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STARTING INSULIN TREATMENT IN TYPE 2 DIABETES

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To my three nieces
Anna, Asta and Ansa

ABSTRACT

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STARTING INSULIN TREATMENT IN TYPE 2 DIABETES

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Type 2 diabetes is a disorder of glucose metabolism characterized by chronic hyperglycemia. Initially type 2 diabetes is characterized by insulin resistance and impaired function of beta cells, leading progressively to insulin deficiency. Type 2 diabetes is treated with diet and other lifestyle changes, and with medication modulating e.g. insulin resistance, liver glucose production and insulin secretion. Injectable insulin is added to the treatment when lifestyle changes and other medication are insufficient to maintain adequate control of hyperglycemia. The aim of the treatment is to remove the symptoms of diabetes and to prevent late complications of diabetes.

Insulin was traditionally started at hospital wards, but from the early 1990's also in outpatient care. The first substudy of this thesis examined retrospectively initiation practices and how successfully insulin treatment was introduced in 1990 – 1996 in Southwestern Finland. This study aimed also at identifying the best methods of controlling plasma glucose. It showed that in the 1990's the incidence of insulin treatment increased and was initiated more often in outpatient care than previously. The use of combination treatment also increased, first with sulfonylureas and later with metformin as the oral drug. In combination therapy the insulin dose was smaller than with insulin monotherapy. HbA1c improved similarly in middle-aged and older age groups. Weight increase associated with insulin initiation was smaller when combined with oral agents.

A prospective insulin initiation study (1994 – 1998) tested the hypothesis that hyperglycemia type (fasting and postprandial hyperglycemia) may affect the outcome of insulin initiation. The type of hyperglycemia was determined by the relation of fasting plasma glucose to HbA1c. Treatment was initiated with insulin Lente or human NPH insulin. In patients treated with insulin monotherapy twice daily the decline in HbA1c was markedly greater for postprandial than fasting hyperglycemia patients suggesting that hyperglycemia type has significance in the selection of the insulin regimen.

Another insulin initiation study showed that patients with fasting hyperglycemia starting on insulin (2004-2005) were significantly more prone to overweight than patients with postprandial hyperglycemia. Irrespective of the insulin preparation (insulin NPH or insulin glargine), patients with fasting hyperglycemia had a greater weight increase compared to patients with postprandial hyperglycemia. Special attention should be paid to prevention of weight increase in these patients.

Key words: Type 2 diabetes, insulin treatment, hyperglycemia type, weight control

TIIVISTELMÄ

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INSULIINIHOIDON ALOITTAMINEN TYYPIN 2 DIABETEKSESSA

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Tyypin 2 diabetes on glukoosiaineenvaihdunnan häiriö, jossa hallitsee krooninen hyperglykemia. Sen patofysiologiaan kuuluu alkuvaiheessa insuliiniresistenssi ja beetasolujen toimintahäiriö, joka johtaa asteittain insuliininpuutokseen. Tyypin 2 diabetesta hoidetaan ruokavaliolla, muilla elämäntapamuutoksilla ja lääkityksellä, joka vaikuttaa esim. insuliiniresistenssiin, maksan glukoosintuotantoon ja insuliinierityksen. Pistettävä insuliini liitetään hoitoon, kun elämäntapamuutokset ja muu lääkitys eivät enää riittävästi hallitse hyperglykemiaa. Hoidolla pyritään poistamaan diabeteksen oireet ja estämään taudin myöhäiskomplikaatiot.

Insuliini on perinteisesti aloitettu sairaalaosastolla, mutta 1990-luvun alusta myös avohoidossa. Tämän väitöskirjan ensimmäisessä osatyössä tutkittiin retrospektiivisesti, miten insuliini oli aloitettu ja miten hoidossa oli onnistuttu Varsinais-Suomessa 1990 – 1996. Tämä tutkimus yritti lisäksi selvittää, mitkä olisivat parhaat menetelmät verenglukoosin hallinnassa. Tutkimus osoitti, että insuliinihoito lisääntyi 1990-luvulla ja sitä toteutettiin aikaisempaa useammin avohoidossa. Yhdistelmähoito myös lisääntyi. Alkuun lääkkeenä oli suun kautta sulfonyyliurea, myöhemmin metformiini. Yhdistelmähoidossa tarvittiin pienempi insuliiniannos kuin pelkkää insuliinia käyttäen. HbA1c parani yhtä paljon vanhimpien potilaiden ryhmässä kuin keski-ikäisillä. Insuliinin aloitukseen liittyi pienempi painonnousu, jos hoidossa olivat mukana oraaliset lääkkeet.

Prospektiivisessa insuliininaloitustutkimuksessa (1994 – 1998) testattiin hypoteesia, jonka mukaan hyperglykemiatyyppi (paastohyperglykemia tai postprandiaalinen hyperglykemia) saattaisi vaikuttaa insuliinihoidon tuloksiin. Hyperglykemiatyyppi määritettiin laskemalla paastoglukoosin ja HbA1c:n suhde. Hoito aloitettiin joko Lente-insuliinilla tai humaani-NPH-insuliinilla. Kun potilaita hoidettiin pelkällä insuliinilla kahdella päivittäisellä annoksella, HbA1c:n lasku oli merkitsevästi parempi postprandiaalisessa hyperglykemiassa kuin paastohyperglykemiassa, mikä viittaa siihen, että hyperglykemiatyypillä on merkitystä insuliinihoitoa valittaessa.

Toisen insuliinitutkimuksen, jossa (2004 – 2005) aloitettiin insuliinihoito joko NPH- tai glargiini-insuliinilla, potilastietoja analysoitaessa havaittiin, että paastohyperglykemiapotilaat olivat merkitsevästi enemmän taipuvaisia ylipainoisuuteen kuin postprandiaalihyperglykeemikot. Riippumatta käytetystä insuliinista hoito aiheutti heille suuremman painonnousun kuin prostprandiaalisessa hyperglykemiassa. Näiden potilaiden hoidossa painonnousun estämiseen tulisi kiinnittää erityistä huomiota.

Avainsanat: tyypin 2 diabetes, insuliinihoito, hyperglykemiatyyppi, painonhallinta

CONTENTS

ABBREVIATIONS

ADA	American Diabetes Association
AGE	advanced glycosylation endproducts
ALT	alanine aminotransferase
AMPK	adenosine monophosphate kinase
ANOVA	analysis of variance
BI	biguanide
BPD	biliopancreatic diversion
CI	confidence interval
DECODE	Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe (study)
DEHKO	Development Programme for the Prevention and Care of Diabetes (Finnish)
DPP	Diabetes Prevention Program
DPP-4	dipeptidyl peptidase-4
DPS	Diabetes Prevention Study
FFA	free fatty acids
FPG	fasting plasma glucose
GAD	glutamic acid decarboxylase
GCK	glucokinase
GDM	gestational diabetes mellitus
GIP	gastric inhibitory polypeptide
GLP-1	glucagon-like peptide -1
HbA1c	glycosylated hemoglobin
HDL	high density lipoprotein
HNF-1α	hepatic nuclear factor 1 alpha
HPLC	high pressure liquid chromatography
hsCRP	high sensitivity C-reactive protein

IFG	impaired fasting glucose
IGT	impaired glucose tolerance
INITIATE	Initiate Insulin by Aggressive Titration and Education (study)
IU	international unit
KATP	ATP-sensitive K+ channel
Kela	Finnish Social Security Institution
LADA	Latent autoimmune diabetes in adults
LANMET	Insulin glargine or NPH combined with metformin in type 2 diabetes (study)
LDL	low density lipoprotein
MET	metformin
MODY	maturity-onset diabetes of the young
NAFLD	non-alcoholic fatty liver disease
NPH	neutral protamin Hagedorn
OHA	oral hypoglycemic agent
PCOS	polycystic ovary syndrome
PIR	poverty income ratio
RYGP	Roux-en-Y gastric bypass
SD	standard deviation
SES	socioeconomic status
SGLT2	sodium-glucose linked transporter -2
SU	sulfonylurea
TZD	thiazolidinedione
UKPDS	The UK Prospective Diabetes Study
WHO	World Health Organization
VLDL	very low density lipoprotein
VO2	oxygen consumption

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which are referred to in the text with Roman numerals: Studies I – III. In addition, this thesis contains unpublished data.

I Vähätalo M, Rönnemaa T, Viikari J. Factors affecting the efficacy of starting insulin treatment in type 2 diabetic patients. A retrospective evaluation. *Scand J Prim Health Care* 2003; 21: 230–6.

II Vähätalo M, Rönnemaa T, Viikari J. Recognition of fasting or overall hyperglycaemia when starting insulin treatment in patients with type 2 diabetes in general practice. *Scand J Prim Health Care* 2007; 25: 147–53.

III Vähätalo M, Viikari J, Rönnemaa T. Starting bedtime glargine versus NPH Insulin in poorly controlled type 2 diabetic patients with various hyperglycemia types (fasting type or postprandial type). *Acta Diabetol* 2014; 51: 233–8.

1 INTRODUCTION

As in most westernized countries, diabetes is a "national disease" in Finland, and its prevalence is increasing rapidly. The incidence of type 1 diabetes is rising for unknown reasons, but the incidence of type 2 diabetes increases particularly in the developing countries, probably due to a rising standard of living. Risk factors for type 2 diabetes are obesity and a lack of sufficient daily exercise. Also modern diet preferences, especially an increasing proportion of refined foodstuffs, affect the risk of diabetes. In the background there is a genetic disposition, possibly due to natural selection. This genetic disposition has favored people whose basal metabolism is slower and the capacity to store fat greater, which has provided a survival benefit during times of famine.

Type 2 diabetes is also a *vascular disease,* because one of its common complications is atherosclerosis of large arteries (*macroangiopathy*), which manifests as coronary heart disease and myocardial infarction, stroke and, in the lower limbs, as claudication and acute ischemia. More than 50% of the mortality and much morbidity in diabetes is related to CVD (Rydén 2013). Diabetic complications may also develop in the small arteries (*microangiopathy)*, specifically the retina, kidneys and nerves.

Type 2 diabetes can be prevented, even to a great extent. There are effective tools for this. The DPS study examined diabetes prevention in patients with impaired glucose tolerance (IGT) with lifestyle modifications, and the incidence of diabetes was reduced by 58% (Tuomilehto et al. 2001). A similar reduction by lifestyle changes was observed in the DPP study (Diabetes Prevention Study Group 2002).

Pharmacological prevention is less effective: the DPP study showed that using metformin for IGT-patients prevents diabetes by 25%. However, in another study troglitazone reduced the incidence of type 2 diabetes in IGT patients by > 50% (Buchanet et al. 2002). The ADA Position Statement (Nathan et al. 2007) did not recommend pharmacological treatment of IGT.

In the developed countries, the population has received ample information on what constitutes a healthy lifestyle. The same information serves as such also type 2 diabetes prevention. The most important beneficial lifestyle changes include increased physical exercise, a eucaloric or, when needed, a low-calorie diet with slowly absorbed carbohydrates instead of rapidly absorbed carbohydrates, unsaturated fat instead of saturated fat and a rich intake of vegetables that contain dietary fiber and protective nutrients. Smoking augments insulin resistance and is exceptionally harmful to people with diabetic complications (Ritz et al. 2000). Practical clinical experience has proven that merely giving information on a healthier lifestyle is beneficial only to a fraction of the people prone to type 2 diabetes. A great majority seems also to be in need of practical involvement and support from the medical personnel. The good results of the diabetes prevention studies DPS and DPP have called for a great contribution from physicians,

nurses and dietitians. There are just too many people in the Western hemisphere with risk factors for type 2 diabetes to make a more substantial contribution by the medical professionals feasible. The resources must be targeted to individuals having the greatest risk of diabetes. Identifying them is easy and effective with questionnaires like The Finnish Diabetes Association's Diabetes Risk Score (Lindström and Tuomilehto 2003). The Diabetes Risk Score has been used as a noninvasive and feasible tool in a nationwide program for prevention of type 2 diabetes in Finland.

Type 2 diabetes can only partly be prevented, and, therefore, society must accept the responsibility for a great number of type 2 diabetes patients. The basis of therapy are lifestyle changes, which are most effective at an early stage of diabetes and in mild cases. The aim of the care is to ensure a good quality of life for the diabetic patient and to prevent diabetic complications.

At the early stage of the disease, when the patient still has endogenous insulin secretion, there is a variety of oral hypoglycemic agents (OHA) to select from. Some of the OHAs work by stimulating insulin secretion, some by increasing insulin sensitivity. Among the newest OHAs are drugs that act by increasing the action of endogenous gut hormones, which increases insulin secretion and decreases glucagon secretion. The new non-OHA drugs mimic the effect of endogenous gut hormones and are administered as subcutaneous injections.

These drugs act as long as the pancreas of the diabetic patient secretes insulin. With time, the secretion of insulin will diminish and come to a stop when the disease progresses. In order to achieve a sufficient therapeutic response when insulin secretion fails, the patient needs injectable insulin. Insulin is effective for all diabetic patients, even when there is no insulin secretion left. Insulin therapy, however, is not without problems: it leads easily to excess weight gain and there is a risk of hypoglycemias which may occasionally be serious.

The decision to start insulin therapy relies on an individual assessment of each patient. The physician in charge of treating the patient for diabetes must take several circumstances into account and importantly, of course, the patient's opinion. It is often that the decision to start insulin is postponed until much later from the time point when the criteria for starting insulin have been fulfilled. Late start of insulin treatment is to a large extent due to both the physician and the patient not knowing well enough how insulin treatment should be carried out.

In the 1980's insulin treatment for type 2 diabetes was not very common in Europe. When insulin was started, this usually took place at a hospital ward. Starting insulin treatment in open care became more common in the 1990's.

The general aims of this study were to investigate how insulin initiation in type 2 diabetic patients has been evolved since 1990, what are the effects of various regimens of insulin

initiation on the metabolic control and weight gain of the patients and whether it is possible to characterize patients who benefit from various specific initiation practices.

The first study in this thesis aimed at finding out how successful insulin treatment was in the municipal health centers in Finland Proper (southwestern Finland). The study included approximately 850 patients. Special attention was paid on how insulin was started in open care, what the impact on the metabolic control was and the patients' body weight changes.

Insulin may be started according to several regimens. The second study aimed at comparing prospectively the effects of various such regimens and, specifically, to examine whether the type of hyperglycemia (fasting type hyperglycemia and postprandial type or overall hyperglycemia) affects the effects of insulin initiation. At that time, long-acting insulin analogues were not available.

The third study was a comparison of insulin glargine and NPH insulin. The study data was analyzed to examine if the different action profiles of an insulin analogue and of NPH insulin could be exploited in treating diabetic patients with fasting or postprandial hyperglycemia. This study also examined possible differences in body weight and weight change after insulin initiation between the two hyperglycemia types.

2 REVIEW OF THE LITERATURE

2.1 Diagnostic criteria of diabetes

The diabetes diagnosis is based on symptoms and laboratory findings. The typical diabetic symptoms are frequent urination, thirst, fatigue and weight loss. Only a part of the diabetes patients develop the typical symptoms before diagnosis. Therefore, most diabetes diagnoses are made solely on the basis of biochemical determinations.

The World Health Organization (WHO) established the first Expert Committee to give a recommendation on the diagnostic criteria for diabetes mellitus. The report of the committee was published in 1965 (WHO, 1965). The recommendation was based on oral glucose tolerance test (OGTT, the glucose load being either 50 g or 100 g). If the glucose concentration of capillary whole blood 2 hours from test start exceeded 140 mg/dl (7.8 mmol/l; 9.0 mmol/l in plasma glucose), or 130 mg/dl (7.2 mmol/l; 8.5 mmol/l in plasma glucose) from a venous specimen the diagnosis was diabetes. There was no exact fasting glucose threshold. At that time, patients today considered to have impaired glucose tolerance (IGT) were considered to be diabetic.

