60-69	29.4 (50)	50.0 (85)	20.6 (35)	73.1 (869)	20.8 (247)	6.1 (73)
	70-79	27.9 (64)	59.0 (135)	13.1 (30)	70.8 (1023)	24.1 (348)	5.1 (74)
	> 79	30.9 (63)	30.1 (113)	25.2 (28)	62.2 (718)	30.6 (353)	7.2 (83)
	All	29.6 (204)	54.3 (375)	16.1 (111)	69.2 (3111)	24.4 (1097)	6.4 (290)
Men							
	<50	30.2 (13)	51.2 (22)	18.6 (8)	57.8 (144)	30.1 (75)	12.0 (30)
	50-59	30.2 (42)	43.2 (60)	26.6 (37)	62.5 (453)	26.5 (192)	11.0 (80)
	60-69	36.1 (123)	52.8 (180)	11.1 (38)	66.5 (1190)	28.3 (507)	5.1 (92)
	70-79	38.8 (116)	49.8 (149)	11.4 (34)	68.0 (1144)	27.1 (455)	4.9 (83)
	> 79	34.7 (43)	50.8 (63)	14.5 (18)	61.7 (436)	29.7 (210)	8.6 (61)
	All	35.6 (337)	50.1 (474)	14.3 (135)	65.4 (3367)	27.9 (1439)	6.7 (346)
Total		33.1 (541)	51.9 (849)	15.0 (246)	67.1 (6478)	26.3 (2536)	6.6 (636)

** GLP-1=GLP-1 agonists i.e. glucagon-like peptide 1*

***Binary logistic regression (HbA1c ≥ 75 mmol/mol) for gender differences: p-value = 0.123; for age category differences: p-value < 0.001 and for treatment category differences: p-value < 0.001*

The highest proportion of those with very high HbA1c levels (≥ 75 mmol/mol) in women using short-term insulins was among those 50-59 years old (39.2%) and of men in the age category of less than 50 years (27.6%). The highest proportions of the patients under long-

term insulins having an HbA1c level higher or equal than 75 mmol/mol were found in women among those more than 79 years old (25.2%) and in men among those 50-59 years old (26.6%).

Figure 4 demonstrates and complements the above mentioned that women using insulins did not achieve so well a good glycemic control compared with men. Only 21.4% of women under short term insulins and 29.6% under long-term insulins are reaching the glycemic targets and the percentages of men under the same insulins are 23.4% and 35.6%, respectively. In fact, there is a statistically significant difference in the proportion of patients having HbA1c level ≥ 75 mmol/mol between genders among those using short-term insulin (binary logistic regression p-value = 0.007).

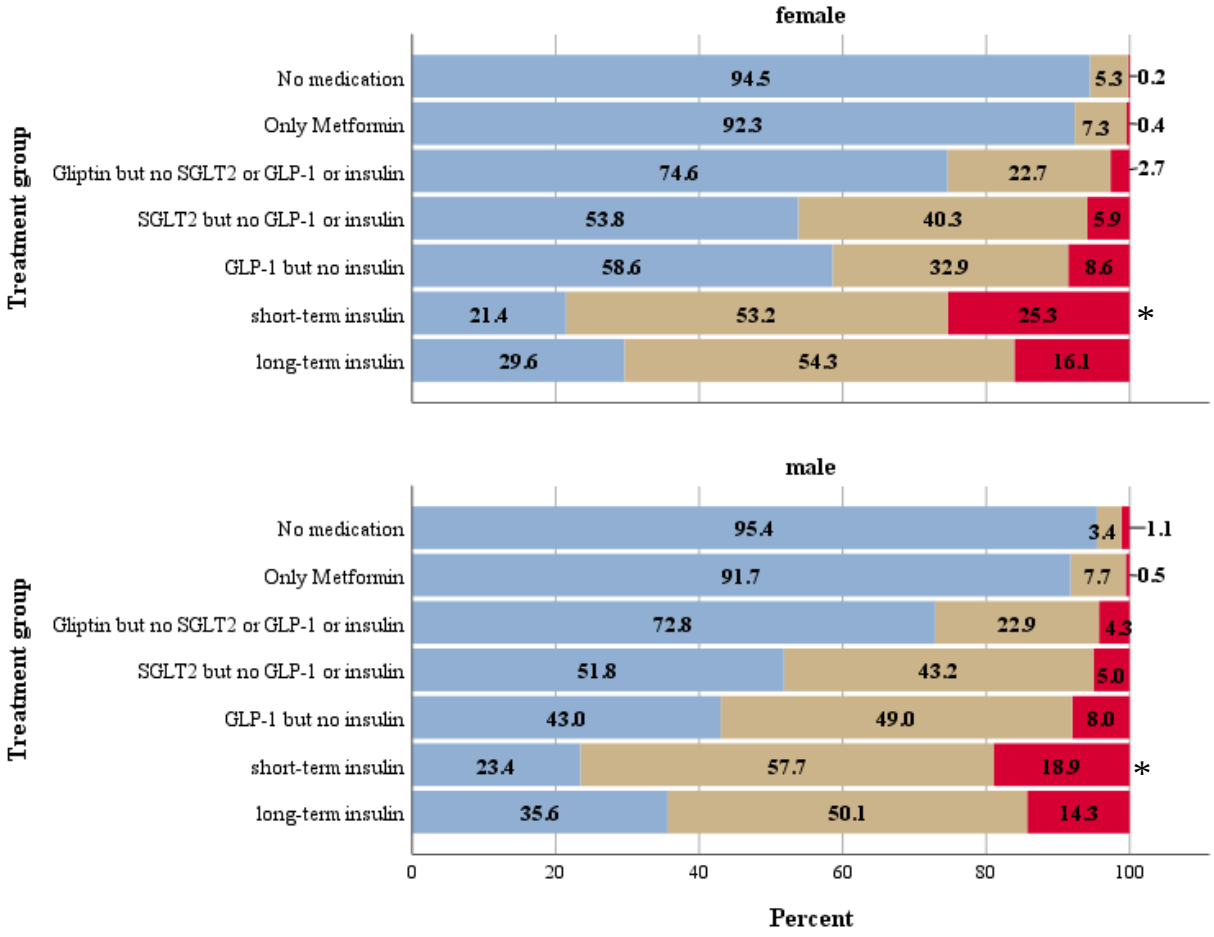

Figure 4. Distribution (%) by HbA1c categories, treatment group and gender. HbA1c categories: HbA1c < 53 mmol/mol or <7% HbA1c 53-74.9 mmol/mol <7-8.9% HbA1c ≥75 mmol/mol or ≥9%

**P-value = 0.007 for association between short-term insulin and HbA1c ≥ 75mmol/mol, binary logistic regression*

In contrast, slightly bigger proportion of women under metformin, gliptins, SGLT2 inhibitors and GLP-1 analogs had HbA1c < 53 mmol/mol or 7% (92.3%, 74.6%, 53.8% and 58.6%, respectively) than men (91.7%, 72.8%, 51.8% and 43.0%, respectively).