In 1979, the National Diabetes Data Group in the USA published a position statement stating that the diagnosis of diabetes could be set, if the patient's concentration of fasting plasma glucose was over 7.8 mmol/l in two separate samples (National Diabetes Data Group 1979). If an OGTT-test was performed, a plasma glucose concentration ≥ 11.1 mmol/l was diagnostic for diabetes. The WHO Expert Committee gave its second recommendation in 1980 (WHO 1980), with values rounded off to the nearest mmol/l, and announced that the fasting plasma threshold is 8.0 mmol/l and OGTT 2 hour value 11.0 mmol/l. The glucose load of the OGTT test was set at 75 g for adults.

The next WHO recommendation was published in 1985 (WHO 1985). More than one sample with a fasting glucose concentration ≥ 7.8 mmol/l (both capillary and venous plasma) was now considered to be diagnostic. In a 2-hour OGTT the diagnosis of diabetes could be made with a venous plasma glucose > 11.0 mmol/l and a capillary plasma glucose of > 12.2 (the corresponding whole blood values were > 10.0 mmol/l from venous and > 11.1 from capillary specimen).

In 1999, the WHO lowered the diagnostic limit of the fasting plasma glucose from 7.8 mmol/l to 7.0 mmol/l (Alberti et al. 1999). This change was considered necessary since population-based studies showed that plasma glucose values higher than 7.0 mmol/l are associated with the typical diabetic microvascular complications. The other diagnostic criteria remained the same.

In 2011, the WHO recommended that glycosylated hemoglobin be included among the diagnostic tests for diabetes (WHO 2011). The cut point was set at ≥ 6.5%. The HbA1c assays were considered to be sufficiently standardized, although the strength of the recommendation was "conditional". The HbA1c value is, however, more important for evaluation of the plasma glucose control and as a guide for diabetes treatment than as a diagnostic criterion (Sacks and John 2014).

Table 1. Diagnostic criteria for diabetes mellitus (values mmol/l)

		Fasting capillary		OGTT		Fasting venous		OGTT		
Issued by	Year	blood	Plasma	Blood	Plasma	blood	Plasma	Blood	Plasma	HbA1c
WHO	1965			≥7.8*)	≥9.0			≥7.2	≥8.5	
NDDG *)	1979	≥6.7	≥7.8	≥11.1		≥6.7	≥7.8	≥10.0	≥11.1	
WHO	1980	≥7.0		≥11.0		≥7.0	≥8.0	≥10.0	≥11.0	
WHO	1985	≥6.7	≥7.8	≥11.1	≥12.2	≥6.7	≥7.8	≥10.0	≥11.1	
WHO	1999	≥6.1	≥7.0	≥11.1	≥12.2	≥6.1	≥7.0	≥10.0	≥11.1	
WHO	2011									≥6.5%

*) U.S. National Diabetes Data Group

2.2 Diabetes types

Diabetes is traditionally divided into type 1 and type 2 diabetes. This division does not cover all diabetes types, nor can the division into type 1 and type 2 diabetes be regarded as very clear-cut in the light of present knowledge (Laakso and Groop 2001).

Type 1 diabetes is caused by autoimmune destruction of the insulin-producing beta cells of the pancreas leading to absolute insulin deficiency typically within 6-12 months from diagnosis. 12 % of Finnish diabetes patients have type 1 diabetes (Saraheimo and Sane 2015).

Latent Autoimmune Diabetes in Adults (LADA) shares features of both type 1 and type 2 diabetes and due to patient's age at its diagnosis, usually over 35 years, is often confounded with type 2 diabetes. Due to similarities with type 1 and type 2 diabetes, LADA is sometimes called "type 1.5 diabetes" (Palmer et al. 2005). It is regarded as a slow-developing form of type 1 diabetes representing approximately 6 % of diabetes cases in Finland (Saraheimo and Sane 2015). Most individuals with LADA are not overweight or obese. Their production of insulin diminishes slowly within a few years and they usually respond to OHAs in the beginning. Determining GAD antibodies is useful in the diagnostics of LADA (Groop et al. 2006).

Type 2 diabetes (approximately 80 % of Finnish diabetes patients) is characterized by insulin resistance and high hepatic glucose output accompanied by deficient insulin secretion. In the early stage of the disease, the plasma glucose of these patients can be normalized with OHAs, but as the disease advances, insulin therapy becomes usually necessary.

Key elements in the pathophysiology of type 2 diabetes are insulin resistance in peripheral tissues and diminished insulin production and increased glucagon production from the pancreas. High concentrations of free fatty acids (FFA) and proinflammatory cytokines are important contributors in the molecular mechanism of insulin resistance. The result of these changes is diminished glucose transport into muscle and fat tissues and increased glucose output from the liver (Rizza 2010). This is accomplished through increased gluconeogenesis and glycogenolysis (Basu et al. 2005). Lipolysis is increased, and this raises FFA levels. Glycogenolysis in the liver is stimulated by glucagon (Shah et al. 2000, Cryer 2012). Type 2 diabetes is characterized by relative hyperglucagonemia. Prolonged, high glucagon secretion stimulates glucose production. The beta cell mass decreases due to apoptosis which is caused, among other things, by glucolipotoxicity and islet amyloid deposition which lead to oxidative and endoplasmic-reticulum stress (Poitout and Robertson 2008, Jurgens et al. 2011, Kahn et al. 2013). Genetic factors play a major role in the reduction in insulin secretion but their role in insulin resistance is less important (Herder and Roden 2011).

Determination of serum proinsulin C-peptide concentration has been used to define the diabetes type. The secretion of C-peptide equals that of endogenous insulin and thus determination of C-peptide reflects endogenous insulin secretion of the patient, not disturbed by any administration of exogenous therapeutic insulin (Madsbad et al. 1981). The C-peptide concentration is a valuable semiquantitative marker of beta-cell function (Brandenburg 2008) and the need of insulin replacement therapy for a diabetes patient can be assessed by C-peptide determination. A cut-off point of 0.2 nmol/l with simultaneous plasma glucose above 7 mmol/l has been used to separate between type 1 and type 2 diabetes (Madsbad et al. 1981). In obese and elderly patients (Thunander et al. 2012) and in patients with renal insufficiency (Covic et al. 2000), the measured C-peptide values at the time of diagnosis may be high and thus lead to misclassification of the diabetes type. The cut-off point for insulin therapy in type 2 diabetes is around 0.6 nmol/l (Jones and Hattersley 2013).

Maturity-onset diabetes of the young (MODY) is a monogenic form of diabetes. It is rare, as MODY patients can be estimated to represent 1-2 % of all diabetic patients (Fajans and Bell 2011), 2 % of Finnish diabetes patients (Saraheimo and Sane 2015). MODY patients are diagnosed either in childhood or early middle-age. At least ten types of MODY are currently known. The most common MODY type is HNF-1α (MODY3), but in Finland there are more patients of the GCK (MODY2) type (Miettinen and Tuomi 2012). The majority (60%) of MODY patients have MODY3 and can first be treated with sulfonylureas but later often some MODY patients need insulin therapy.

Mitochondrial diabetes is maternally inherited and typically presents with bilateral hearing impairment. It is uncommon and treated with OHAs or with insulin (Maassen et al. 2004, Martikainen 2012).

Secondary diabetes (1 % of Finnish diabetes patients, Saraheimo and Sane 2015) can be caused by one massive or repeated less severe bouts of acute pancreatitis which lead to partial or total destruction of endocrine pancreas tissue. Alcohol abuse is a common cause of pancreatitis, but trauma to the pancreas or abdominal surgery may also result in diabetes. Hemochromatosis or pancreatic carcinoma may cause secondary diabetes, as well (ADA 2010).

Gestational diabetes mellitus (GDM) is defined as diabetes diagnosed during pregnancy and it usually vanishes after delivery (Guide to Diabetes Education for Health Professionals). It is treated with insulin and occasionally with metformin. Typically, GDM is associated with a stronger insulin resistance than normal pregnancy and insufficient insulin secretion (Pridjian and Benjamin 2010).

2.3 Etiology of diabetes

2.3.1 Genetic background

Type 1 diabetes is not considered to be genetically predestined, but susceptibility to this disease may be inherited, as indicated by the 30 – 50% concordance of identical twins to develop type 1 diabetes (Adeghate et al. 2006). Moreover, 95% of type 1 diabetics are positive for HLA-DR3, HLA-DR4 or both (Kumar and Clark 1999). The risk of type 1 diabetes can be predicted using the determination of two susceptibility alleles and two protective alleles in the HLA BQB1 region (Ilonen et al. 1996).The incidence of type 1 diabetes is particularly high in the Nordic countries, especially Finland, but this does not seem to be related to genetic background.

The role of genetic factors in type 2 diabetes has been well documented. The concordance in monozygotic twins is almost 100% (Adeghate et al. 2006). The phenotypes may vary and the grade of insulin resistance varies by ethnic group, which has led to an assumption that the disease has various subtypes (Adeghate et al. 2006). Several genotypes have been associated with type 2 diabetes. Common risk factors, however, can help to predict new cases of type 2 diabetes equally well as the genotype of the patient (Meigs et al. 2008, Laakso 2011). Genetic factors do cause impaired glucose tolerance, but a large twin study concluded that other factors than genetic can cause the progression to an overt type 2 diabetes (Poulsen et al. 1999). The gene strongest related to type 2 diabetes risk is transcription factor 7-like 2 (TCF7L2) (Grant et al. 2006).

The genes involved in the hereditability of type 2 diabetes affect almost always (90%) insulin secretion, but there are also genes that are associated with insulin resistance, but their role is much smaller. Currently identified gene polymorphisms explain only 10 – 20% of type 2 diabetes cases (Herder and Roden 2011).

2.3.2 Non-genetic factors

Several environmental factors are involved in the development of diabetes.

The etiological role of viruses in type 1 diabetes has become more evident (Schneider and Herrath 2013). There is strong evidence that enteroviruses are associated with type 1 diabetes and attempts at developing a vaccine have been made, but since the enteroviruses are manifold, difficulties have been encountered (Schneider and Herrath 2013). Other environmental factors, e.g., cow's milk, have been studied (Åkerblom et al. 2002, Knip and Simell 2012).

A strong proof for the critical role of environmental factors in the etiology of type 2 diabetes comes from rising incidence of the disease during the last three decades because our genome has not changed during that time. The etiology is apparently heterogeneous. Many risk factors are known, but all people with a risk factor do not develop diabetes.

Obesity is a well-known risk factor for type 2 diabetes (Sullivan et al. 2005). A new term 'diabesity' has been suggested. If overweight coincides with abdominal fat distribution, it might account for 80 - 90% of type 2 diabetes cases (Astrup and Finer 2000). The risk increases already in non-obese subjects: women with BMI 24.0-24.9 kg/m^2 had a 5-fold age adjusted relative risk rise compared to women with BMI < 22.0 kg/m^2. When BMI was ≥31.0 kg/m^2, the relative age-adjusted risk was 40-fold (Colditz et al. 1997). For men, the risk rise started from BMI 23.0 kg/m^2, there was a steep rise at the BMI level of 29.0 kg/m^2 and at BMI ≥ 35 kg/m^2 the risk ratio was the highest, 42.1 (Chan et al. 1994). Abdominal obesity was an independent risk factor. Obesity during childhood and adolescence seems to increase the risk of diabetes further.

Physical inactivity is another important risk factor for type 2 diabetes, though less important than obesity (Rana et al. 2007). In the Nurses' Health Study the risk of type 2 diabetes was 2.66 times higher in the least active group (physical activity < 2.1 hours/ week) than in the most active group (≥21.8 hours/week) (Rana et al. 2007). Both well-known diabetes prevention studies (DPS and DPP) found increased exercise beneficial in preventing type 2 diabetes in IGT patients.

Gender plays a role in the development of type 2 diabetes. Adult males (20 – 60 years) have a higher incidence of diabetes than females of similar age (Awa et al. 2012), which might be due to men having more visceral fat that is hormonally active than women (Nishizawa et al. 2002). On the other hand, testosterone reduces the concentration of adiponectin in the plasma, which reduces insulin sensitivity. The effect of cultural factors on the incidence has been studied in Japanese men that have immigrated to the USA. Similar studies have been performed in the Brazilian-Japanese population. These studies have shown even a two-fold greater incidence of type 2 diabetes in the Japanese immigrants compared to the Japanese population in Japan (Fujimoto et al. 1987). The finding was similar in Sao Paulo, Brazil (Célia et al. 2011). These differences

in type 2 diabetes prevalence seem to be due to changes in lifestyle and diet which have occurred in a short time.

Low socioeconomic status (SES) is also a factor that affects the incidence of type 2 diabetes in women; in male patients it has a weaker impact (Robbins et al. 2005). The socioeconomic status was estimated based on three factors: poverty income ratio (PIR), education and occupational status. In women, all three measured factors correlated with diabetes incidence. In men PIR and education correlated negatively with the diabetes incidence, but occupational status was indifferent. One mediating factor between low socioeconomic status and type 2 diabetes incidence is considered to be low-grade inflammation, which could be due to chronic inflammation in gingival tissues (Stringhini et al. 2013). Also smoking increases the risk of type 2 diabetes (Carlsson et al. 2004, Xie et al. 2009).

There are also regional differences in type 1 diabetes prevalence: the prevalence is high in the Nordic countries, and lower in southern Europe. This geographical distribution is not systematic. Although the prevalence is low in Macedonia (Kocova et al. 1993), the prevalence of diabetes is high in Sardinia (Muntoni et al. 1995).

2.3.3 Role of ectopic fat

Ectopic fat means fat (triglyceride droplets) that is stored elsewhere than in adipose tissue, in tissues which normally contain only little fat, i.e., the liver, pancreas and muscle tissue (Snel et al. 2012). Normally the result of excessive energy intake and decreased energy consumption (due to physical inactivity) would be energy storage to fat cells, adipose tissue hyperplasia. When adipocytes become too large, they become dysfunctional and produce excessive inflammatory adipokines and cytokines, leading to chronic inflammation. This leads to ectopic fat deposition, because all fat cannot be stored normally in adipocytes (Snel et al. 2012, Shulman 2014).

Fat can accumulate between cells or inside cells in the target organs of ectopic fat deposition. Fat inside the cells is associated with impaired insulin sensitivity. Intracellular fat can impair the function of the target organ. Lately, the good results of bariatric surgery not only on weight loss, but also on glucose homeostasis have generated a theory that accumulation of fat in the liver and pancreas is essential in the etiology of type 2 diabetes (Taylor 2013). Ectopic fat accumulation as cardiac fat has been shown to be associated with development of atherosclerosis (Montani et al. 2004, Gastaldelli and Basta 2010).

2.4 Prevalence

The global prevalence of diabetes has increased from 153 million in 1980 (8.3% of males and 7.5% of females) to 347 million in 2008 (9.8% and 9.2%) (Danaei et al. 2011). This increase is explained by changes in the diet and decreased physical activity among the

population but also partially by changes in the diagnostic criteria of type 2 diabetes. The increase in this time interval has been greatest in Oceania, South Asia, Latin America and the Caribbean. The increase has been smallest in the countries with a high income level, especially Western Europe. It has been predicted that the prevalence of diabetes in Europe rises in twenty years (2010 – 2030) from 8.1% to 9.5%. The International Diabetes federation has estimated that the number of diabetic patients in 2030 will globally rise to 552 million (9.9% prevalence), approximately 50% of them being undiagnosed. The percentage of type 2 diabetic patients of all patients with diabetes is 85 – 95% (Alberti et al. 1999).

The incidence and prevalence of diabetes rise with advancing age. The rise starts in the age group 45-54 years, and continues to rise, until it diminishes in the oldest age group (> 75 years of age) (Kenny et al. 1995).

In Finland, the number of diabetic patients with drug reimbursement was 93,831 in 1988 and 184,721 in 2002 (prevalence 5.1%) (Niemi and Winell 2005). In a statistics report of the DEHKO project, the estimated number of diabetic patients at the end of 2007 was approximately 500,000. If IFG and IGT patients were included, the percentage of abnormal glucose regulation was 43% in men and 33% in women (age group 45-74 years, Peltonen et al 2006). The number of patients who received reimbursed pharmacological treatment for their diabetes was 284,832. The number of patients with undiagnosed diabetes was estimated to be approximately 200,000. This report estimates that the number of diabetic patients on pharmacological treatment doubles every 12 years. Type 2 diabetes accounts for 85% of all diabetic patients in Finland, as elsewhere (Peltonen et al. 2006, Sund and Koski 2009). Also in Finland, the rapid rise in the number of diabetic patients is partially explained by the change of diagnostic criteria. One reason for the increased number in Finland is related to changes in the age distribution of the population: the largest age cohorts born in 1946-1952 are now reaching the age when the incidence of type 2 diabetes is especially high. In 2012, the number of new type 2 diabetics on pharmacological treatment was estimated to be 22,500 (Kela 2012).

2.5 Late complications

Diabetic late complications may be divided into microvascular and macrovascular complications.

Diabetic retinopathy and diabetic nephropathy are microvascular complications. Diabetic neuropathy is only partially based on impairment of microcirculation (Kasalova et al. 2006, Calleghan et al. 2012, Albers and Pop-Busui 2014). The macrovascular complications constitute significant risks to the life expectancy of a diabetic patient. They include coronary heart disease (Haffner et al. 1998), stroke (Laakso and Kuusisto 2007) and obliterating atherosclerosis of the lower limbs (Jude et al. 2001).

The microvascular complications are largely caused by the oxidative stress that results from chronic hyperglycemia. Hyperglycemia is a risk factor also for the macrovascular complications. The three major risk factors for atherosclerotic cardiovascular diseases include high total cholesterol, hypertension and smoking and the same risk factors prevail in diabetes (Stamler et al. 1993). One additional important risk factor is diabetic dyslipidemia, characterized by small dense LDL-particles, low HDL cholesterol and high triglycerides (Syvänne and Taskinen 1997). Small dense LDL particles have a long half-life, which promotes LDL oxidation and trapping in the arterial wall (Kawahito et al. 2009). Hyperglycemia causes large vessel disease by increasing oxidative stress, leucocyte adhesion to the endothelium and glycosylation in almost all proteins of the body. Accumulation of advanced glycosylation end products (AGE) in the body leads to stiffening of the arterial walls (Kawahito et al. 2009). In animal studies a connection between hyperglycemia and atherosclerosis has not been unquestionably established and as to humans, the association between hyperglycemia and macrovascular disease is inevitably weaker than between hyperglycemia and microvascular disease (UKPDS Study Group 1988). The culprit behind atherosclerosis in diabetes is apparently a combination of risk factors: insulin resistance and its consequences, hyperinsulinemia, hypertension, dyslipidemia (especially small and dense LDL) and abdominal obesity (Reusch 2003). It is most significant if a person in the pre-diabetic state has rather impaired insulin sensitivity than insufficient insulin secretion. In insulin resistance, high glucose seems to be a stronger predictor of vascular complications than levels related to impaired insulin secretion (Vauhkonen et al. 1998, Laakso 1999).

2.6 Treatment of type 2 diabetes

2.6.1 Non-pharmacological treatment

2.6.1.1 Diet therapy

An appropriate diet is vital for diabetes prevention. It also forms the basis of treating type 2 diabetes. Without a balanced diet, the desired effect of pharmacotherapy cannot be achieved. The aim of diet therapy is to achieve near-normoglycemia and thereby to prevent microvascular and macrovascular diseases. Diet therapy should be carried out individually, and it needs to take into account the willingness and skills of the pre-diabetic or diabetic patient in making lifestyle changes (ADA Position Statement 2008). Diet is an essential tool for weight control. In overweight patients a hypocaloric diet - with special emphasis on the proportion of fat in daily energy intake - has been recommended since the 1930's (Barach 1932). Such a diet has a high proportion of carbohydrates, which should mainly consist of complex carbohydrates with high fiber content. Added sugar (sucrose) should be limited to < 10% of the caloric intake. The intake of carbohydrates should be balanced to prevent not only a high rise of plasma glucose postprandially but also to prevent a medication-induced fall in plasma glucose before the next meal.

A balanced intake of carbohydrates means that mainly slowly absorbing carbohydrates should be consumed at each meal. Data on the glycemic index, which describes rise of plasma glucose after ingestion of a certain carbohydrate compared to that of glucose, may be used for planning the diet, although the value of the glycemic index is limited due to variability (Greenwood et al. 2013). The ketogenic diet (formerly known as the Atkins diet) has been popular. In this diet, carbohydrate intake is radically reduced and replaced with protein and fat. This diet can be used short term for weight reduction, but its long-term effects are not fully known and it can be even hazardous (Paoli 2014). Latest recommendation by the American Diabetes Association states that there is not an ideal percentage of macronutrients (carbohydrate, protein, fat) in the daily caloric intake that could be applied to all diabetics; the macronutrient distribution should be assessed individually (Evert et al. 2014).

The number of meals can be reduced. Due to the action profiles of modern rapid-acting insulin analogues, snacks that were essential in the past are usually no longer needed. The predictable and even action of long-acting insulin analogues is advantageous also in this respect. A disadvantage of snacks is that they easily raise the total energy intake over the energy expenditure and cause weight gain (Virtanen et al. 2008).

Dietary counseling includes education on nutrients (carbohydrates, proteins, fats) and, for those using mealtime insulin, instructions on carbohydrate counting. Counting carbohydrates allows flexibility in meals and reduces plasma glucose oscillations postprandially (Dungan et al. 2013). Patients who count their carbohydrate intake need smaller insulin doses than patients taking standard doses at meals (Bergenstal et al. 2008).

A proper composition of the dietary fat is important for prevention of arterial disease. Cutting down on saturated fat and avoiding trans-fat can reduce the risk of coronary heart disease. Saturated fatty acids are best replaced with monounsaturated and polyunsaturated fatty acids including omega-3 fatty acids derived from fish oil. This dietary change has an advantageous effect on insulin sensitivity, plasma lipids, blood pressure and blood coagulation (Virtanen et al. 2008).). In the KANWU study a 20 % increase of insulin sensitivity was found with a monounsaturated fat-rich diet compared with a saturated fat-rich diet, as long as the total proportion of fat did not exceed 37 % of the caloric intake (Vessby et al. 2001). This observation, however, has not been confirmed in later studies (Jebb et al. 2010).

2.6.1.2 Body weight control

Obesity is reaching epidemic proportions in the western hemisphere. Obesity increases the risk for diabetes especially among people who are genetically at risk. The proportion of overweight or obese people (BMI > 25 kg/m^2) in the USA was no less than 69% in 2011 – 2012 (Ogden et al. 2014). In 2008, 34.4% of the world's population was overweight (Stevens et al. 2012). The mechanisms which cause this increase in the proportion of

overweight people are not fully understood, but an increased caloric intake is certainly one obvious reason; in the USA there has been an average daily increase in caloric intake of 200 kcal over the last 20 years (Nielsen et al. 2002). At the same time, the amount of daily physical exercise has decreased and currently 32% of Americans pursue a sedentary lifestyle (Go et al. 2013). The percentage of the population who exercises enough according to present recommendations is about 49% (U.S. Department of Health and Human Services 2012). As to diabetes risk, the significance of the BMI is greater. Increasing BMI adds to the diabetes risk regardless of the amount of exercise. It has been estimated that 1 kg of weight gain adds 4.5% to the diabetes risk (Mokdad 2000).

Overweight may cause insulin resistance, but most overweight people do not develop hyperglycemia, since the beta cells of the pancreas are able to compensate for the decline of insulin action by increasing insulin secretion (Kahn et al. 2006, Festa et al. 2006). Overproduction of free fatty acids (FFA) is the one important cause of insulin resistance. The distribution of adipose tissue is also important: central obesity (adipose tissue mainly intra-abdominally) impairs insulin sensitivity (Cnop et al. 2002, Kahn et al. 2006).

Moderate weight loss (7% of body weight) is an effective means of preventing diabetes in diabetes-prone individuals. In the Finnish DPS study, a modest or moderate weight loss of 5 – 7%, combined with increased exercise, was an efficient means of counteracting diabetes (Tuomilehto et al. 2001). A similar result was obtained in the DPP study in USA (The Diabetes Prevention Program (DPP) Research Group 2002). In the DPP study the lifestyle changes proved to be more effective in preventing diabetes than metformin.

In the two landmark diabetes prevention studies (DPS and DPP), the weight control program was carried out by trained dietitians who gave individual counseling. Group counseling was not used. It is questionable how this approach could be used in ordinary clinical practice. The number of high risk patients is already great and the services of dietitians are limited. The cost of specialized services is notoriously high. As we do not have efficient weight reducing medication, dietary counseling is our only means to maintain patients' weight control, but this needs to be carried out in groups, not individually.

Some antidiabetic medications (GLP-1 analogues, SGLT2-inhibitors) have also a weight-reducing effect. This matter is dealt with in detail in the chapter on antidiabetic medications.

Several studies have shown that bariatric surgery produces an effective and permanent weight reduction (Schauer et al. 2014). Surgically induced weight loss produces generally a 10-fold weight reduction compared to conservative management, but this benefit has not yet been studied in clinical trials for diabetes prevention. A substantial percentage of type 2 diabetic subjects (75 – 95%) can be cured of their diabetes at

least for a few years (Sugerman et al. 2003, Mingrone et al. 2012). The remission of diabetes is not, however, only due to weight loss. In Roux-en-Y gastric bypass (RYGB) and biliopancreatic diversion (BPD) surgery, ingested food is led to pass through the upper small intestine, which might activate the incretin system (Salinari et al. 2009, Holst 2013). These operations are associated with diabetes remissions regardless of the initial weight or BMI of the patient. Bariatric surgery is available only to a limited number of diabetes patients. The surgical mortality rate is 0.3% for both laparoscopic (RYGB) and open (BPD) operations (Maggard et al. 2005). The patients for this therapy must be carefully selected and the great changes in lifestyle both preoperatively and after the operation require in-depth information and counseling. The long term results are encouraging (Sjöström and Lindroos 2004). There seems to be a positive effect not only on body weight, but also on diabetes, hypertriglyceridemia and hyperuricemia and ultimately on mortality (Sjöström et al. 2007). The surgical procedures which are prone to cause malabsorption – particularly BPD – may cause nutritional late complications (hypoalbuminemia, D-vitamin deficiency, calcium deficiency) (Mingrone et al. 2012).

2.6.1.3 Physical exercise

Regular physical activity prevents overweight, heart disease, hypertension (Drygas et al. 2000), diabetes (Rauramaa 1984, Tuomilehto et al. 2001) and untimely death (Paffenbarger et al. 1993). In the USA, 49% of the population (> 18 years old) took aerobic exercise which met the federal guidelines (U.S. Department of Health and Human Services 2012). In Finland, a similar survey showed that 55% of the population (19 – 65 years old) took fitness-training at least four times a week (Kansallinen liikuntatutkimus 2009-2010 2013). The typical target in diabetes intervention studies has been 150 minutes of brisk walking per week. Supervised training gives better results than spontaneous training (Colberg et al. 2010). Effective weight loss by exercise as the main means requires a substantial amount of exercise, up to 60 minutes daily (Klem and Wing 1997, Saris et al. 2003, Colberg et al. 2010).

The ADA and American College of Sports Medicine issued a Position Statement (Colberg et al. 2010) which recommended aerobic exercise for at least 150 minutes spread over three non-consecutive days in a week for type 2 diabetics. The intensity of exercise should be at least moderate, corresponding to approximately 40 – 60% of VO_{2max}. The exercise could consist of brisk walking or other forms of exercise that involve large muscle groups and induce a high pulse rate during the whole duration of the exercise. Resistance training is an alternative, which was recommended to be performed at least three times per week with moderate or high intensity. The duration of the resistance training sessions is dependent of the form of training. Persons doing resistance training should also take aerobic exercise. When the plasma glucose is high but below 15 mmol/l, there is no need to avoid exercise, as long as liquid intake is sufficient. However, in a clear insulin deficient state vigorous exercise may result in ketoacidosis. The risk of hypoglycemia during exercise is small in most patients with type 2 diabetes.

Diabetic patients using insulin or insulin secretagogues may, however, be exposed to hypoglycemia if physical exercise is prolonged. To avoid this, they should take 5 – 30 grams of carbohydrate every 30 minutes during the exercise (Colberg et al. 2010). Certain diabetic complications cause limitations although do not rule out physical exercise. These complications include coronary heart and cerebrovascular diseases, proteinuria and more severe nephropathy, active proliferative retinopathy, severe neuropathy and foot ulcers. Exercise is recommended for patients with occlusive atherosclerosis of the lower extremities. Exercise may alleviate the symptoms of peripheral neuropathy (Dixit et al. 2013). In diabetic nephropathy resistance training should be preferred. A diabetic patient with microalbuminuria does not have to give up exercise (Colberg et al. 2010).

The effect of physical activity on glucose metabolism and cardiovascular functions of type 2 diabetic patients has been examined in several relatively short-term studies (Moura et al. 2014). In a controlled randomized 4-month study VO_{2max} increased by 10% and HbA1 decreased by 1.0 per cent points (Rönnemaa et al. 1986). In an 8-week exercise study, the plasma fructosamine level of diabetic patients sank by 15% and the VO_{2max} increased by 14.8% (Moura et al. 2014). Diabetic patients who had been physically active throughout their life were physically more fit than sedentary controls; their insulin sensitivity was significantly higher and their risk of cardiovascular death was lower (Schreuder et al. 2014). The arterial endothelial function was also clearly better compared to patients not physically active. The VO_{2max} was 50% higher in the active group than in the sedentary lifestyle group (Schreuder et al. 2014).

Aerobic exercise may also be beneficial with respect to diabetic complications: in an 8-week study (Dixit et al. 2013) a group of diabetic patients with peripheral neuropathy was compared with a control group. The need for antihyperglycemic medication in the physically active group was significantly reduced and neuropathy changes in terms of nerve conduction velocity were also improved. The improvement may have been due to improved oxygenation of peripheral nerves (Dixit et al. 2013).

The effects of physical exercise on glucose and lipid metabolism

Physical activity increases glucose uptake into the muscles, which is compensated for by glycogenolysis and gluconeogenesis in the liver and by other sources of energy, as free fatty acids (Suh et al. 2007). The energy source which is used depends on the duration and intensity of the exercise. At the beginning of the exercise, glycogen stored in the liver is used. When exercise continues, the body moves to using glucose produced by gluconeogenesis from other sources, such as lipids stored in fat tissue. Lipids are still used as a source for glucose production during the recovery stage after exercise. The physical strain may produce hypoglycemia, but this risk is small, unless the person uses insulin or insulin secretagogues (Suh et al. 2007). Intensive and prolonged physical activity increases the insulin action also after the activity, but the duration of the enhanced sensitivity depends on circumstances like age and physical condition of the patient (Short et al. 2003, Hawley and Lessard 2008).

Both aerobic and resistance training increase the insulin action. For diabetes prevention and as a therapeutic life style change, however, aerobic training is preferable. Exercise has only a small effect on plasma lipids (Rönnemaa et al. 1988), the best results are achieved when exercise and weight reduction are combined (Colberg et al. 2010). Many studies have shown that physical exercise lowers the systolic, but not the diastolic blood pressure. Exercise has a mitigating effect on cardiovascular and all-cause mortality (Church et al. 2004, Vepsäläinen 2013).

2.6.2 Pharmacological treatment other than insulin

2.6.2.1 Traditional oral hypoglycemic agents (metformin, sulfonylureas, meglitinides, insulin sensitizers*)*

Metformin

Metformin is a drug of the biguanide group of pharmaceuticals. It was developed at the end of the 1950's from guanidine, a plant extract (Graham et al. 2011, Quianzon and Cheikh 2012). Phenformin and metformin were introduced simultaneously, but the former was banned in the 1970's due to its association with lactic acidosis. Metformin was kept on the market, except in USA where it was also banned and re-introduced only in 1995 (DeFronzo and Goodman 1995). Today, metformin is the base of the pharmacological treatment of type 2 diabetes and is used for treatment as well as for prevention of diabetes. Metformin can be combined with most OHAs, insulin and GLP-1-analogues.