Table 8 a and b describe that there were no statistically significant differences between genders in the proportion of patients having HbA1c level ≥ 75 mmol/mol (binary logistic regression, p-value = 0.123). However, there was a statistically significant difference between age categories in the proportion of patients having HbA1c level ≥ 75 mmol/mol (binary logistic regression p-value < 0.001). Men and women that were in the age categories 70-79 years and 60-69 years demonstrated to have better glycemic control than patients in the other age categories. The percentages of patients that had an HbA1c level < 75 mmol/mol in these age groups were 95% and 94.3%, respectively. On the other hand, the age groups that had a poor glycemic control and the highest percentage (around 9%) of patients in the HbA1c level ≥ 75 mmol/mol were those under 50 years and those who were 50-59 years old.

There was a statistically significant difference between treatment groups and the proportion of patients having HbA1c level ≥ 75 mmol/mol (binary logistic regression p-value < 0.001). Comparing patients with HbA1c level ≥ 75 mmol/mol taking metformin and no medication there was not statistically significant difference (p value = 0.523) but comparing metformin with the other treatments there was a statistically significant difference (p value < 0.001).

Patients having no medication, using metformin monotherapy or gliptin had a good glycemic control with proportion of patients having HbA1c level <75 mmol/mol 99.3%, 99.5% and 96.5%, respectively. Patients using insulins were more likely to have poorer glycemic control and the proportions of patients with HbA1c levels <75 mmol/mol was 78.4% for those using short-term insulins and 85% for those using long-term insulins only.

5.2 Geographical variation in glycemic control and treatment lines

The distribution of the study population by municipalities in North Karelia, Finland is shown in table 9. Based on Statistics Finland's rurality classification of municipalities 39.3%

(n=3827) of patients lived in rural areas, 33.0% (n=3213) in urban areas and 27.8% (n=2706) in semi-urban areas.

Although the majority of individuals from the study population were in the age category of 70-79 years, in some municipalities most of the patients were between 60-69 years (Kontiolahti (36.4%), Ilomantsi (33.2%), Liperi (32.7%), Polvijärvi (35.1%), Rääkkylä (30.7%) and Valtimo (35.9%)). A higher percentage of patients in the municipality Kontiolahti were in the age group less than 50 years of age (8.3%) compared with the other municipalities. Municipality Heinävesi had the highest proportion of patients over 79 years (23.4%).

Table 9. Distribution of study population by municipalities and age categories

Rurality classification	Municipality	Age categories (years)					Total
		<50	50-59	60-69	70-79	>79	
		% (n)	% (n)	% (n)	% (n)	% (n)	n
Urban	Joensuu	5.4 (173)	12.9 (413)	29.5 (947)	33.5 (1076)	18.8 (604)	3213
Semi urban	Kontiolahti	8.3 (42)	13.2 (67)	36.4 (185)	29.9 (152)	12.2 (62)	508
	Outokumpu	4.2 (24)	13.5 (78)	29.9 (173)	31.5 (182)	20.9 (121)	578
	Lieksa	5.1 (52)	10.8 (110)	29.7 (301)	32.9 (334)	21.4 (217)	1014
	Nurmes	3.6 (22)	11.4 (69)	31.2 (189)	34.0 (206)	19.8 (120)	606
Rural	Heinävesi	2.4 (8)	10.3 (34)	28.0 (92)	35.9 (118)	23.4 (77)	329
	Ilomantsi	2.7 (12)	13.7 (61)	33.2 (148)	29.6 (132)	20.9 (93)	446
	Juuka	3.7 (16)	15.3 (66)	30.7 (132)	34.0 (146)	16.3 (70)	430
	Kitee	3.0 (26)	11.3 (97)	29.8 (255)	32.9 (282)	22.9 (196)	856
	Liperi	6.2 (42)	15.9 (108)	32.7 (222)	29.5 (200)	15.8 (107)	679
	Polvijärvi	3.7 (12)	12.6 (41)	35.1 (114)	30.2 (98)	18.5 (60)	325
	Rääkkylä	5.0 (11)	12.4 (27)	30.7 (67)	29.8 (65)	22.0 (48)	218
	Tohmajärvi	4.0 (15)	12.3 (46)	31.0 (116)	32.6 (122)	20.1 (75)	374
	Valtimo	2.4 (4)	11.2 (19)	35.9 (61)	27.6 (47)	22.9 (39)	170

Table 10 reveals that the distribution of treatment groups varies between municipalities. Kontiolahti categorized as a semi-urban area has the highest percentage of patients using only metformin (43.7%) or SGLT2 inhibitors (10.2%) compared with the other municipalities.

Table 10. Distribution of study population by treatment group and municipality

Rurality classification	Municipality	No medication % (n)	Only Metformin % (n)	Gliptin but no SGLT2* or GLP-1* or insulin % (n)	SGLT2* but no GLP-1* or insulin % (n)	GLP-1* but no insulin % (n)	short-term insulin % (n)	long-term insulin % (n)	Other % (n)
Urban	Joensuu	8.6 (275)	35.7 (1147)	18.9 (607)	5.2 (167)	1.6 (53)	14.0 (449)	15.3 (490)	0.8 (25)
Semi urban	Kontiolahti	5.7 (29)	43.7 (222)	11.4 (58)	10.2 (52)	2.0 (10)	9.3 (47)	15.0 (76)	2.8 (14)
	Outokumpu	15.9 (92)	37.0 (214)	11.9 (69)	5.9 (34)	3.3 (19)	4.7 (27)	21.3 (123)	0
	Lieksa	9.0 (91)	37.2 (377)	19.9 (202)	5.5 (56)	1.6 (16)	10.6 (107)	15.8 (160)	0.5 (5)
	Nurmes	9.9 (60)	27.4 (166)	20.0 (121)	5.6 (34)	3.5 (21)	16.5 (100)	14.7 (89)	2.5 (15)
Rural	Heinävesi	5.8 (19)	32.5 (107)	24.0 (79)	1.5 (5)	2.4 (8)	16.7 (55)	15.5 (51)	1.5 (5)
	Ilomantsi	13.0 (58)	36.3 (162)	17.9 (80)	3.4 (15)	0.9 (4)	15.2 (68)	12.6 (56)	0.7 (3)
	Juuka	9.5 (41)	35.1 (151)	11.2 (48)	10.2 (44)	0.7 (3)	7.4 (32)	25.6 (110)	0.2 (1)
	Kitee	5.0 (43)	33.6 (288)	21.7 (186)	9.5 (81)	0.9 (8)	10.0 (86)	18.3 (157)	0.8 (7)
	Liperi	12.7 (86)	31.4 (213)	15.8 (107)	8.1 (55)	1.5 (10)	10.2 (69)	19.7 (134)	0.7 (5)
	Polvijärvi	16.0 (52)	32.6 (106)	16.3 (53)	4.6 (15)	1.8 (6)	10.8 (35)	16.9 (55)	0.9 (3)
	Rääkkylä	11.9 (26)	30.7 (67)	20.6 (45)	8.3 (18)	0.5 (1)	11.0 (24)	17.0 (37)	0
	Tohmajärvi	4.5 (17)	29.1 (109)	19.0 (71)	5.1 (19)	2.1 (8)	20.6 (77)	17.6 (66)	1.9 (7)
	Valtimo	11.8 (20)	33.5 (57)	13.5 (23)	2.4 (4)	1.8 (3)	14.7 (25)	18.8 (32)	3.5 (6)
Total		9.3 (909)	34.7 (3386)	17.9 (1749)	6.1 (599)	1.7 (170)	12.3 (1201)	16.8 (1636)	1.0 (96)

** SGLT2=SGLT2 inhibitors i.e. sodium-glucose cotransporter-2 inhibitors, GLP-1=GLP-1 agonists i.e. glucagon-like peptide 1*
P-value < 0.001 for municipality code differences in use of treatment (χ^2-test)

Juuka likewise presented a high percentage of diabetic patients under SGLT2 inhibitors (10.2%) and long-term insulins (25.6 %), but a low percentage of patients under gliptins (11.2%). Analogously, municipality Outokumpu had a low percentage of patients under gliptins (11.9%) and the lowest percentage of patients taking short-term insulins (4.7%) and it did not have patients taking other diabetic treatments than the main treatment lines.