The antihyperglycemic effect of metformin is based on decreased glucose production in the liver and to a lesser extent on increased uptake of glucose in peripheral tissues (Bailey and Turner 1996, Inzucchi et al. 1998, Shaw et al. 2005). In the liver cells, metformin enhances the suppression of gluconeogenesis caused by insulin and decreases glucagon-stimulated gluconeogenesis. The inhibition of gluconeogenesis is due to inhibition by metformin of adenosine monophosphate kinase (AMPK) in the liver (Shaw et al. 2005). Metformin increases glucose uptake into muscles. It also increases glucose uptake into adipose tissue, which augments adipose tissue formation. Metformin strengthens the binding of insulin to its receptor and reduces insulin resistance in liver and adipose cells. It enhances GLP-1 secretion (Mulherin et al. 2011).

Metformin lowers the plasma glucose concentration both after fasting and after ingestion of glucose. Metformin decreases fatty acid oxidation, which lowers plasma glucose through inhibition of the glucose-fatty acid cycle. Metformin can reduce HbA1c with approximately 1.5 per cent points (Nathan et al. 2006).

Metformin is generally well tolerated. Its most important side effects are gastrointestinal: gastric rumble, pinching and loose stools may make some of the patients even discontinue metformin therapy. However, most patients tolerate metformin if the therapy is started

carefully. Other known side effects of metformin include decreased B12 vitamin absorption which may lead to B12 vitamin deficiency, which usually does not, however, lead to anemia or neuropathy (de Groot Kamphuis et al. 2013). A serious but rare side effect of metformin is lactic acidosis. It can be avoided by careful observation of the contraindications. Renal insufficiency adds to the risk of lactate acidosis and metformin intoxication, because metformin is excreted only through the kidneys (Graham et al. 2011, Lipska et al. 2011). For the same reason metformin should not be administered if the patient is at risk of dehydration, as during acute gastrointestinal infections. Coadministration of intravenous contrast media for medical imaging increases the risk for lactate acidosis, and therefore metformin administration should be withheld when contrast media are used (Goergen et al. 2009). Liver disease, severe cardiac failure and heavy alcohol consumption are contraindications to the use of metformin.

The dosage of metformin is determined by glycemic response and tolerability. The maximal daily dose for an otherwise healthy diabetic patient is 3000 mg, usually divided in two doses. If the doses are not equal, the greater dose is given in the evening. To avoid gastrointestinal side effects, metformin is best taken with meals. Combining with many OHAs is possible and often useful, and many combination tablets are available.

Metformin is weight neutral or even slightly weight reducing. It lowers plasma triglycerides and – to a lesser amount – the total plasma cholesterol (Wu et al. 1990, Bailey and Turner 1996). Metformin reduces the incidence of type 2 diabetes in persons with IGT by 25% (DPP). Metformin is, however, not recommended for diabetes prevention, but it can be considered for persons with a high diabetes risk, who are unable to perform sufficient lifestyle changes (Diabetes: Current Care Guidelines 2013). Metformin can be used with certain preconditions in gestational diabetes (Tertti et al. 2013). Metformin has a preventive or even antitumor effect that has been studied particularly in breast cancer (Martin-Castillo et al. 2010).

Sulfonylureas

Sulfonylureas have been among the most used type 2 diabetes drugs since the 1950's (Groop 1992). Sulfonylureas are an effective and inexpensive alternative, but their usefulness has been limited by their propensity to cause hypoglycemia and excess weight gain. The plasma glucose lowering potency of synthetic sulfur compounds was discovered in the 1930's (Quianzon and Cheikh 2012). The first sulfonylurea that became commercially available was tolbutamide (in 1956), followed by chlorpropamide, carbutamide and tolazamide. These have later been called first generation sulfonylureas. The second generation sulfonylureas include compounds like glibenclamide, glipizide and gliclazide which were marketed in the 1970's. The latest newcomer is glimepiride (1995), which is said to represent the third generation of sulfonylureas (Quianzon and Cheikh 2012). For approximately 40 years, sulfonylureas have been the primary alternative for patients who do not tolerate metformin and in combination with metformin if the effect of metformin monotherapy is insufficient.

The effect of the sulfonylureas is based on biphasic stimulation of insulin secretion, i.e., boosting of both the first phase insulin response and the more prolonged insulin secretion peak in the second phase. These drugs do not actually increase insulin synthesis in the beta cells of the pancreas. Sulfonylureas bind to beta-cell receptors, which may form a part of the ATP-dependent potassium channels (Schmid-Antomarchi et al. 1987). This binding results in closing of the potassium channels, which causes depolarization of the cell, followed by calcium influx and subsequent exocytosis of insulin granules. This is the mechanism by which sulfonylureas increase insulin secretion (Groop 1992). It is noteworthy that the stimulation of insulin secretion by sulfonylureas is not dependent on the prevailing glucose concentration. There is also evidence that sulfonylureas have extrapancreatic effects, including decreased glucagon concentrations, increased insulin sensitivity and decreased hepatic glucose production, but these effects do not seem to have clinical significance (Groop 1992).

Sulfonylureas bind strongly to proteins (> 90%). They are metabolized in the liver and excreted through the kidneys and into the feces. The pharmacokinetics of the different sulfonylureas are not similar, and these drugs exhibit differences in absorption, metabolism and excretion.

The greatest risk of sulfonylurea use is prolonged hypoglycemia. Among the earlier sulfonylureas, chlorpropamide and glibenclamide have the highest risk of severe hypoglycemia (Groop 1992). Prolonged hypoglycemia is hard to detect especially in elderly patients, and hypoglycemia may be interpreted as a cerebrovascular event. The dosage of these drugs must be reduced in patients with renal insufficiency; severe renal insufficiency is a contraindication (Krepinsky 2000, Yale 2005).

The effect on plasma glucose of the sulfonylureas is rapid and potent: the plasma glucose level is reduced with 3 – 4 mmol/l and the HbA1c with 0.8 – 2.0 per cent points. The effect is more potent in recently diagnosed than in long-term diabetes. There are no significant differences in the effectiveness of the various sulfonylureas but glipizide has shortest duration of action.

The sulfonylureas are well tolerated. They may only rarely cause gastrointestinal side effects (nausea, dyspepsia) and very rarely hematologic side effects (thrombocytopenia, hemolytic anemia, agranulocytosis). They may increase liver enzyme activities (Groop 1992). Chlorpropamide has a prolonged hypoglycemic effect and can cause hyponatremia and fluid retention. The sulfonylureas may cause mild weight gain or are weight neutral.

The most recent sulfonylurea is **glimepiride.** It has a prolonged effect and can be administered as a single daily dose (in the morning 30 minutes before breakfast) (Basit et al. 2012). The initial dosage is 1 mg and is rapidly increased according to the glucose response. The recommended maximal daily dose is 6 – 8 mg. Glimepiride is clearly more effective in lowering postprandial glucose than metformin. Glimepiride causes a smaller

increase in insulin secretion in relation to the achieved metabolic control than the other sulfonylureas, but may still cause hypoglycemia, al-though to a lesser extent than other sulfonylureas. Glimepiride can be combined with other antidiabetic drugs, including insulin. There is no benefit from combining two sulfonylureas. The effect of glimepiride on body weight is neutral. Glimepiride does not prevent ischemic preconditioning of cardiac muscle cells, in contrast to the other sulfonylureas. This might reduce cardiac muscle cell injury in ischemia. Glimepiride is thus considered to be safer than the other sulfonylureas in treating the diabetes of coronary heart disease patients (Basit et al. 2012).

Meglitinides

The meglitinides were developed at the end of the 1970's from the non-sulfonylurea part of glibenclamide. The first meglitinide on the market was repaglinide (Balfour and Faulds 1998). It was followed by nateglinide in 2000 (Walter et al. 2000). The meglitinides have a shorter duration of action than the sulfonylureas and are therefore suitable for preprandial use (prandial tablets) combined with an antidiabetic drug with longer duration of action (e.g., metformin or insulin sensitizer) (Dornhorst 2001).

Repaglinide induces insulin secretion by closing the K_{ATP} channel, but its point of action is different from that of the sulfonylureas. Repaglinide is not active inside the beta cell (unlike the sulfonylureas). The drug is eliminated through the kidneys, but moderate renal insufficiency does not cause accumulation of the drug (van Heiningen et al. 1999, Scott 2012),

Repaglinide induces a rapid postprandial insulin response. The duration of its effect is maximally 4 hours. Because of the short duration of action repaglinide produces less hypoglycemia than the traditional sulfonylureas (Damsbo et al. 1999). Repaglinide is well tolerated and it has no effect on body weight.

The effect of nateglinide starts sooner than of repaglinide and the drug has a shorter duration of action. Therefore it causes even less hypoglycemia than repaglinide (Walter et al. 2000). Nateglinide is well tolerated and has no effect on body weight.

Both repaglinide and nateglinide are more specific to beta cell receptors than traditional sulfonylureas and therefore do not inhibit ischemic preconditioning (Scott 2012).

Insulin sensitizers

The thiazolidinediones were developed in Japan. The first one to be marketed was troglitazone in 1997 (Quianzon and Cheikh 2012). It was quickly withdrawn because of hepatotoxicity. Rosiglitazone and pioglitazone were approved in the USA in 1999. The FDA restricted the use of rosiglitazone in 2010 because of a possible association with ischemic cardiac events leaving pioglitazone as the only thiazolidinedione on the market.

The thiazolidinediones exert their primary effect on adipose tissue, where they prevent lipolysis. They act via an effect on nuclear receptor called PPAR gamma (Yki-Järvinen 2004). They enhance insulin sensitivity especially in muscle tissue (Stumvoll 2003). They reduce both fasting and postprandial plasma glucose concentrations and the concentration of free fatty acids (Miyazaki et al. 2001). The concentration of insulin is reduced and insulin-stimulated glucose uptake in tissues is enhanced. The thiazolidinediones "keep the fat where it should be" (Yki-Järvinen 2004), i.e., they increase subcutaneous fat and decrease liver fat (Mori et al. 1999). The concentration of adiponectin in plasma rises, which is associated with a reduction in hepatic fat and an increase in hepatic insulin sensitivity (Bajaj et al. 2004).

At maximal doses, the thiazolidinediones reduce the HbA1c in type 2 diabetes with 1.0 – 1.5 per cent points; their antihyperglycemic effect places them in the middle class of antidiabetic drugs. They are more effective than the meglitinides, but less effective than sulfonylureas or metformin. A combination with other glucose-lowering drugs does not increase the effect of the thiazolidinediones (Yki-Järvinen 2004).

The thiazolidinediones increase body weight by 2 – 4 kg. Some patients develop peripheral edema due to fluid retention and increased plasma volume. Cardiac failure may ensue when thiazolidinediones are combined with insulin. In Europe, combining thiazolidinediones with insulin was prohibited for some years at the beginning of the previous decade. Thiazolidinediones may cause anemia. Meta-analyses have shown an increased risk of peripheral bone fractures in postmenopausal women treated with thiazolidinediones (Loke et al. 2009), which may be caused by thiazolidinedione-induced reduction in osteoblastic activity and accumulation of adipose tissue in the bone marrow (Berberoglu et al. 2010). Pioglitazone may enhance the growth of bladder cancer cells (Barbalat et al. 2012).

Although the thiazolidinediones have a positive effect on patients with PCOS (polycystic ovary syndrome) (Romualdi 2003, Stout and Fugate 2005) or NAFLD (non-alcoholic fatty liver disease) (Belfort et al. 2006), the thiazolidinediones are not indicated to treat these conditions.

2.6.2.2 Novel oral hypoglycemic agents (DPP-4-inhibitors, SGLT2-inhibitors)

It has been known since the 1960's that glucose absorbed in the intestine causes a stronger stimulation of insulin secretion than glucose administered intravenously (Elrick et al. 1964). This observation led to the concept of *incretins,* i.e., factors behind the difference mentioned above. The first incretin, GIP (glucose-dependent insulinotropic polypeptide) was purified from an extract of porcine gut. GLP-1 (glucagon-like peptide 1) is secreted from the distal ileum and the colon. The secretion starts only a few minutes after the start of food intake. GLP-1 secretion is stimulated by both neural signals and by meal-induced stimulation of neuroendocrine L-cells of the gut (Drucker and Nauck 2006). A GLP-1 infusion lowers plasma glucose in type 2 diabetes by stimulating the

glucose-dependent insulin secretion. At the same time, glucagon secretion is suppressed and gastric emptying slows down (Willms et al. 1996).

The endogenous enzyme DPP-4-aminopeptidase causes rapid breakdown of endogenous GLP-1. Therefore, the half-life on endogenous GLP-1 is only a few minutes and cannot thus be used as a drug. Several pharmacological agents affect the incretin system. DPP-4-inhibitors reduce DPP-4-acitivity in the plasma and maintain a relatively high GLP-1 concentration postprandially. GLP-1 agonists are resistant to the action of DPP-4, bind to GLP-1 receptors and cause a prolonged stimulation of the receptors (Drucker and Nauck 2006).

DPP-4 inhibitors

DPP-4 (dipeptyl-peptidase 4) is a ubiquitous enzyme in the endothelium of various organs and it is present also in the plasma in measurable activities (Thornberry and Gallwitz 2009). DPP-4 inactivates GLP-1 within a few minutes after it has been secreted. GLP-1 and GIP are endogenous substrates for the DPP-4 enzyme. The first marketed DPP-4-inhibitor was sitagliptin. Since then several new DPP-4-inhibitors have been introduced, such as vildagliptin, saxagliptin, linagliptin and recently also alogliptin (Gerich 2010).

DPP-4-inhibitors have a strong affinity for DPP-4. When this enzyme is inhibited, the postprandial GLP-1-concentration rises 2-3-fold, which during hyperglycemia increases insulin secretion and decreases glucagon production. In a state of hypoglycemia, the reactive glucose output from the liver – caused by glucagon – is not inhibited (Ahrén et al. 2004). DPP-4-therapy enhances the sensitivity of alpha cells to glucose (Ahrén and Foley 2008). There is evidence that DPP-4-inhibitors can increase murine beta cell mass and prevent beta cell apoptosis (Duttaroy et al. 2011). Sitagliptin was approved for patient use in the US in 2006. The first DPP-4-inhibitors (2002) were toxic because they also inhibited DPP-8 and DPP-9. Sitagliptin is the first so called selective inhibitor, and it has been well tolerated in clinical studies (Lyseng-Williamson 2007).

DPP-4-inhibitors lower the HbA1c with 0.7 % points (sitagliptin) or 0.6 % points (vildagliptin) (Richter et al. 2008, Gerich 2010). The reduction in HbA1c for patients treated with sitagliptin with a baseline HbA1c ≥ 9% was greater than those with a baseline HbA1c < 8%. The placebo-subtracted fasting plasma glucose concentration was reduced with 1 mmol/l and the 2-h postprandial glucose with 2.6 mmol/l (Aschner et al. 2006, Karasik et al. 2008).

DPP-4-inhibitors can be combined with most antidiabetic drugs including insulin (Vilsbøll et al. 2010).

The DPP-4-inhibitors are well tolerated. The risk for hypoglycemia is small and the effect on body weight is neutral. Gastrointestinal side effects are rare. There may be a rise in transaminases, but these drugs cannot be considered hepatotoxic. There are some

reports on DPP-4-associated pancreatitis, but causality has been recently excluded (Giorda et al. 2014). In renal insufficiency the dose of DPP-4-inhibitors must be reduced, except for linagliptin which is not eliminated through kidneys (Gallwitz 2013).

SGLT2-inhibitors

The sodium-glucose cotransporter 2 (SGLT2) receptor is located in the proximal renal tubules and reabsorbs most of the glucose that is filtrated through the kidneys (Wood and Trayhurn 2003, Rahmoune et al. 2005). In healthy, non-diabetic persons all glucose that is excreted during the day is reabsorbed. In diabetic patients, when the renal glucose threshold (approximately 10 – 14 mmol/l plasma glucose) is exceeded, glucose flows over into the urine and is eliminated from the body. Glucose reabsorption can be prevented with drugs that affect the function of the SGLT-2.

Several SGLT2-inhibitors have been developed in recent years (Chao and Henry 2010). The first one approved for clinical use was dapagliflozin followed by empagliflozin. Dapagliflozin prevents about 50% of the daily glucose reabsorption (approximately 180 g) (Abdul-Ghani and DeFronzo 2008, Ferrannini et al. 2010). This results in increased loss of glucose into the urine and a reduction of the plasma glucose level. The amount of glucose excreted into the urine depends on the prevailing plasma glucose level. Use of SGLT2-inhibitors causes a daily loss of 200 – 300 kcal and body weight decreases slightly.

In a 12-week study dapagliflozin lowered fasting plasma glucose with 0.9 – 1.7 mmol/l and the HbA1c sank with 0.55 – 0.90 per cent points (List et al. 2009). In contrast to postprandial glucose and HbA1c, the decline of the fasting glucose level was dose-dependent. Total urinary glucose excretion ranged from 52 g to 85 g at different doses of dapagliflozin.

The mechanism of action of dapagliflozin does not expose the patient to hypoglycemia. Some of the patients in the study reported hypoglycemia-like symptoms, but these could not be verified with simultaneous SMBG results. There was no increase in urinary tract infections due to dapagliflozin despite the urinary glucose excretion, but the occurrence of genital infections (vulvovaginitis and balanitis) was higher than in the control group (4 – 6% vs. 1%). The dose of dapagliflozin and the amount of glucose excreted had no effect on the incidence of genital infections (Johnsson et al. 2013).

2.6.2.3 GLP-1-agonists

The first GLP-1-agonist, exenatide, is a synthetic modification of exendin-4, a substance purified from the saliva of the Gila monster (*Heloderma suspectum)*. Administration of exenatide produces greater concentrations and a much longer effect than natural GLP-1 (Drucker and Nauck 2006). Exenatide was approved for the treatment of type 2 diabetes in the USA in 2005. Although exenatide has a much longer duration of action than natural GLP-1, the pharmaceutical product is still short-acting and needs to be administered

twice daily. Thus, a long-acting form of exenatide has been developed (LAR, long-acting release) (Gedulin et al. 2005), where a polylactide-glycolide microsphere suspension is used to prolong the effect. Currently, several GLP-1-agonists with varying duration of action (liraglutide, lixisenatide and dulaglutide) are marketed for the treatment of type 2 diabetes. They are generally used when OHA drugs fail and also as an alternative to insulin treatment of type 2 diabetes.

GLP-1-agonists bind to GLP-1-receptors in the beta-cell and lower the plasma glucose in hyperglycemia by stimulating insulin secretion, suppressing glucagon secretion and delaying gastric emptying. The concentration of the GLP-1-agonists in the blood is pharmacological, i.e., much higher than that of physiological GLP-1 and they can withstand the natural degrading effect of the DPP-4 enzyme.

GLP-1-agonists lower plasma glucose in relation to the specific mechanism of action of each drug. Thus, the effect can be more pronounced on fasting plasma glucose or on postprandial glucose. GLP-1-agonists lower the HbA1c by 1 – 2 per cent points and are more effective than the DPP-4-inhibitors.

The GLP-1-agonists are relatively well tolerated. The most common side effect is nausea, which often subsides as therapy continues (Buse et al. 2009, Bergenstal et al. 2010). 6 – 10% of patients need to stop treatment with GLP-1-agonists because of side effects (Kanoski et al. 2012). Hypoglycemia is unlikely, since the glucose lowering effect fades as the plasma glucose reaches normal values. In a meta-analysis of 22 studies, exenatide and liraglutide were associated with a significant increase in the heart rate of the patients (Robinson et al. 2013).

GLP-1-agonistis reduce the body weight of most diabetic patients. This effect is dose-dependent (DeFronzo et al. 2005, Vilsbøll et al. 2012). They also have a significant beneficial effect on blood pressure, possibly mediated via the autonomous nerve system (Robinson et al. 2013).

GLP-agonists are most often used when glycemic goals are not reached with oral antidiabetic drugs. Lately, combination of GLP-agonists with long-acting insulin has been used to lower the need for large insulin doses and to achieve lower postprandial glucose values (Vora 2013).

2.6.3 Insulin therapy

2.6.3.1 Development of insulin products

In 1869, Langerhans described the regions within the pancreas that were to carry his name, the islets of Langerhans. He could not tell their function, but in 1890, von Mering and Minkowski discovered the role of the pancreas in carbohydrate metabolism. Ople was close to understanding the development of diabetes when he discovered the hyaline degeneration of the islets in 1900 (Rosenfeld 2002).

Insulin was discovered by the Canadian scientists Frederick Banting and Charles Best in 1921. They ligated the pancreatic duct of a dog and made an extract of the pancreas once it had become atrophic. Similar extracts had been made by other researchers earlier, and they had shown that the extract lowered the blood glucose of laboratory animals. Banting and Best performed the first human test using this extract in 1922. A 14-year diabetic boy had his blood glucose lowered, but there were no obvious clinical advantages. One year later the test was repeated with a purified extract and this time the effect was notable: the blood glucose sank from 0.520% (29 mmol/l) to 0.120% (7.5 mmol/l), the daily urinary glucose excretion from 71 grams to 9 grams and the clinical condition of the patient improved (Rosenfeld 2002).

Determining the blood glucose was troublesome in those days. The amount of blood needed for one assessment was 10 – 20 ml and the result was inaccurate. Glucose excretion into the urine was easier to measure and to follow (Rosenfeld 2002). A *saccharometer* was used to measure urine density, which changed mainly as a function of the glucose concentration (Polonsky 2012).

Banting and McLeod were awarded the Nobel Prize for inventing insulin in 1923. The production of insulin was started in the Connaught laboratory affiliated to the Toronto General Hospital. In the same year, Eli Lilly and Company started manufacturing insulin from pork pancreases (Banting and Best had been using pancreases of fetal calves).

Insulin became available in Finland quite soon. The first treatments were given already in 1923, and insulin production in Finland was started 1925 (Suomen Diabetesliitto).

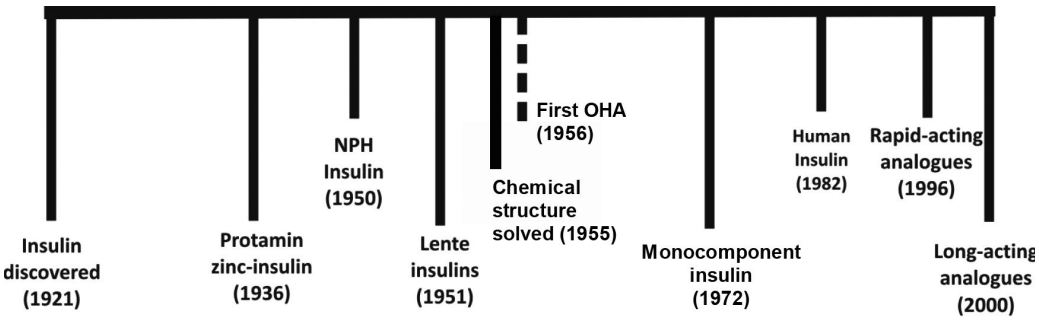

Figure 1. History of insulin (adapted from Kramer and Sauer 2010).

The human insulin molecule consists of 51 amino acids which form two polypeptide chains (the A- and the B-chain) linked together by two disulfide bridges. Chain A contains an internal disulfide bridge. Short-acting insulin in the vial is hexameric .After a subcutaneous injection, the insulin concentration is reduced due to diffusion, the dimeric form of insulin increases. In the blood circulation, insulin is monomeric. The absorption rate varies also by the volume injected – large volumes are absorbed more slowly than small volumes (Søeborg et al. 2009).

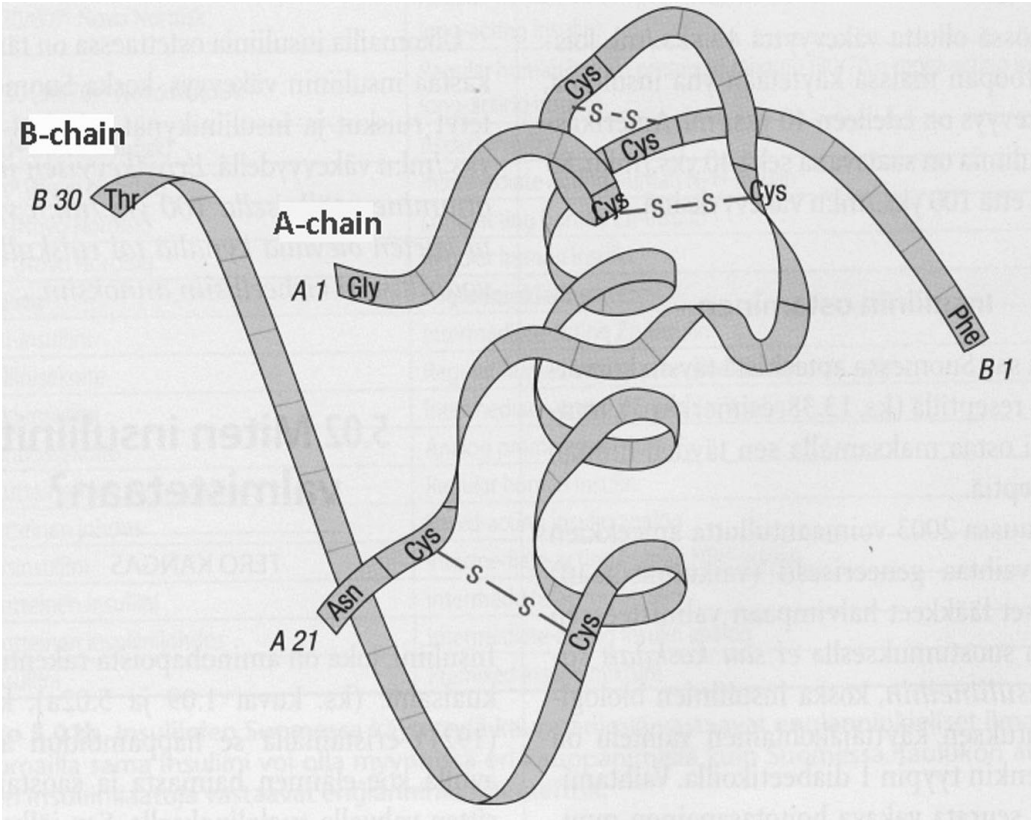

Figure 2. Three-dimensional structure of insulin. The disulfide bridges between A-chain and B-chain are marked with –S-S- (adapted from Kangas 2003).

The first long-acting insulin was zinc-protamine insulin (1936). NPH-insulin (Neutral Protamine Hagedorn) was developed in 1950. NPH insulin does not diffuse, but when NPH crystals are broken, soluble hexameric insulin is released and spreads in the tissue and is later absorbed as monomers. NPH-insulin could be mixed with short-acting insulin in any proportion. The lente-insulins (semilente, lente, ultralente) were of an amorphous composition and were marketed in 1951. They did not contain protamine, but the different action profiles were achieved by changing the zinc concentration (Teuscher 2007). Highly purified (proportion of impurities lower than 1 pmol/l) animal insulin was prepared with chromatographic techniques in 1974. Insulin produced with this technique reduced insulin-induced lipoatrophy and dystrophy at injection sites and allergy caused by insulin antibodies (Teuscher 2007).

Human insulin was prepared synthetically for the first time in 1963 and with gene technology in 1980. The first human insulins produced with gene technology, short-acting and NPH, were marketed in 1982 (Mirouze et al. 1982, Teuscher 2007).

The action of short-acting human insulin begins 0.5-1 hours after subcutaneous injection, peaks at 1-3 hours and the total duration of action varies from 5 to 8 hours.

The action of human NPH insulin begins approximately 1-2 hours after a subcutaneous injection, peaks after 4 to 10 hours and lasts for 12-18 hours (Frier et al. 2013). Because the insulin in NPH insulin preparations is in crystal form the product has to be shaken carefully just before injection.

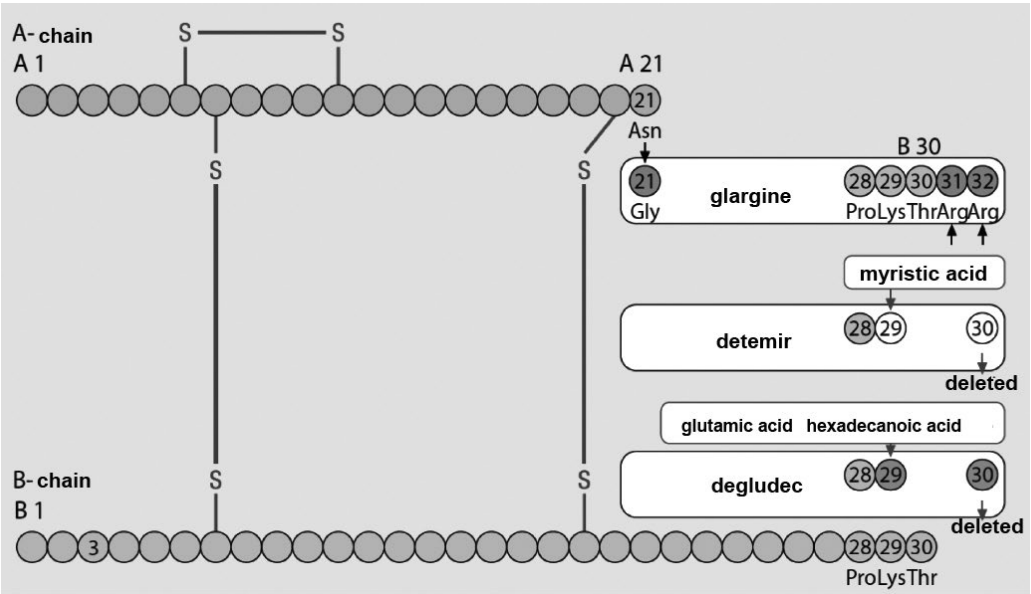

Figure 3. Structural changes in long-acting analog insulins (adapted from Rönnemaa and Ilanne-Parikka 2015).

Insulin glargine (Lantus™) was the first approved long-acting insulin analogue and became available in 2000. With the use of DNA-technology two arginine residues were added to position 30 in the C-terminal end of the B-chain and an asparagine residue was exchanged for glycine at position 21 of the A-chain. The insulin glargine preparation is a clear solution and does not need shaking because it is acidic and forms crystals only in the neutral pH of the subcutaneous tissue. Compared with NPH insulin it dissolves more slowly into tissue fluid, which prolongs its time of action (Owens 2011). Its action begins approximately 2-4 hours after injection, it may have a smooth peak and the total duration of effect varies from 20 to 30 hours. Due to a more stable action it also causes less night time hypoglycemia compared with NPH insulin (Rosenstock et al. 2005).

Insulin detemir (Levemir™) was marketed in 2006. It is a long-acting insulin analogue. With the use of gene technology, a threonine residue is removed from position B30 and a myristic acid moiety is added to lysine at position B29 (Kurtzhals 2004). Myristic acid binds to albumin leading to slower absorption. Detemir is a clear solution in the vial. The duration of action of detemir insulin is shorter than of insulin glargine (16 - 20 h) in a dose-dependent way (Porcellati et al. 2007). This difference may explain the lower lipogenic potential of detemir observed in several studies. Detemir increases

body weight less than glargine, which may also be due to its lower lipogenity (Porcellati et al. 2007).

The newest long-acting insulin analogue is **degludec-insulin** (Tresiba™). The action profiles of glargine and detemir have some intraindividual variation. Degludec insulin was developed to achieve an action profile that is as constant as possible (Gough et al. 2013). The structure of the human insulin molecule has been modified in position B29, where hexadecanoic acid is connected to the lysine residue, and in position B30, where a threonine residue has been removed (Jonassen et al. 2012). After a subcutaneous injection of soluble degludec, numerous multihexamers are deposited. Insulin is released from this deposit slowly as monomers or dimers (Garber et al. 2012). The duration of action of a degludec-injection exceeds 24 hours, and both the interindividual and intraindividual variability of the insulin effect on consecutive days is significantly smaller than for glargine insulin (Heise et al. 2012).