Unexpectedly, one municipality (Tohmajärvi) had a high proportion of patients under short-term insulins (over 20%) and in the same municipality, the proportion of patients taking only metformin (29.1%) and patients without medication (4.5%) was significantly lower than in the other municipalities.

The lowest percentage of patients taking GLP-1 analogs (0.5%) was found in Rääkkylä. Also, in this municipality, not any patient was under other diabetic treatments than the main treatment lines. On the contrary, Valtimo had the highest percentage of patients taking other diabetic treatments but a low percentage of patients taking SGLT2 inhibitors (2.4%).

The distribution of patients by HbA1c categories and municipalities were depicted in figure 5. There was a statistically significant association between municipalities and HbA1c level ≥ 75 mmol/mol (binary logistic regression (HbA1c ≥ 75 mmol/mol) p-value = 0.007). Municipalities like Ilomantsi and Juuka had a higher proportion of patients with HbA1c levels ≥ 75 mmol/mol (9.9% and 8.6% respectively) than the other municipalities. In contrast, most of the patients that lived in Kontiolahti had a good glycemic control with only 3% of patients with HbA1c level ≥ 75 mmol/mol.

Figure 5 also illustrates that in some municipalities the recommended HbA1c levels (< 53 mmol/mol) were achieved better than in others. For example, Valtimo (74.4%) and Outokumpu (74.2%) had the highest percentage of patients with HbA1c < 53 mmol/mol. On the other hand, in some municipalities much lower proportion of patients achieved good control such as in Rääkkylä (61.5%), Juuka (62.2%) and Tohmajärvi (62.9%).

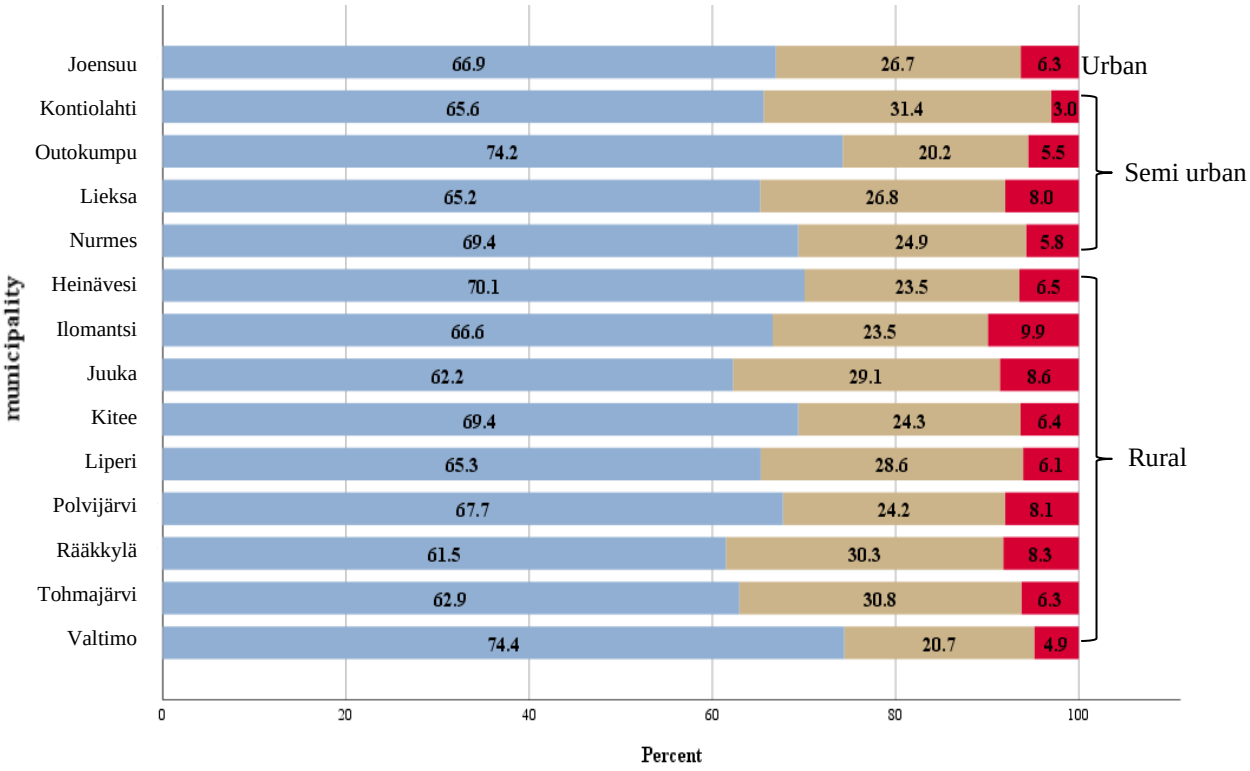

Figure 5. Distribution (%) by HbA1c categories in municipalities. HbA1c categories:
HbA1c < 53 mmol/mol or <7% HbA1c 53-74.9 mmol/mol <7-8.9% HbA1c ≥75 mmol/mol or ≥9%
P-value = 0.007 for municipality association to HbA1c ≥ 75mmol/mol, binary logistic regression
P-value = 0.161 for ruralty association to HbA1c ≥ 75mmol/mol, binary logistic regression

Binary logistic regression analysis showed that rurality (urban, semi-urban and rural) was not associated with high HbA1c levels (≥ 75 mmol/mol) (p-value = 0.161). When analyzing the possible effect of differences in treatment lines to the differences observed in glucose control between the municipalities a significant interaction (p=0.001) was noticed indicating that patients in different municipalities with same treatment had differences in the achievement of good glycemic control. Further analysis showed a significant difference ($p < 0.001$) on HbA1c between municipalities and the patients in the following treatment groups: only metformin, gliptin, SGLT2 inhibitors and both insulins (Figure 6). Patients with no medication and taking GLP-1 analogues had no statistically significant difference on HbA1c levels in different municipalities.

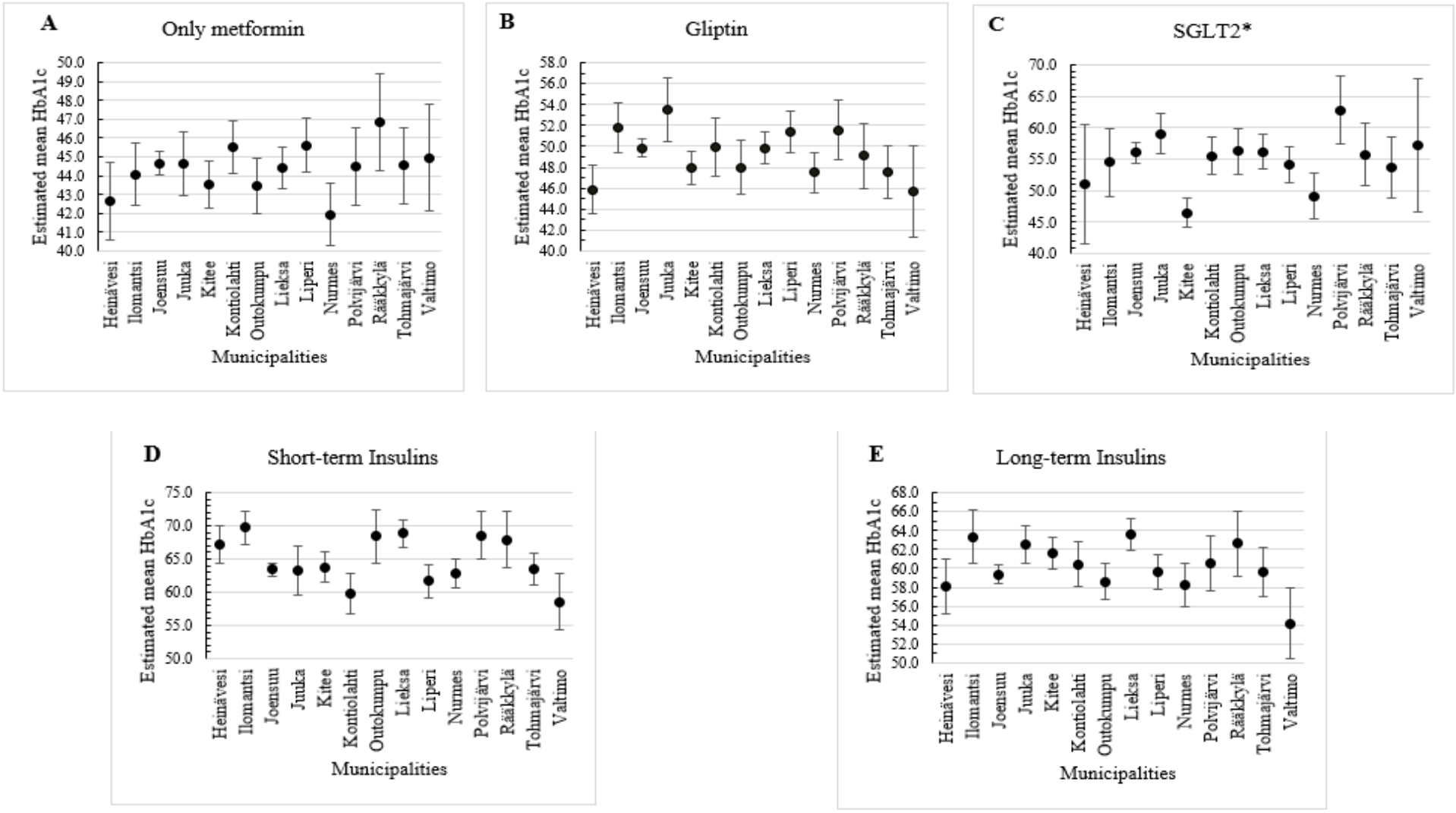

Figure 6. Estimated mean HbA1c (gender and age categories adjusted) with 95% CI by municipalities. * SGLT2=SGLT2 inhibitors i.e. sodium-glucose cotransporter-2 inhibitors.

6 DISCUSSION

6.1 Treatment lines by gender and age

This study has evaluated and compared the differences in the glycemic levels between diabetic treatments and demographic factors among T2DM patients in North Karelia, Finland. The study shows that there are differences in the selected treatment lines by age and gender as well as differences in glycemic outcomes.

Since T2DM is a common disorder in the ageing population (Tuomilehto et al. 2003 & Felton & Hall 2015) most of the diabetic patients belonged to the age groups of 60-69 years and 70-79 years also in North Karelia. It is likely that the age distribution of the patient population affects to the selected treatment lines in the area.

Important differences were found in the distribution of patients by age groups and treatment lines. A significant percentage of diabetic patients who do not use any diabetic medication are 80 years or older. One explanation could be that geriatric patients are also monitored 3-6 months after diagnosis with lifestyle changes and, if these patients are close to the glycemic targets it is preferable to continue with that intervention instead of directly initiating pharmacological therapy. The glycemic target is also not very strict (HbA1c < 58-64 mmol/mol) for the reason that elderly patients generally are more vulnerable to hypoglycemia events or they have more comorbidities and might use multiple drugs compared with younger patients (Yakarylmaz & Öztürk 2017 & Type 2 Diabetes: Current Care Guidelines 2018).

Another explanation can be that elderly patients are more likely to be treated in housing services or long-term care (nursing homes and wards). Over 9 % of people older than 75 years in North Karelia were living in housing services, nursing homes or wards at the end of December 2018 (Terveyden ja hyvinvoinnin laitos 2020). It might be that these patients have better dietary control and care to achieve diabetes targets than those who do not have nursing support. In addition, the prescriptions of these patients living in care homes might not be all included in the Mediatri database classifying them as patients with no medication in this study.

Also, lower percentage of elderly patients were under metformin monotherapy (27.4%) compared with the other age groups. Metformin is contraindicated in patients with severe renal impairment, which is usually becoming more prevalent in T2DM patients along with ageing (Type 2 Diabetes: Current Care Guidelines 2018). Iseki K (2005) found that impairment of renal function is associated with ageing in both men and women, and among the elderly population more than 50% of the individuals screened experienced CKD (Chronic Kidney Disease) stages 3-5. There are, however, three other possible explanations for the low percentage of elderly patients taking metformin: weight loss, gastrointestinal side effects and lactic acidosis. The last one should be cautiously observed (Yakarylmaz & Öztürk 2017 & Type 2 Diabetes: Current Care Guidelines 2018)

In fact, the most preferred pharmacological choices for patients older than 79 years of age were insulins (33.1 %). This finding suggests that insulins are selected because elderly patients are likely to have more hyperglycemia events than younger patients, and due to the progression of the disease more than half of T2DM patients will need insulin therapy at some point (Gough & Narendran 2017). Also, according to the Finnish Current Care Guidelines insulins are the best option for these patients.

In this study, insulins were the second most common treatment in the whole study population. This may be due to the high proportion of the patients who were over 60 years old. Besides, an important finding was that a significant percentage of diabetics use short-term insulins. These insulins are only recommended when glucose targets are not met with long-acting insulin (Type 2 Diabetes: Current Care Guidelines 2018 & American Diabetes Association 2019). This is in line with the observation showing that patients of this study under short-term insulins have a mean HbA1c value higher than the recommendations and these patients also had the highest proportion of patients with poor glycemic control (≥75 mmol/mol) compared with the other treatments; indicating that these patients are really in need of such intensification of treatment.

Short-term insulins should be added at mealtime to control the expected postprandial increment in the blood glucose and Yakarylmaz & Öztürk (2017) suggest that these insulins are more effective and useful in diabetics who live for example in nursing homes because they eat regular meals and they have care support to administer the treatment properly. According to our results, the highest proportion of patients under short-term insulins were

among the oldest age groups who might be living in nursing homes or at least are likely to receive regular home care.