Human short-acting insulin peaks too slowly to mimic physiological insulin secretion during a meal. Therefore, more physiological mealtime insulins were developed. In the 1990's two rapid-acting insulin analogues became available: insulin lispro (Humalog™) in 1996 and insulin aspart (Novorapid™) in 1999. The most recent rapid-acting insulin analogue, insulin glulisine (Apidra™) became available in 2006 (Dailey and Rosenstock 2004). These rapid-acting analogues are fairly similar in their effect. They are used as mealtime insulins and can be administered just before starting the meal, as their action begins 10 - 20 minutes after injection, while short-acting human insulin is administered 30 minutes before the meal. Due to a more physiological duration of action (peak at 1 - 2 h, total duration 3 - 5 h) compared with human insulin, the need for snacks is less between main meals (Rönnemaa and Viikari 1998). A meta-analysis that compared 13 clinical studies (Mannucci et al. 2009) found that rapid-acting insulin analogues provide better postprandial glucose control than human insulin. The insulin analogues are equally effective in lowering the HbA1c. Effective lowering of HbA1c requires three or more daily injections of the insulin analogue and adequate dosing of basal insulin. Fixed combinations of a rapid-acting insulin analogue mixed with an intermediate-acting insulin analogue in two daily injections do not give as good results (Holman et al. 2007). Obesity slows down the effect of rapid-acting insulin analogues (Holman et al. 2009). Insulin glulisine may be more effective in obese diabetic patients than the other rapid-acting analogues (Becker et al. 2005).

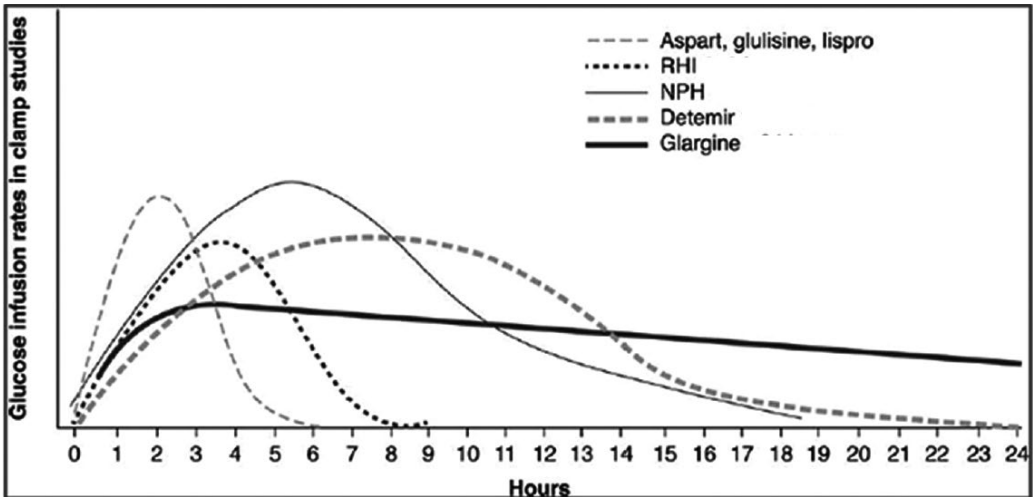

Figure 4. Action profiles of insulins (RHI= regular human insulin, NPH= Neutral Protamin Hagedorn). Adapted from Lavernia 2011.

2.6.3.2 Insulin therapy: indications, requirements, contraindications

Insulin is the most potent drug for normalizing plasma glucose in hyperglycemic conditions. In principle, insulin is used in type 2 diabetes either to compensate for severe insulin resistance or to substitute failing insulin secretion. Insulin therapy will become inevitable in the long-term for type 2 diabetics, because type 2 diabetes is a progressive disease. With increasing duration of the disease, it is not so much the insulin resistance that increases but rather the beta cell function that deteriorates (UK Prospective Diabetes Study Group 1998). In the UKPDS study, also in the intensively treated patient group, the fasting plasma glucose exceeded 7-8 mmol/l after 6 years of treatment, regardless of the form of therapy (UK Prospective Diabetes Study Group, UKPDS 16 1998). Insulin therapy should be started when other therapies fail. In Finland, the therapy recommendations consider the trigger value of HbA1c for intensification of treatment to be 7%, although the most recent revisions of the recommendations emphasize that therapy should be tailored individually with special consideration of the patient's age and concomitant chronic illnesses (Diabetes. Current Practice Guidelines 2013). The US recommendation is < 7%, and likewise patient-centered targeting is to be preferred (ADA 2010, Inzucchi et al. 2012).

Symptomatic diabetes is also an indication to insulin therapy. If the diabetic patient has, despite other forms of therapy, typical diabetic symptoms like thirst, polyuria or weight loss, insulin therapy is indicated (Donner and Muñoz 2012).

Contraindications to other forms of therapy can also be an indication to insulin treatment (Ahmann and Riddle 2002).

Insulin therapy may also be applied transiently. Insulin is indicated as first-line treatment for diabetic patients who at the time of diabetes diagnosis have very high fasting

glucose values (> 17 mmol/l). Insulin therapy may be withdrawn when the plasma glucose is in control, and OHAs may be instituted. Other indications for temporary insulin treatment are, acute infections, pregnancy, physical or mental stress (major surgical operations, stroke, myocardial infarction) and, occasionally, high-dose oral or parenteral corticosteroid treatment (Diabetes. Current Care Guidelines 2013).

The requirements for insulin therapy include safe administration of the insulin. Insulin is given by the patient him/herself, or by a family member or home care personnel if the patient is unable to self-inject due to poor vision, dementia or other reasons (ADA 2004). Self-monitoring of plasma glucose is also necessary and is performed by the patient, a family member or home care personnel. Home glucose measurements are needed for assessment of the appropriate insulin dose. Home glucose measurements are necessary particularly in case of concomitant illnesses. SMBG results must be available to the professionals who are responsible for the treatment of the diabetic patient (International Diabetes Federation Guideline Development Group 2014).

The only absolute contraindication to specific insulin brands is allergy, which is usually due to additives, like preservatives, in the insulin preparation (Rajpar et al. 2006). This situation is usually overcome by a change of the insulin preparation (Heinzerling et al. 2008). There are some relative contraindications to insulin therapy for patients who have some, albeit insufficient, endogenous insulin secretion, e.g., the conditions for carrying out insulin injections and following treatment with home glucose monitoring are not met and recurrent severe hypoglycemias occur (Mayfield and White 2004).

There were approximately 40,000 type 1 diabetic patients in Finland at the end of 2007 (Koski 2010). The number of type 2 diabetic patients with medication was estimated to be 245,000. The number of type 2 diabetic patients using insulin can be estimated to be 74,000. In 2012, Kela (The Finnish Social Insurance Institution) reimbursed insulin costs for 69.8 million € and OHA costs for 57.4 million € (Suomen lääketilasto - Finnish statistics on Medicines 2012). In USA, 12% of type 2 diabetic patients use insulin as their only antidiabetic medication, 14% use a combination of insulin and OHAs (Centers for Disease Control and Prevention 2011).

2.6.3.3 Implementing insulin therapy

The aims of insulin therapy in diabetes are correction of hyperglycemia and prevention of diabetic complications. Correcting hyperglycemia removes diabetic symptoms such as thirst, fatigue and weight loss. Microvascular complications, particularly diabetic retinopathy and nephropathy, can be prevented by treating the patient's diabetes well (UK Prospective Diabetes Study Group, UKPDS 16 1998), while the results on prevention of macrovascular complications is somewhat contradictory: the UKPDS study reported that the 10-year risk of myocardial infarction is reduced by 15%, but in the ORIGIN study a similar effect was not found during 7 years of follow-up (Holman et al. 2008, Del Prato et al. 2013).

It has also been shown that achieving near-normoglycemic metabolic control in long-term diabetes does not have a positive influence on cardiac or overall mortality. ACCORD (The ACCORD Study Group 2008), ADVANCE (Heller 2009) and VADT studies (Skyler et al. 2009) have shown that even though the general goal of < 7% of HbA1c is beneficial for most patients, less tight goal should be applied to patients with previous severe hypoglycemia, limited life expectancy and extensive comorbidities.

The insulin dosage should mimic physiological insulin secretion. This would require a long-acting basal insulin and rapid-acting insulin at mealtimes. In type 1 diabetes such multiple-injection therapy is always indicated. This can be carried out with multiple subcutaneous injections or with insulin pump therapy (Owens et al. 2001, Daneman 2006). In type 2 diabetes this kind of treatment is necessary only when the disease has progressed to the insulin-deficient phase.

When started early in type 2 diabetes (Gerstein et al. 2006, Hanefeld and Bramlage 2013), a single, daily basal insulin injection can provide good metabolic control (Holman et al. 2009, Del Prato et al. 2013).

In type 2 diabetes, insulin treatment can be initiated with four different patterns: basal insulin once daily, basal + 1-3 mealtime insulins, OHA + mealtime insulins, premixed insulins. The simplest one is one daily injection of long-acting insulin, NPH insulin or insulin analogue (Yki-Järvinen et al. 1999, Inzucchi et al. 2012). The main advantage of long-acting insulin analogues is that they cause less hypoglycemia (Riddle et al. 2003). A majority of type 2 diabetics can achieve adequate metabolic control with this form of insulin therapy, the effect of which is mainly based on controlling hepatic glucose production at night-time and between meals (Inzucchi et al. 2012). Metformin will be continued, but the effect of sulfonylureas and meglitinides is small once insulin has been introduced. Also the dose of thiazolidinediones is reduced (or stopped) to prevent edema and weight increase (Inzucchi et al. 2012). However, they may be useful when the patient is very insulin-resistant and the insulin doses become substantial (Yki-Järvinen 2004, Strowig and Raskin 2005). DPP-4 inhibitors may also be used with basal insulin. They may substitute for prandial insulin, with less risk of hypoglycemia and weight gain (Vora 2013).

There are several studies of using GLP-1-analogues with basal insulin. A retrospective analysis of combining exenatide to basal insulin (3397 patients) showed a decrease of HbA1c (-0.54 per cent points at 2 years), a weight loss (-5.5 kg at 2 years) and a decrease in the total insulin dose of 3.5% (Yoon et al. 2009). In a prospective study exenatide twice daily combined with insulin glargine improved glucose control more than insulin titration alone (HbA1c change -0.68 per cent units) without excessive risk of hypoglycemia and with modest weight loss (Buse et al. 2011). Short-acting GLP-1-analogues such as lixisenatide lower prandial glycemia, long acting GLP-1-analogues are more effective in lowering HbA1c. When GLP-1-analogues are added to insulin therapy, a reduction of insulin dose is often necessary to avoid hypoglycemia (Vora 2013). A recent meta-analysis and review of combining GLP-1 agonist and basal insulin states

that it can achieve the ideal trifecta: glucose control with no increased hypoglycemia and weight gain (Eng et al. 2014).

The usual starting dose of basal insulin is 10 IU. The starting dose can also be estimated by formulas that are based on the fasting plasma glucose values of the patient (Strange 2007). This dose is up-titrated, e.g., increased with two IU every three days until the target fasting plasma glucose is reached (Yki-Järvinen et al. 2006). The target fasting plasma glucose level is around 4.0 – 5.5 mmol/l, according to the LANMET (Yki-Järvinen et al. 2006) and INITIATE (Yki-Järvinen et al. 2007) studies. If fasting plasma glucose is below 4.0 mmol/l, the dose is reduced according to individual instructions. The dose titration can be performed by most patients themselves according to individual instructions, and the patient contacts a health care professional at appointed intervals or if problems arise. The basal insulin can be administered in the morning or in the evening. When insulin detemir is used, fewer night time hypoglycemic events occur if the dose is taken in the morning (Philis-Tsimikas et al. 2006). Similar findings have been reported for insulin glargine (Fritsche et al. 2003).

Adding mealtime insulin to the treatment is indicated if fasting plasma glucose can be maintained within the desired target values, but postprandial glucose values exceed the goal and the HbA1c does not reach the goal. The response to treatment will usually require mealtime insulin three times daily, at each main meal (Pala et al. 2007, Mannucci et al. 2009). There is evidence that the relation of the basal and mealtime insulin doses should be approximately 1:1 to achieve good metabolic control (Leeuw et al. 2005, Bergenstal et al. 2008). Also a treatment model called “Basal plus” has been published: basal insulin is administered as usual, but there is only one mealtime rapid-acting insulin dose administered at the largest meal (Ampudia-Blasco et al. 2011).

Mealtime rapid-acting insulin can also be used as the initial insulin treatment. Here, rapid-acting insulin is added to the patient’s OHA therapy and rapid-acting insulin is administered at one or more of the main meals in an attempt to combat large postprandial glucose excursions, which predispose the patient to both microvascular and macrovascular complications (The DECODE Study Group 1999). The disadvantages of this therapy are a greater body weight increase and more hypoglycemic events compared to treatment with basal insulin (Holman et al. 2007).

Insulin treatment can also be initiated with premixed insulin. Several fixed proportions of rapid-acting and long-acting insulin are available, e.g., 70% basal insulin and 30% rapid-acting insulin. Studies have been performed with mixtures containing NPH insulin as the long-acting component and human insulin as the short-acting component (Janka et al. 2005) and with biphasic aspart-insulin (BiAsp, Novomix™) which contains 70% of protamine-crystallized aspart insulin and 30% of soluble aspart insulin (Raskin et al. 2005). In the study by Janka et al., premixed insulin was compared with insulin glargine, and using glargine resulted in a better metabolic control than the premixed insulin. In the study by Raskin et al., insulin glargine and the biphasic insulin mixture

were compared, and the premix insulin gave a better metabolic control. The premixed insulin was better especially for patients with poor metabolic control (HbA1c > 8.5%). In both studies the patients using premixed insulin had more hypoglycemic events than the patients treated with basal insulin. In a systematic review of 48 studies, the target (HbA1c < 7%) was reached by 46.5% of the patients treated with premixed insulin and by 41.4% of the patients treated with basal insulin (Giugliano et al. 2011).

2.6.3.4 Conditions for successful therapy

The aim of insulin therapy is to remove diabetic symptoms, to bring the plasma glucose to a predefined level to result in HbA1c below 7% or even to below 6.5% (Laakso and Cederberg 2012) and to prevent diabetic complications. The goal should be reached without the patient experiencing hypoglycemia or a significant body weight increase. When these targets are reached, the treatment can be considered successful. Intensive insulin therapy can be cost-effective because it reduces diabetic complications (Wake et al. 2000).

When the conditions for initiation of insulin therapy are met (insulin can be administered according to the approved plan, plasma glucose can be monitored according to the needs of diet and insulin therapy), the next key factor for successful therapy is dose titration. Several titration algorithms have been used in studies on insulin initiation (Strange 2007). The patient's progress in following the instructions for dose titration can be supervised centrally by a health care professional (physician or trained nurse) (Riddle et al. 2003) or decisions on dose adjustments can be entrusted to the principal investigator (Fritsche 2003) or, at least partly, to the diabetic patient him/herself (Yki-Järvinen et al. 2006). The algorithm can be taught in a group session, which improves the effectivity of the work of health care professionals and allows peer support for participating novices of insulin treatment (Yki-Järvinen et al. 2007).

Insulin treatment has, unavoidably, some disadvantages. An implicit problem in insulin treatment is hypoglycemia. In type 1 diabetes, the insulin dose needed to achieve normoglycemia is greater than the dose that causes significant hypoglycemic events (Little et al. 2011). In type 2 diabetes, severe hypoglycemias have been shown to be linked to vascular events and all-cause mortality (Zoungas et al. 2010, Bonds et al. 2010). Risk factors for hypoglycemia are long diabetes duration, advanced age, low BMI and dementia or other cognitive disorders (Hamaty 2011). Hypoglycemia can be avoided by individualizing the HbA1c target. For a frail elderly patient the HbA1c target might be 7.6 – 8.5%, while the target for a healthy 85-year-old might be 7.0 - 7.5% (Sinclair et al. 2011). Several studies have shown that NPH insulin causes more hypoglycemia than long-acting insulin analogues (Yki-Järvinen 2004, Hermansen et al. 2006) and that premixed insulins cause more hypoglycemia than basal insulin (Janka et al. 2005). Patient guidance is important for preventing hypoglycemia: the patient is instructed in how to estimate the carbohydrate content of a meal and how to adapt the carbohydrate content to the treatment plan (ADA 2010). When mealtime insulin

is used, carbohydrate counting makes the treatment more flexible (ADA, 2010). The patient is instructed in how to recognize hypoglycemic symptoms and how to treat them independently (Dungan et al. 2013). In order to further prevent hypoglycemia, the effect of exercise must also be taken into account when assessing the carbohydrate content of meals (ADA 2010).