The current study found that new drugs such as SGLT2 inhibitors (25%) and GLP-1 analogues (7.9%) were preferred among patients younger than 60 years of age. These agents are chosen for patients that need a substantial glycemic reduction or weight loss, or when there are potential concerns like the risk of hypoglycemia or other insulin drawbacks (Charbonnel & Cariou 2011 & American Diabetes Association 2019). These treatments are less selected for elderly patients because of the side effects, for example dehydration, genital and urinary system infections, weight loss and dose adjustment in renal failure cases. GLP-1 analogues have two additional drawbacks, the first one is that it causes nausea and the second one is that the route of administration is parenteral making its use difficult for elderly patients (Yakarylmaz & Öztürk 2017 Type 2 Diabetes: Current Care Guidelines 2018). Furthermore, these new antidiabetic medicines are considered more expensive than the old conventional medications (sulfonylureas, metformin, thiazolidines, glinides) being not affordable for all diabetics (Pemminati et al. 2016) specifically elderly adults that have multiple drugs and live on fixed incomes (Zhang et al. 2018). Furthermore, GLP-1 analogues are only partially reimbursed in Finland compared with full reimbursement of insulins (Niskanen et al. 2018).

Consistent with the literature and clinical recommendations, this research found that there is a low percentage of T2DM patients who use conventional medications (sulfonylureas, thiazolidinediones, glinides). For instance, Ramzan et al. (2019) describe in their meta-analysis a fall in the prescription and the use of sulfonylureas in many countries like France, Spain and Germany already between 2007-2013. Authors associate this effect to the new international diabetes prescribing guidelines where metformin is recommended as first treatment line instead of sulfonylureas. In the same study, they found that thiazolidinediones are not very well accepted by physicians because of the adverse effects. The decrease in the use of thiazolidinediones was evident in the Netherlands, Spain and France. The Finnish Current Care Guidelines states that there is no evidence that efficacy of glinides is maintained in long-term (Type 2 Diabetes: Current Care Guidelines 2018).

6.2 Glycemic control by gender, age and treatment groups

It is noteworthy to mention that there was a slightly higher percentage of diabetics achieving the glycemic targets in this study compared with the previous findings of Nazu et al. (2019) from the same region (67.1% vs 65%, respectively). This improvement in glycemic targets may be due to better efforts in individualised strategies in treatment and better baseline situation and more intensive control among newly diagnosed patients.

In this study, an important finding was that patients under no medication and metformin showed an average HbA1c level below the glycemic targets and just a minor distribution of patients with poor glycemic levels (less than 1% with HbA1c $\geq$ 75 mmol/mol). This demonstrates that lifestyle interventions and metformin are many times sufficient options for the control of blood glucose levels. Those patients who are not fulfilling the targets should be treated according to the guidelines and their treatment should be intensified. Nevertheless, it is also possible that those patients having high HbA1c values in this study were already in the process to be evaluated and other interventions were already considered, which cannot be captured in a cross-sectional study.

Contrary to expectations, this study demonstrated that although insulins are highly effective reducing hyperglycemia, a high percentage of patients with insulin had a poor glycemic control. Effectiveness of insulins is highly dependent on the appropriate administration, training, adjustment of dose when the diet changes, activities or weight, titration, and proper storage, which all can partly explain the challenges faced in achieving the treatment targets with insulin. Also, patients may have other challenges in the implementation of the insulin regimen such as fear of injection, pain, lipohypertrophy, complex regimens and they may experience functional impairments like visual, cognitive or psychological limiting either the administration or efficacy (Valencia & Flores 2014 & Davies et al. 2018).

It seems also possible that these results are due to the fact that insulins are preferred when the personalized blood glucose targets are not achieved with the maximum dose of non-insulin agents. These patients are likely to have progressed disease, clear insulin deficiency and thus need insulin treatment. On the other side some of these patients may have just started insulin therapy and the real effect of this intervention is still not reflected. In accordance with these findings, previous studies have demonstrated that statistically significant improvements in

glucose control, for instance, with insulin detemir is seen at week 24 from baseline (Echtay et al. 2013). Also, in Lebanese population it was found an increase in the percentage of persons who achieve the target (HbA1c<7%) from 0.7% at baseline to 39% at week 24 (Echtay et al. 2017). Other study showed that not all the diabetics that are under insulin glargine treatment reach the glycemic targets because of the fear to experience hypoglycemia, and thus patients tend to administer smaller or less insulin doses than prescribed which may delay the achievement of glycemic goals showing also a lack of glycemic control (Cigrovski Berkovic et al. 2016).

Patients under gliptins, SGLT2 inhibitors and GLP-1 analogues had less often a good glycemic control (73.6%, 52.6% and 49.4%, respectively) compared with patients on metformin monotherapy, even though these treatments are considered as new and effective diabetic treatments. Pemminati et al. (2016) suggested that one of the problems with patients' compliance is the direct cost of treatment to the diabetic patients. This problem is magnified by the fact that diabetic medications causing financial, behavioral and emotional challenges are lifelong. And, as new treatments, gliptins, SGLT2 inhibitors and GLP-1 analogues are more expensive than the conventional medications, patients might not use them as recommended. To tackle this issue, these patients should be strongly advised to use the drug therapy as prescribed explaining to them the risk related to the disease and the need for continuous medication. If the cost of the treatment is an issue, patients should communicate with the physicians in order to change to more affordable medicines.

In general, statistically significant differences were not seen between genders and HbA1c levels even though there were some gender differences in the use of different medications. This may be due to the similarities in treatment adherence and lifestyle changes in both men and women resulting in also similar treatment outcomes. The study by Galdino et al. (2016) showed that the adherence to the medical therapy, food regimen and foot care was equal regardless of the gender in elderly patients attending to the primary care.

A slight difference in the mean of HbA1c levels was noticed between men and women using insulins and a statistically significant difference in the proportion of patients having poor glycemic control (binary logistic regression p-value = 0.007) was observed between men and women using short-term insulins indicating slightly poorer glycemic control among women than men. These results are in agreement with those obtained by McGill et al (2013) where

females got smaller HbA1c decrement and were less likely to reach glycemic targets (HbA1c ≤ 53 mmol/mol) than males despite higher insulin doses. A Swedish study also demonstrated that men diabetics older than 60 years had better control of blood pressure and better glycemic levels than female patients although both genders had similar antidiabetic treatment. Researchers propose that these gender differences may be due biological mechanism linked to diabetes (β-cell function) or compliance in spite of similar drug treatment (Nilsson et al. 2004).

6.3 Geographic differences in treatment lines and glycemic control

With respect to the second research question, it was found that there were differences in the use of medications between municipalities. For instance, the proportion of patients using metformin monotherapy in Kontiolahti was 43.7% meanwhile in Tohmajärvi the proportion of patients using the same treatment was 29.1%. The proportion of patients taking short-term insulins in Outokumpu was very low (about 4%) compared with Tohmajärvi where the proportion was around 20%. Differences in social and economic situation in municipalities could influence the treatment choices similarly to how these aspects have influenced diabetes risk and prevalence (Williams et al. 2012). Also practices of professionals might differ between municipalities.

However, it should not be ignored that the more frequent use of insulins in some areas may reflect patient populations with more complications and the more use of metformin monotherapy in the other areas the more controlled patients (Niskanen et al. 2018). Also, it is possible that some areas may have a higher number of patients with different comorbidities than other areas. Some areas may also have a higher proportion of elderly patients partly explaining these treatment differences. This is observed for example in Kontiolahti where the majority of the patients were 60-69 years (36.4%) and the minority of patients were >79 years (12.2%), and the most used medication in this municipality was metformin monotherapy (43.7%) and a low proportion of patients were using insulins (24.3%).

Differences in HbA1c levels between patients from different municipalities that are under the same treatment can have many reasons. One reason is the lack of information about dosing regimen because some patients may take higher doses per day than other patients under the same medication. Also, it is unknown if some patients truly take the prescribed medication or

if they modify the medication regimen. Other reasons may be that in some municipalities different training in the administration of the medication and management of their disease (self-care) are provided or some health care professionals may motivate better their patients to follow the treatment recommendations.

6.4 Strengths and limitations

This study has several strengths. One of the most important is that the used data was collected from the regional electronic patient database; thus, it was possible to avoid selection bias because all the diagnosed patients with T2DM in North Karelia were included in the study. As all the laboratory test results are entered directly to the database in the laboratory and almost 100% of prescriptions made in public health services in North Karelia are e-prescriptions the problems with missing information and incorrect values in laboratory investigations and medications were avoided. In addition, the same regional laboratory having standardized methods for the quantification of HbA1c levels is used in all the municipalities of North Karelia ensuring the comparability of the data. Also, information on patients place of domicile was available making it possible to analyze area level differences in treatment lines and achievement of treatment targets.

The most important limitation was that there was not possibility to analyze socio-economic characteristics (income, level of education, employment status) and lifestyles (nutrition, physical activity, smoking, treatment adherence and other behaviors) of the patients because this particular information is not recorded in the electronic patient database. That information could explain some of the differences in the treatments and the achievement of the treatment targets. The scope of this study was also limited in terms of unknown information about the possible long-term care of diabetic patients causing likely some missing information on their prescriptions in the patient database. In addition, only information on prescriptions was available, which does not necessarily mean that patients had purchased all the medications prescribed. Also, there is a possibility that some patients with diabetes have not been registered in the patient database for example if they are only using private services.

7 CONCLUSIONS

The results of this study show that there were differences in the used medications by age and gender as well as in glycemic control by age and treatment options among T2DM patients in North Karelia, Finland in the year 2017. There were also differences in the use of medications and the achievement of the treatment targets between municipalities in North Karelia.

The relevance of the Finnish Current Care Guidelines was clearly supported by the findings of this study because most of the patients that demonstrated a good glycemic control are in the first line therapy (no medication or metformin monotherapy) per recommendations and the patients with poor glycemic control were using insulins. Insulins were also the second most common option among patients who were over 60 years old. The new diabetic treatments were most common in patients less than 60 years of age and it was observed that conventional treatments (sulfonylureas, TZD and glinides) are not much used among T2DM patients in North Karelia. Hence, the treatment practices in the area seem to be based on guidelines and clinical indications.

This study suggests that the variance in treatment options and glycemic control by demographic factors are most likely explained by the differences in the age and/or other possible causes such as different management of their disease (self-care), treatment adherence, training or cost preferences.

Patients with tablet medication seem to have mostly good glucose control. Those patients that have a poor glycemic control were mostly on insulin treatment, which is more challenging both for patients and professionals. Health care professionals should pay more attention to this patient population and work closely with them to support their self-care. Explaining to them the risks of the non-compliance and poor glycemic control is important.

Further studies could reveal if the health care system continue following appropriately the clinical guidelines and how this is reflected in the treatment outcomes. More broadly, research is also needed to determine which factors are affecting or improving the treatment outcomes. A more robust patient database including also information on patients' lifestyle factors and socioeconomic status could help to answer several questions that still remain to be unknown.

8 REFERENCES

Abate N, Chandalia M. The impact of ethnicity on type 2 diabetes. J Diabetes Complications 2003;17:39-58.

American Diabetes Association. Standards of Medical Care in Diabetes-2019 Abridged for Primary Care Providers. Clinical diabetes: a publication of the American Diabetes Association 2019;37:11-34.

Bellamy L, Casas J, Hingorani AD, Williams D. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. The Lancet 2009;373:1773-1779.

Bellou V, Belbasis L, Tzoulaki I, Evangelou E. Risk factors for type 2 diabetes mellitus: An exposure-wide umbrella review of meta-analyses. PloS one 2018;13:e0194127.

Bryan J, Crane A, Vila-Carriles WH, Babenko AP, Aguilar-Bryan L. Insulin secretagogues, sulfonylurea receptors and K(ATP) channels. Current pharmaceutical design 2005;11:2699.

Buse JB, Wexler DJ, Tsapas A, Rossing P, Mingrone G, Mathieu C, D'Alessio DA, Davies MJ. 2019 Update to: Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes care 2020;43:487-493.

Butler PC, Elashoff M, Elashoff R, Gale EAM. A Critical Analysis of the Clinical Use of Incretin-Based Therapies: Are the GLP-1 therapies safe? Diabetes care 2013;36:2118-2125.

Carrera Boada CA, Martínez-Moreno JM. Pathophysiology of diabetes mellitus type 2: beyond the duo "insulin resistance-secretion deficit". Nutricion hospitalaria 2013;28 Suppl 2:78-87.

Cefalu WT, Buse JB, Del Prato S, Home PD, Leroith D, Nauck MA, Raz I, Rosenstock J, Riddle MC. Beyond metformin: safety considerations in the decision-making process for selecting a second medication for type 2 diabetes management: reflections from a diabetes care editors' expert forum. Diabetes care 2014;37:2647.

Charbonnel B, Cariou B. Pharmacological management of type 2 diabetes: the potential of incretin-based therapies. Diabetes, Obesity and Metabolism 2011;13:99-117.

Chatterjee S, MD, Khunti K, Prof, Davies MJ, Prof. Type 2 diabetes. The Lancet 2017;389:2239-2251.

Cigrovski Berkovic M, Petrovski G, Grulovic N. Effectiveness of insulin glargine in type 2 diabetes mellitus patients failing glycaemic control with premixed insulin: Adriatic countries data meta-analysis. Acta diabetologica 2016;53:709-715.

Colberg SR, Sigal RJ, Yardley JE, Riddell MC, Dunstan DW, Dempsey PC, Horton ES, Castorino K, Tate DF. Physical Activity/Exercise and Diabetes: A Position Statement of the American Diabetes Association. Diabetes care 2016;39:2065-2079.

Dabadghao P, Roberts BJ, Wang J, Davies MJ, Norman RJ. Glucose tolerance abnormalities in Australian women with polycystic ovary syndrome. Medical Journal of Australia 2007;187:328-331.

Davies M, D'Alessio D, Fradkin J, Kernan W, Mathieu C, Mingrone G, Rossing P, Tsapas A, Wexler D, Buse J. Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 2018;61:2461-2498.

DeFronzo RA, Goodman AM. Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. The Multicenter Metformin Study Group. The New England journal of medicine 1995;333:541.

Echtay A, Andari E, Atallah P, Moufarrege R, Nemr R. Insulin detemir in combination with oral antidiabetic drugs improves glycemic control in persons with type 2 diabetes in near east countries: results from the lebanese subgroup. Ethnicity & disease 2017;27:45-54.