Increased body weight is another problem associated with insulin therapy. In the intensive therapy arm of the UKPDS study, patients starting insulin therapy gained most weight, on average 6.5 kg in 10 years (UK Prospective Diabetes Study Group, UKPDS 33 1998)). The patients that were obese already at the outset gained most weight (Russell-Jones and Khan 2007). The weight increase is due to several factors. High concentrations of glucose in the plasma cause urinary glucose excretion, which results in energy loss. When effective insulin therapy normalizes the plasma glucose, hundreds of calories per day which were earlier lost are saved preferentially as adipose tissue presuming that caloric intake remains constant (Carlson and Campbell 1993). The anabolic effect of insulin promotes weight gain, as well. Insulin affects the metabolism of free fatty acids towards storage in the form of triglycerides in adipose tissue and it also enhances protein synthesis (Russell-Jones and Khan 2007). Effective insulin therapy can cause hypoglycemia which is counteracted by extra carbohydrate intake (The DCCT Research Group 1988, De Leeuw et al. 2005). This is a further reason for excess weight gain. Anticipating hypoglycemia has a similar effect: the patient's fear of hypoglycemia leads readily to overcorrection by extra carbohydrate intake. Weight regulation by the central nervous system is affected by insulin, leptin and nutrient intake. Impaired signaling increases appetite, and causes weight increase and hepatic insulin resistance (Schwartz and Porte 2005). The body weight increases during the first years after initiation of insulin treatment for type 2 diabetes, later intensification of the insulin treatment does not usually generate large additional weight increase. Thus, the weight gain associated with starting insulin therapy is to a significant extent the result of normalization of the body weight to compensate for the weight loss caused by the diabetes itself (Larger 2005). There is a general awareness of the risk of weight gain when insulin is started, and this may also make diabetic patients unwilling to start insulin therapy (Carver 2006).

Nutritional counseling is very important for prevention of insulin-induced weight gain. Insulin dosing must also mimic the physiological insulin secretion. When mealtime insulin is taken as instructed and the doses meet the need, basal insulin doses need not be excessively high. This is beneficial, since too high basal insulin and too high mealtime insulin doses cause hypoglycemia and extra weight gain. The selection of the insulin preparation is also important: insulin detemir causes less weight gain than insulin glargine or NPH insulin (Haak et al. 2005). Weight gain can also be prevented by critical selection of OHAs: metformin reduces weight increase (Lee and Morley 1998, Mäkimattila et al. 1999) due to diminished caloric intake. The use of GLP-1 agonists in the therapy is also associated with smaller weight gain (Riddle and Henry 2006).

2.6.3.5 Insulin initiation studies, randomized

Table 2. Insulin initiation studies, NPH

First author	Year	n	Diabetes duration (y)	BMI (kg/m²)	Trial time (weeks)	Treatment		HbA1c (%)		FPG (mmol/l)			Titration	Insulin dose		Hypo-glycemia		Severe hypo-glycemia	
						Insulin	Oral	Base-line	End	Base-line	End	Target		IU	IU/kg	%	ev/pat year	%	ev/pat year
Yki-Järvinen H	2000	208	10,0	28,5	52	NPH	various	8,9	8,2	10,3	7,6	6,7	investigator	21	0,25	51			
Fritsche A	2003	234	9,3	29	28	NPH	SU	9,1	8,3	13,5	7,7	6,2	investigator	37	0,46	58			0,12
Riddle M	2003	389	9,0	32	24	NPH	various	8,6	7,0	10,8	6,7	5,6	central	42	0,42		12,9	1,8	
Eliaschewitz F	2006	250	10,8	27	24	NPH	SU	9,2	7,8	12,4	7,1	6,2	investigator	31		63			4,40
Yki-Järvinen H	2006	49	9,0	31	36	NPH	MET	9,3	7,2	12,9	5,7	5,6	patient, clini	70	0,66	57	7,7		0,00
Hermansen K	2006	225	9,8	29	26	NPH	various	8,5	6,6	10,8	6,6	6,0	central	45	0,54	80	16,0		0,08
Philis-Tsimikas A	2006	164	10,0	30	20	NPH	various	9,2	7,4	11,4	7,4	6,0	algorithm	30	0,40	32		0,0	
Pan C	2007	223	10,0	25,1	24	NPH	SU	9,1	8,1	12,4	6,6	6,7	algorithm	33			9,9		0,3
clini=clinician	**ev/pat year=events per patient year**					**MET= metformin, SU=sulfonylurea**													

Table 3. Insulin initiation studies, detemir

First author	Year	n	Diabetes duration (y)	BMI (kg/m²)	Trial time (weeks)	Treatment		HbA1c (%)		FPG (mmol/l)			Titration	Insulin dose		Hypo-glycemia		Severe hypo-glycemia	
						Insulin	Oral	Base-line	End	Base-line	End	Target		IU	IU/kg	%	ev/pa year	%	ev/pa t year
Hermansen K	2006	227	9,6	29	26	detemir	various	8,6	6,8	11,1	6,9	6,0	central	66	0,77	64	8,6		0,01
Rosenstock J	2008	291	9,1	31	52	detemir	various ex TZD	8,6	7,2	10,8	7,1	6,0	patient, clini		0,78		5,8		0,00
Meneghini L	2013	226	8,0	29	26	detemir	MET	8,0	7,5	8,7	6,2	5,0	investigator	57	0,70	24	1,2		0,00
Philis-Tsimikas A	2006	165	10,5	30	20	detemir m	various	9,1	7,5	11,5	8,6	6,0	algorithm	43	0,50	19		0,0	
Philis-Tsimikas A	2006	169	10,5	30	20	detemir e	various	8,9	7,4	10,8	7,2	6,0	algorithm	37	0,40	16		1,2	
m=morning dose, e=evening dose				**ev/pa year=events per patient year**				**clini=clinician**				**MET= metformin, TZD=thiazolidinedione**							

Table 4. Insulin initiation studies, glargine

			Diabetes duration	BMI	Trial time	Treatment		HbA1c (%)		FPG (mmol/l)			Titration	Insulin dose		Hypo-glycemia		Severe hypo-glycemia	
First author	Year	n	(years)	kg/m²	(weeks)	Insulin	Oral	Base-line	End	Base-line	End	Target		IU	IU/kg	%	ev/pat year	%	ev/pat year
Yki-Järvinen H	2000	214	10,0	29	52	glargine	SU/MET	9,1	8,3	11,3	7,8	7,4	investigator	23	0,27	33			
Fritsche A	2003	229	8,2	29	28	glargine e	SU	9,1	8,1	13,3	7,5	6,2	investigator	39	0,48	43			0,04
Fritsche A	2003	237	9,0	29	28	glargine m	SU	9,1	7,9	12,1	7,0	6,2	investigator	40	0,47	56			0,06
Riddle M	2003	367	8,4	33	24	glargine	various	8,6	7,0	11,0	6,5	5,6	central	47	0,48		9,2	2,5	
Janka H	2005	177	9,9	30	24	glargine	SU+MET	8,9	7,2	10,6	7,1	6,2	central	28	0,33	61	2,6		0,00
Raskin P	2005	118	9,8	31	28	glargine	MET+TZD	9,8	7,4	13,5	6,5	6,1	investigator	61	0,55	16	0,7		
Davies M	2005	2315	12,3	29	24	glargine		8,9	7,9	10,4	6,9	6,2	investigator	41	0,51	26		0,9	1,87
Davies M	2005	2273	12,3	29	24	glargine		8,9	7,7	10,4	6,7	6,2	patient, clini	45	0,55	30		1,1	2,36
Heine R	2005	260	9,2	31	26	glargine	MET+SU	8,3	7,2	10,4	7,5	5,6	patient, clini	25	0,28		6,3	1,5	
Kennedy L	2006	3953	8,4	34	24	glargine	various exTZD	8,9	7,6	11,7	7,4	5,6	patient, clini	50			3,7		0,09
Kennedy L	2006	3940	8,6	34	24	glargine	various exTZD	8,9	7,3	11,7	6,8	5,6	central	56			6,0		0,14
Eliaschewitz F	2006	132	10,3	27	24	glargine	SU	9,1	7,7	12,4	7,1	6,2	investigator	33		53			2,60
Rosenstock J	2006	103	8,5	35	24	glargine	MET+SU	8,8	7,1	10,4	6,8	5,6	central	39	0,40	55	7,7	2,9	
Yki-Järvinen H	2006	61	9,0	32	36	glargine	MET	9,1	7,1	13,0	6,1	5,6	patient, clini	68	0,69	54	5,0		0,00
Gerstein H	2006	206	7,6	31	24	glargine	MET/SU, 0	8,6	7,0	10,6	6,7	5,5	patient, clini	38	0,41	49			
Yki-Järvinen H	2007	63	8,0	32	24	glargine	MET/SU, ie[1]	8,7	6,9	13,0	6,3	5,5	patient, clini	62	0,64	44	3,5	0,0	
Yki-Järvinen H	2007	58	7,0	31	24	glargine	MET/SU, ge[2]	8,8	6,8	12,9	6,4	5,5	patient, clini	56	0,80	40	3,1	0,0	
Meneghini L	2010	129		34	48	glargine	MET/SU, 0	9,4	6,9	12,5	6,8	5,3	central	77		49		5,0	
Rosenstock J	2008	201	9,1	31	52	glargine	various exTZD	8,6	7,1	10,8	7,0	6,0	patient, clini		0,44		6,2		0,00
Meneghini L	2013	227	8,4	29,1	25	glargine	MET	7,9	7,1	8,5	6,1	5,0	investigator	51,0	0,61	32	1,5		0,00
Pan C	2007	220	10,3	24,8	24	glargine	SU	9,0	7,9	12,5	6,5	6,7	algorithm	30,8			6,7		0,05
1) individual education, 2) group education					**clini=clinician**														
m=morning dose, e=evening dose					**ev/pat year=events per patient year**			**MET= metformin, SU=sulfonylurea, TZD=thiazolidinedione**											

NPH

All the studies referred to here (Table 2.) were head-to-head studies comparing NPH and glargine (6) or NPH and detemir (2). Patients that were recruited and randomized were overweight or obese (BMI 25.1 – 32 kg/m^2), most often the inclusion BMI was < 35 kg/m^2. The mean duration of diabetes was approximately 10 years. OHAs were used, only one study limited to metformin, usually various oral agents were allowed in combination therapy. The final insulin doses were, on average, 0.40 – 0.54 IU/kg, with the exception of the aggressive titration of the LANMET study (Yki-Järvinen et al. 2006), where the final dose was on average 0.66 IU/kg. The duration of the studies ranged from 20 to 36 weeks, only one lasted 52 weeks. Most of them had a fasting plasma glucose target of 6.0 mmol/l, which was reached only in two studies. The most aggressive titration of the LANMET study had the greatest decline of HbA1c, -2.1 per cent points. Only one study (Fritsche et al. 2003) found that the hypoglycemia rate was the same as with the analog insulin that was compared with NPH. Usually patients treated with NPH had a clearly higher risk of hypoglycemia.

Detemir

Insulin detemir (Table 3.) has been compared with NPH (3 studies) and with glargine (2 studies). In addition to a single bedtime dose of detemir, one study allowed two daily doses (Rosenstock et al. 2008) and one study had two groups, one with a morning detemir dose and one with an evening dose (Philis-Tsimikas et al. 2006). The inclusion criteria were similar as in the NPH studies. The fasting plasma glucose target was not reached in any of the studies, the decline of HbA1c was from 1.4 to -1.6 per cent points, only one of the studies had a mean end HbA1c below 7.0 per cent points. The body weight gain was smaller with detemir than with NPH or glargine in all studies, with the exception of the Rosenstock et al. study, where two daily doses of detemir were allowed when pre-dinner glucose did not meet the target with a bedtime dose only. Diabetic patients that administered a morning and an evening dose had a weight gain that was similar to that of the glargine group in the study. The detemir dose at the end of that study was also higher (0.78 IU/kg). The hypoglycemia rates with detemir were smaller than with NPH or glargine patients: Two daily doses of detemir raised the hypoglycemia rate to the same level as with glargine patients in that study.

Glargine

Insulin initiation studies with glargine (Table 4.) (21 study groups using glargine in 17 different studies) compared insulin glargine with NPH insulin (Fritsche et al. 2003, Riddle et al. 2003, Eliaschewitz et al. 2006, Pan et al. 2006), detemir insulin (Rosenstock et al. 2008, Meneghini et al. 2013), exenatide (Heine et al. 2005) and rosiglitazone (Rosenstock et al. 2006). There were also comparisons with premixed insulin (Janka et al. 2005), biphasic insulin (Raskin et al. 2005) different titration algorithms (Davies et al. 2005) and with different types of patient education in insulin initiation (Yki-Järvinen 2007). One large retrospective study from registries compared the results when glargine

was initiated with an active or a standard titration algorithm (Kennedy et al. 2006). Gerstein et al. 2006 compared glargine with insulin avoidance.

Most of the studies were combination therapy studies. Metformin was the most common OHA used. The study subjects were obese, with an initial BMI of approximately 30 kg/m^2. Only a few of the studies reached the targeted fasting plasma glucose. The mean HbA1c values at the end of the studies were close to good metabolic control (< 7%). Glargine insulin caused less hypoglycemia than NPH insulin, but still more than insulin detemir. The occurrence of severe hypoglycemias was small, with the exception of the study which had the greatest decline of HbA1c (-2.5 per cent points) and also the largest mean insulin dose (77 IU) (Meneghini et al. 2010). The body weight increase with insulin glargine varied from 1.0 kg to 3.9 kg at the end of the study. In head-to-head comparisons, NPH usually caused more weight gain, detemir less.

In all insulin initiation studies mentioned here, the decline of HbA1c was the greater, the higher the baseline HbA1c was.

2.7 Additional measures to prevent diabetes complications in patients with type 2 diabetes

A crucial goal of diabetes treatment is prevention of diabetic complications. The plasma glucose level has a clear effect on microvascular complications (retinopathy, nephropathy and neuropathy) in patients with long-term type 2 diabetes (UK Prospective Diabetes Study Group UKPDS 33 1998, Callaghan et al. 2012, Albers 2014). A direct preventive effect of optimal glucose control has not been proven regarding macrovascular complications (heart and brain events) (The ACCORD Study Group 2008, Heller 2009) in patients with long-term type 2 diabetes in poor glycemic control. In recently diagnosed patients with type 2 diabetes, however, an advantageous long-term effect of good glycemic control on cardiovascular complications has been documented (Holman et al. 2008).

A type 2 diabetic patient has a high risk of cardiovascular complications. The majority of European CVD patients (54.5%) has IFG, IGT or overt type 2 diabetes mellitus (Bartnik et al. 2004). The risk of myocardial infarction is equally high as for non-diabetic patients that have had an infarction (Haffner et al. 1998, Laakso 2001). The glucometabolic state at hospital admission has also a predictive value for the outcome of the myocardial infarction of a diabetic patient (Malmberg et al. 1999). Normalizing plasma glucose is an effective measure against atherosclerosis of diabetic patients, but not sufficient alone. At least three other measures should be taken: smoking cessation, treatment of hypertension and treatment of dyslipidemia.

Cigarette smoking is associated with CHD events in diabetic patients similarly as in non-diabetic patients (Stamler et al. 1993, Tonstad 2009) and also with diabetic nephropathy

(Ritz et al. 2000). Therefore attention should be paid to advising diabetic patients to give up smoking, maybe assisted with pharmacotherapies to augment smoking cessation.