Echtay A, Tsur A, Hasan M, Abu-Hijleh M, Al Khatib N, Andari E, Atallah P, Qureshi S, Zafar J, Sandalci L, Ademogulları A, Haddad J, Dagan B. Clinical experience with insulin detemir in patients with type 2 diabetes from the near east countries. Diabetes therapy 2013;4:399-408.

Edelman S, Pettus J. Challenges associated with insulin therapy in type 2 diabetes mellitus. Am J Med 2014;127:S1-S16.

Felton A, Hall M. Diabetes in Europe policy puzzle: the state we are in. International Diabetes Nursing 2015;12:3-7.

Finnish Diabetes Association. Programme for the Prevention of Type 2 Diabetes in Finland. Finland: Finnish Diabetes Association, 2003. https://www.diabetes.fi/files/1108/Programme_for_the_Prevention_of_Type_2_Diabetes_in_Finland_2003-2010.pdf (Accessed Mar 29, 2020).

Franz MJ, Boucher JL, Rutten-Ramos S, VanWormer J. Lifestyle Weight-Loss Intervention Outcomes in Overweight and Obese Adults with Type 2 Diabetes: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. Journal of the Academy of Nutrition and Dietetics 2015;115:1447-1463.

Galdino Felix L, Fernandes Bezerra A, Herculano Lemos LG, Vidal de Negreiros R, de Araújo Leite Medeiros, Fabíola, Marques Andrade de Souza, Ana Paula, Oliveira de Sousa, Alana Tamar, Malzac Freire de Santana, Emanuelle, Gonçalves de Brito, Karen Krystine, Duarte de Oliveira Matos, Suellen, da Costa Andrade, Smalyanna Sgren, Alves da Silva M, Souza Silva de Aguiar, Elizabeth, Vitorino Diniz I, Cavalcante Cartaxo do Nascimento, Mona Lisa, André Gouveia, Bernadete de Lourdes, Guimarães de Oliveira Soares, Maria Júlia. Adherence of older people with diabetes to self-care activities: a study on gender differences. International Archives of Medicine 2016;9:1-9.

Garber A, Henry R, Ratner R, Garcia-Hernandez PA, Rodriguez-Pattzi H, Olvera-Alvarez I, Hale PM, Zdravkovic M, Bode B. Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomised, 52-week, phase III, double-blind, parallel-treatment trial. The Lancet 2009;373:473-481.

Germino FW. Noninsulin Treatment of Type 2 Diabetes Mellitus in Geriatric Patients: A Review. Clinical Therapeutics 2011;33:1868-1882.

Goldberg T, Wong E. Afrezza (Insulin Human) inhalation powder: a new inhaled insulin for the management of type-1 or type-2 diabetes mellitus. P & T: a peer-reviewed journal for formulary management 2015;40:735-741.

Gough S, Narendran P. Insulin and insulin treatment. In book: Textbook of Diabetes. Chichester, UK: John Wiley & Sons, Ltd 2017, p. 399-413.

Hasslacher C. Safety and efficacy of repaglinide in type 2 diabetic patients with and without impaired renal function. Diabetes care 2003;26:886-891.

Hypertension. Current Care Guidelines. Working group set up by the Finnish Medical Society Duodecim and the Finnish Hypertension Society. Helsinki: The Finnish Medical Society Duodecim, 2014. https://www.kaypahoito.fi/hoi04010#s26 (Accessed Apr 21, 2020)

International Diabetes Federation. Global Diabetes Plan 2011–2021. Belgium: International Diabetes Federation, 2011. https://www.idf.org/our-activities/advocacy-awareness/resources-and-tools/129:global-diabetes-plan-2011-2021 (Accessed Mar 29, 2020).

Iseki K. Factors influencing the development of end-stage renal disease. Clin Exp Nephrol 2005;9:5-14.

Kahn S, Buse J. Medications for type 2 diabetes: how will we be treating patients in 50 years?. Diabetologia 2015;58:1735-1739.

Kahn SE, Cooper ME, Del Prato S. Pathophysiology and treatment of type 2 diabetes: perspectives on the past, present, and future. The Lancet 2014;383:1068-1083.

Kansaneläkelaitos. Suomen lääketilasto. Finland: KELA, 2019. https://www.kela.fi/tilastojulkaisut_suomen-laaketilasto (Accessed May 07,2020).

Kario K, Okada K, Kato M, Nishizawa M, Yoshida T, Asano T, Uchiyama K, Niijima Y, Katsuya T, Urata H, Osuga J, Fujiwara T, Yamazaki S, Tomitani N, Kanegae H, Hoshide S, Yamamoto M, Eguchi K, Mizuno A, Nakano S, Kemi Y, Iwashita C, Wada K, Kaneko A, Ryan N. Twenty four hour blood pressure lowering effect of a sodium glucose cotransporter 2 inhibitor in patients with diabetes and uncontrolled nocturnal hypertension: results from the randomized, placebo-controlled SACRA study. Circulation 2019;139:2089-2097.

Kautzky-Willer A, Harreiter J, Pacini G. Sex and gender differences in risk, pathophysiology and complications of type 2 diabetes mellitus. Endocrine Reviews 2016;37:278-316.

Kung J, Henry RR. Thiazolidinedione safety. Expert opinion on drug safety 2012;11:565-579.

Levene S, Donnelly R, Hobbs R. Management of Type 2 Diabetes Mellitus. London: Elsevier Health Sciences 2008.

Levene S, Donnelly R, Hobbs R. Management of type 2 diabetes mellitus. London: Elsevier Health Sciences 2008.

Lindström J, Tuomilehto J. The diabetes risk score: A practical tool to predict type 2 diabetes risk. Diabetes care 2003, 26(3):725-31.

McGill JB, Vlajnic A, Knutsen PG, Recklein C, Rimler M, Fisher SJ. Effect of gender on treatment outcomes in type 2 diabetes mellitus. Diabetes research and clinical practice 2013;102:167-174.

Mohan V, Mohan V, Unnikrishnan R. Type 2 diabetes mellitus. New Delhi, India: Jaypee Brothers Medical Publishers (P) Ltd 2014.

Nadeau KJ, Anderson BJ, Berg EG, Chiang JL, Chou H, Copeland KC, Hannon TS, Huang TT, Lynch JL, Powell J, Sellers E, Tamborlane WV, Zeitler P. Youth onset type 2 diabetes consensus report: current status, challenges, and priorities. Diabetes care 2016;39:1635-1642.

National Institute for Health and Welfare. The cost of diabetes. Finland: Terveyden ja hyvinvoinnin laitos, 2016. http://thl.fi/en/web/kansantaudit/diabetes/diabeteksen-kustannukset (Accessed Mar 29, 2020).

National Nutrition Council. (2019) Eating together - food recommendations for families with children. Helsinki: National Institute for Health and Welfare, 2019. http://urn.fi/URN:ISBN:978-952-343-264-2. (Accessed 14.4.2020).

Nazu NA, Lindström J, Rautiainen P, Tirkkonen H, Wikström K, Repo T, Laatikainen T. Maintenance of good glycaemic control is challenging – A cohort study of type 2 diabetes patient in North Karelia, Finland. Int J Clin Pract 2019;73.

Nguyen Q, Nguyen L, Felicetta J. Evaluation and management of diabetes mellitus. American health & drug benefits 2008;1:39-48.

Nilsson PM, Theobald H, Journath G, Fritz T. Gender differences in risk factor control and treatment profile in diabetes: a study in 229 Swedish primary health care centres. Scand J Prim Health Care 2004;22:27-31.

Niskanen L, Hahl J, Haukka J, Leppä E, Miettinen T, Mushnikov V, Sipilä R, Tamminen N, Vattulainen P, Korhonen P. Type 2 diabetes and treatment intensification in primary care in Finland. Acta diabetologica 2018;55:1171-1179.

Pemminati S, Millis RM, Kamath A, Shenoy AK, Gangachannaiah S. Are the newer antidiabetic agents worth the cost? Journal of clinical and diagnostic research: JCDR 2016;10:FL01.

Ramzan S, Timmins P, Hasan SS, Babar Z. Trends in global prescribing of antidiabetic medicines in primary care: A systematic review of literature between 2000–2018. Primary Care Diabetes 2019;13:409-421.

Reddy P, Greaves C, Williamson D. Prevention of diabetes. Somerset: Wiley 2013.

Rees A, Levy M, Lansdown A. Chapter 10 Diabetes Mellitus. In book: Clinical endocrinology and diabetes at a glance. Chichester, West Sussex, UK; Hoboken, NJ: John Wiley & Sons Incorporated 2017, p. 101-146.

Reini, K. Diabetes causes substantial losses for the Finnish economy. Tampere, Finland: 2013. https://www.julkari.fi/bitstream/handle/10024/104476/URN_ISBN_978-952-245-905-3.pdf?sequence (Accessed Mar 29, 2020).

Scobie IN, Campbell IW, Samaras K. Diabetes Mellitus. Abingdon, Oxford, UK: Health Press Limited 2009.

Sheehan J, Ulchaker MM. Obesity and type 2 diabetes mellitus. New York: Oxford University Press 2012.

Shi L, Zhao Y, Szymanski K, Yau L, Fonseca V. Impact of thiazolidinedione safety warnings on medication use patterns and glycemic control among veterans with diabetes mellitus. Journal of diabetes and its complications 2011;25:143-150.

Sikiö M, Tykkyläinen M, Tirkkonen H, Kekäläinen P, Dunbar J, Laatikainen T. Type 2 diabetes care in North Karelia Finland: Do area-level socio-economic factors affect processes and outcomes? Diabetes Res Clin Pract 2014;106:496-503.

Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. Diabetes care 1993;16:434-444.

Terveyden ja Hyvinvoinnin Laitos. Hyvinvointikompassi. Alueellisen hyvinvoinnin seurantaan, 2020. https://www.hyvinvointikompassi.fi/fi/web/hyvinvointikompassi (Accessed Apr 16,2020).

Tilastokeskus. Paavo data descriptions. Statistics Finland 2020. http://www.stat.fi/tup/paavo/paavon_aineistokuvaukset_en.html (Accessed Mar 14, 2020).

Toivakka M, Pihlapuro A, Tykkyläinen M, Mehtätalo L, Laatikainen T. The usefulness of small-area-based socioeconomic characteristics in assessing the treatment outcomes of type 2 diabetes patients: a register-based mixed-effect study. BMC public health 2018;18:1258.

Tuomilehto J, Lindström J, Keinanen-Kiukaanniemie S, Hiltunen L, Kivela SL, Gallus G, Garancini MP, Schranz A, Bouter LM, Dekker JM, Heine RJ, Nijpels G, Pajak A, Castell C, Lloveras G, Tresserras R, de Pablos-Velasco PL, Martinez-Martin FJ, Roiguez-Perez F, Gabriel R, Serrano-Rios M, Pladevall M, Muniz J, Eliasson M, Stegmayr B, Lundberg V, Unwin N, George K, Alberti MM, Hayes L, Borch-Johnsen K, Eriksson J, Qiao Q, Hu G, Balkau B. Age- and sex-specific prevalences of diabetes and impaired glucose regulation in 13 European cohorts. Diabetes care 2003;26:61-69.

Turner R, Holman R, Cull C, Stratton I. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). The Lancet 1998;352:837-853.

Type 2 Diabetes. Current Care Guidelines. Working group set up by the Finnish Medical Society Duodecim, the Finnish Society of Internal Medicine and the Finnish Diabetes Association. Helsinki: The Finnish Medical Society Duodecim, 2018. ttps://www.kaypahoito.fi/hoi50056 (Accessed Mar 26, 2020)

UK Prospective Diabetes Study Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). JAMA, The Journal of the American Medical Association 1998;280:1644 d.

Umpierrez GE, Gonzalez A, Umpierrez D, Pimentel D. Diabetes Mellitus in the Hispanic/Latino Population: An Increasing Health Care Challenge in the United States. The American Journal of the Medical Sciences 2007;334:274-282.

Uusitupa M, Hermansen K, Savolainen MJ, Schwab U, Kolehmainen M, Brader L, Mortensen LS, Cloetens L, Johansson Persson A, Önning G, Landin Olsson M, Herzig K, Hukkanen J, Rosqvist F, Iggman D, Paananen J, Pulkki KJ, Siloaho M, Dragsted L, Barri T, Overvad K, Bach Knudsen KE, Hedemann MS, Arner P, Dahlman I, Borge GIA, Baardseth P, Ulven SM, Gunnarsdottir I, Jónsdóttir S, Thorsdottir I, Orešič M, Poutanen KS, Risérus U, Åkesson B. Effects of an isocaloric healthy Nordic diet on insulin sensitivity, lipid profile and inflammation markers in metabolic syndrome – a randomized study (SYSDIET). Journal of Internal Medicine 2013;274:52-66.

Valdés S, Botas P, Delgado E, Álvarez F, Cadórniga FD. Does the new American Diabetes Association definition for impaired fasting glucose improve its ability to predict type 2 diabetes mellitus in Spanish persons? The Asturias Study. Metabolism 2008;57:399-403.

Valencia WM, Flores H. Pharmacological treatment of diabetes in older people. Diabetes, Obesity and Metabolism 2014;16:1192-1203.

Villegas R, Delahanty R, Gao Y, Long J, Williams SM, Xiang Y, Cai H, Li H, Hu F, Cai Q, Zheng W, Shu X. Joint effect of genetic and lifestyle risk factors on type 2 diabetes risk among Chinese men and women. PloS one 2012;7:e49464.

Villegas R, Gao Y, Dai Q, Yang G, Cai H, Li H, Zheng W, Shu XO. Dietary calcium and magnesium intakes and the risk of type 2 diabetes: the Shanghai Women's Health Study. The American journal of clinical nutrition 2009;89:1059-1067.

Williams ED, Magliano DJ, Zimmet PZ, Kavanagh AM, Stevenson CE, Oldenburg BF, Shaw JE. Area-Level Socioeconomic Status and Incidence of Abnormal Glucose Metabolism: The Australian Diabetes, Obesity and Lifestyle (AusDiab) study. Diabetes care 2012;35:1455-1461.

World Health Organization. The top 10 causes of death. Geneva: World Health Organization, 2018. https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death. (Accessed Mar 29, 2020).

Yakarylmaz FD, Öztürk ZA. Treatment of type 2 diabetes mellitus in the elderly. World Journal of Diabetes 2017;8:278-285.

Zhang JX, Bhaumik D, Huang ES, Meltzer DO. Change in insurance status and cost-related medication non-adherence among older U.S. adults with diabetes from 2010 to 2014. Journal of health & medical economics 2018;4.