Hypertension plays an important role in the pathophysiology of diabetic microangiopathy and macroangiopathy. Type 2 diabetics with hypertension have increased arterial stiffness compared with patients with hypertension or diabetes alone (Schrier et al. 2007). The treatment of hypertension should be started promptly and ACE inhibitors or ARBs should be considered as the first line treatment. The goal of treatment according to ADA is a blood pressure level below 140/90 (ADA 2015), as in the latest Finnish recommendation < 140/90 (Diabetes. Current Care Guidelines 2013). Effective treatment of hypertension causes a reduction in diabetes-related deaths and complications of diabetes (UK Prospective Diabetes Study Group, UKPDS 38 1998).

Type 2 diabetic patients are known to have a lipid disorder that is prone to small, dense LDL particle formation, low HDL cholesterol and high triglycerides (Rydén et al. 2013). Statin therapy reduces the 5-year incidence of major vascular events by 20% per every mmol/l that LDL-cholesterol is lowered (Kearney et al. 2008). Therefore, all diabetic patients that have a history of vascular disease should be on statin therapy. In the Finnish recommendation (Dyslipidaemias. Current Care Guidelines 2013), the LDL-cholesterol target is < 2.5 mmol/l, as it is in the corresponding European recommendation (Rydén et al. 2013). The U.S. recommendation is < 2.6 mmol/l (ADA 2013). For patients with known CVD the treatment goal is < 1.8 mmol/l, or at least 50% of the value before treatment. Such therapy is also cost-effective, as shown in the Heart Protection Study (Mihaylova et al. 2006). It seems to be evident that all type 2 diabetic patients in the age group of over 40 years benefit from hypolipidemic pharmacotherapy with statin drugs. This seems to be the case regardless of the initial lipid status and also for patients that do not have known atherosclerosis (Colhoun et al. 2004, Gæde et al. 2003 and 2008).

3 AIMS OF THE STUDY

The general aims of this study were to investigate how insulin initiation in type 2 diabetic patients has been evolved in Finland after 1990, what are the effects of various regimens of insulin initiation on the metabolic control and weight gain of the patients and whether it is possible to characterize patients who benefit from various initiation practices.

The specific aims were:

1 to examine the practices of insulin initiation in Finland in the 1990s and how they had evolved (**Study I**).

2 to examine the effects of insulin initiation on metabolic control and weight gain to characterize factors associated with successful therapy (**Study I**).

3 to compare insulin alone with insulin in combination with oral hypoglycemic drugs when starting insulin therapy in type 2 diabetes (**Study II**).

4 to examine if the type of hyperglycemia (fasting or postprandial) affects treatment outcomes (**Study II**).

5 to examine if the type of hyperglycemia (fasting or postprandial) is related to the efficacy of treatment with insulin glargine and insulin NPH (**Study III**).

6 to elucidate if the hyperglycemia type (fasting or postprandial) predicts which patients are particularly prone to body weight increase after insulin is initiated (**Study III**).

4 SUBJECTS AND METHODS

Study I was a retrospective, observational study carried out by collecting data from all patients with insulin initiation in 1991-1997 in all hospitals and health centers of Finland Proper (southwest Finland) of the Turku University Central Hospital district. The collection was performed by one person, the author of this thesis.

Study II was a prospective randomized study on various treatment options in insulin initiation. The treatment was given by hospital outpatient clinic physicians and health center physicians in the same area as **Study I.**

Study III was a post hoc analysis of data collected in a multicenter, multinational trial, the LANMET trial (Yki-Järvinen et al. 2006) where the author of this thesis was one of the investigators.

4.1 Patients

Study I

Data were collected from all patients in Finland Proper (southwest Finland) who started insulin treatment for type 2 diabetes in 1991 - 1997. The number of inhabitants was approximately 250,000. Diabetes treatment was managed in the hospitals of the area (the university central hospital, 3 regional hospitals, 1 hospital mainly for the Swedish-speaking local communities and 1 city hospital) and in 17 health centers, where general practitioners treated type 2 diabetics either in outpatient care or in the health center wards.

The best way to identify the patients was to collect registry information of the persons who had started using insulin injection supplies during the period. The distribution of supplies was managed exclusively by the health centers. 950 patients started receiving insulin injection supplies during the 6 years' time included in the study. Of them, 34 were excluded due to a probable diagnosis of type 1 diabetes, as judged by the fasting C-peptide values (below 0.20 nmol/l). 8 patients used insulin for less than 3 weeks, and were also excluded. If no C-peptide measurement had been performed, the diagnosis of type 2 diabetes was based on clinical criteria (63.5% had a recorded value for C-peptide). Finally, 883 patients were included in the study population. The sex distribution of the patients was even, 441 men and 442 women. The mean age of all subjects was 64.2 years, 61.4 (range 40 to 91) years in men and 66.9 (range 43 to 87) years in women. The initial body weight of men in the study was 85.3 (± 13.6) kg, BMI 28.0 (± 4.6) kg/m^2 and of women 74.0 (± 13.6) kg, BMI 28.5 (± 4.7) kg/m^2. The diabetes duration averaged 12.8 years (Table 5.).

Study II

Patients were recruited in 1994 – 1998. The recruitment sites were hospital outpatient clinics and health centers in Finland Proper (southwest Finland). A diabetic patient could be included in the study, if the person had had type 2 diabetes for more than 5 years, was 40 – 75 years old, had a body mass index < 35 kg/m², an HbA1c > 7.5% and a fasting serum/plasma glucose > 8.0 mmol/l. The meal-stimulated C-peptide value had to be > 0.6 nmol/l with a concomitant serum/plasma glucose > 7.0 mmol/l. With this test, type 1 diabetics and insulin-deficient type 2 diabetics were excluded.

Fifty-two patients were randomized (35 male and 17 female). 45 were treated at hospital outpatient clinics and 7 at municipal health centers. Their mean BMI was 28.5 kg/m². The range of their fasting plasma glucose was 6.8 – 20.2 mmol/l, mean 12.5 mmol/l. The range of their baseline HbA1c was 7.6 – 11.3%, mean 9.9%. Postprandial glucose was not recorded because of logistic difficulties in timing the postprandial measurements and estimating the carbohydrate content of the meals.

Exclusion criteria were a serum creatinine concentration > 150 µmol/l and alanine aminotransferase (ALT) > 80 IU/l, cardiac failure, drug or alcohol abuse and inability to SMBG or inject insulin. Patients were recruited in 6 hospital outpatient clinics and 3 health centers in the area.

Study III

The patients that were included had an age range of 35 – 75 years and a BMI range of 20 – 40 kg/m². They were type 2 diabetics with poor glycemic control (defined as HbA1c ≥ 8.0%). After the screening visit, the patients were requested to measure their fasting plasma glucose (SMBG) daily and for inclusion the mean glucose value had to be ≥ 7.0 mmol/l. The OHAs before the study could include any sulfonylurea at any dose and metformin (≥ 1.5 g) or metformin alone and the same therapy had to be used for at least 3 months before screening. The fasting C-peptide criterion was ≥ 0.33 nmol/l.

Patients with prior insulin use or using other OHAs than metformin or metformin + a sulfonylurea were excluded. Further exclusion criteria were positive GAD antibodies, a history of ketoacidosis, abnormal liver test results (serum alanine aminotransferase, serum aspartate aminotransferase, serum alkaline phosphatase) over three times the upper limit of the normal range or a serum creatinine ≥ 120 µmol/l. Alcohol or drug abuse, night shift work, pregnancy, major systemic disease, any mental health disorder endangering compliance with the study protocol or interpreting the results of the study and retinopathy requiring surgical treatment immediately prior to the study or during the study were also exclusion criteria. The patient was not eligible for the study if SMBG was not performed during the 2-week time frame as requested.

157 patients were screened and 109 were eligible. Their mean age was 56 years and the mean duration of their diabetes was 9 years.

4.2 Methods

4.2.1 Study designs

Study I was a retrospective, observational study. **Study II** was a 52-week, open, randomized multicenter study comparing the efficacy of 5 different treatment regimens, with insulin alone or insulin in combination with OHAs. 6 hospital outpatient clinics and 3 municipal health centers recruited and managed the patients. **Study III** was a post hoc analysis using of data from the LANMET study (Yki-Järvinen et al. 2006). The LANMET study was a 36-week, open, randomized multicenter study that compared the efficacy and safety of glargine versus NPH insulin in combination with metformin. 6 centers in two countries (Finland and Great Britain) recruited and managed the patients.

4.2.2 Practical procedures

Study II

Randomization was performed with numbered envelopes that were given to participating centers and opened at the randomization visit of each eligible patient.

The treatment group was allotted with sealed envelopes. There were 5 treatment groups: (1) NPH twice daily (insulin only group), (2) NPH at bedtime + glipizide in the morning, (3) NPH at bedtime and metformin in two doses, (4) Lente-insulin at bedtime and glipizide in the morning and (5) Lente-insulin at bedtime and metformin in two doses. The glipizide dose was 10 mg in the morning, the target dose of metformin was 2.5 g. If metformin caused side effects, the patient took the maximal tolerated dose. The insulin injections in the insulin only group were administered before breakfast and at bedtime.

The two groups where NPH insulin or Lente insulin was used with metformin were analyzed combined, because the changes in HbA1c were not statistically different among the two groups. For the same reason, the two insulin (NPH or Lente) groups using also glipizide were analyzed combined. Thus, there were three treatment groups for analysis: (1) insulin twice daily, (2) bedtime insulin + glipizide and (3) bedtime insulin + metformin.

Insulin was started according to the practice of the time of the study in a ward either at a hospital or health center. The patients were instructed how to inject insulin and perform SMBG 4 times a day.

Clinic follow-up visits took place 2 weeks, 4 weeks, 2 months, 3 months, 6 months, 9 months and 12 months after the baseline visit. They were performed as outpatient visits either in the hospital outpatient clinic or in the health center that had started the insulin therapy. Each visit included weight recording and laboratory analysis of fasting serum/plasma glucose. Postprandial glucose was not recorded because of logistic difficulties

in timing of the postprandial measurements and estimating the carbohydrate content of the meals. The SMBG results were reviewed and the insulin dose adjusted. At 3, 6, 9 and 12 months an HbA1c measurement was performed. Plasma total cholesterol, HDL-cholesterol and triglycerides were measured at baseline and at the final study visit 12 months after the start of insulin treatment.

Study III

The LANMET study, which provided the data for **Study III**, included a screening visit (- 4 weeks) when screening laboratory tests were performed. The patients were instructed about the SMBG device. They used a modem for transmission of the SMBG data, the use of which also was taught. The patients had to perform daily SMBG testing and a diurnal glucose profile three times during the 4 week screening period. At the baseline visit, the results of the laboratory tests were checked (pre-check already at a phone contact at week -2) and patient compliance was ensured by monitoring the FPGs and the diurnal profiles. Eligible patients were randomized by an internet-based system. The patients were assigned to two groups using minimization of differences. If the patient used a sulfonylurea, it was discontinued, but metformin continued at the previous dose.

Insulin therapy was started with insulin glargine for the patients of one group and NPH insulin for the other. Those who had been using metformin alone had an initial dose of 10 IU of both insulins, previous sulfonylurea users started with 20 IU. The insulin dose was increased according to the following algorithm which the patients were closely familiarized with: if the mean SMBG fasting glucose of three consecutive days was ≥ 5.5 mmol/l, the dose was increased with 2 IU, if it was ≥ 10 mmol/l, with 4 IU. The target fasting glucose concentration was 4.0 – 5.5 mmol/l. If lower values occurred, the dose was reduced. The success of following the algorithm was monitored in connection with regular phone contacts (n = 14) and clinical visits (n = 4). The patients were asked to measure the FPG every morning and to perform 5-point diurnal glucose profiles on 9 of 252 study days. When the patient stood in contact with the study site, self-adjustment of the insulin dose was encouraged and adverse events (particularly hypoglycemia) were monitored.

The clinic visits were performed at 6, 12, 24 and 36 weeks and phone contacts at 1, 2, 4, 8, 10, 14, 16, 18, 20, 26, 28, 30, 32 and 34 weeks.

4.2.3 Analytical procedures

Glucose measurements

In **study I** fasting blood (not plasma or serum) glucose values were collected. Glucose measurements were performed with various methods, at that time clinical decisions were based on central laboratory determinations, local health center laboratory determinations and also self-monitoring of blood glucose results.

In **study II** the fasting blood (not plasma or serum) glucose was used and all assessments were done at hospital laboratories.

In **study III**, the fasting plasma glucose was determined using routine methods in local laboratories. The SMBG was performed with a personal glucose meter (Glucometer DEX 2, Bayer, Leverkusen, Germany).

HbA1c assays

In **studies I and II**, HbA1c was measured with fast pressure liquid chromatography (Pharmacia Sweden, reference range 4.2 – 6.0%).

In **study III** the HbA1c assay method was fully automated Glycosylated Hemoglobin Analyzer System (Bio-Rad, Richmond, CA, USA), and the reference range was 4.0 – 6.0%.

C-peptide and serum lipids

Serum C-peptide was measured using radioimmunoassay using Novo antisera (**Study I and III**) (Madsbad et al. 1981). In **Study I** and **III** fasting C-peptide was analyzed in the fasting state, in **study II** the C-peptide was measured two hours after the meal to stimulate its secretion (Double Antibody C-Peptide method, Diagnostic Products Corp., LA, CA, USA).

In **studies I** and **II** total cholesterol was assessed with an automated analyzer of the Hitachi series, using an enzymatic (cholesterol esterase, cholesterol oxidase) photometric method for measuring total cholesterol. HDL-cholesterol was measured after precipitation. Triglycerides were assessed with an enzymatic (lipoprotein lipase, glycerol kinase, glycerol phosphate oxidase) photometric method. LDL-cholesterol was calculated with the Friedewald formula (Friedewald et al. 1972). In **study III** serum lipid measurements were performed using routine methods in local laboratories.

Definition of hyperglycemia type

The **fasting plasma glucose – HbA1c –ratio** was calculated to define the hyperglycemia type of a patient. The unit of the ratio is mmol/l/%. Values ≥ 1.3 mmol/l/% were considered to signify fasting hyperglycemia and < 1.3 mmol/l/% postprandial hyperglycemia. The cut-off point 1.3 was derived from the ratio of the upper normal (non-diabetic) glucose and HbA1c values, which were 7.8 mmol/l for fasting glucose and 6.0 for HbA1c at the time of the study (7.8/6.0 = 1.3) (WHO 1985).

4.2.4 Weight, height and BMI

Body weight was registered by the nurses using mechanical beam scales, at some health centers also using scales with a spring-controlled display were used. **Height** was measured with a telescopic measuring rod attached to the beam scale, or with a

wall-mountable tape measure. The **BMI** (weight kg/(height m)^2) was calculated for the patients whose height and weight were recorded in the database.

4.2.5 Statistical analyses

The **Study II** patients were divided into two groups according to their type of hyperglycemia – fasting hyperglycemia or postprandial hyperglycemia. Those with a FPG/HbA1c ratio ≥ 1.3 mmol/l/% were defined as having fasting hyperglycemia (see "Definition of hyperglycemia type", above), those with a ratio < 1.3 mmol/l/% postprandial hyperglycemia (at that time, word "overall" was used instead of postprandial).

In **Study III**, data from the LANMET study was analyzed after dividing the patients into groups according to their hyperglycemia type, as in **Study II**.

Statistical analyses in all three studies were performed with the SPSS-software, version 14. The t-test, the paired samples t-test, ANOVA and ANOVA of repeated measures analysis were used as applicable.

4.3 Ethical considerations

The study plan of the **Study I** was approved by the administrative diabetes group of the hospital district (Turku University Central Hospital). Then special permission to use relevant information was obtained from each institution where data collection took place. The joint Ethics Committee of the City of Turku and of the Turku University Central Hospital approved the study plan of **Study II**. Each patient gave informed oral consent at study entry; consent was registered in the patient documents. In **Study III**, there were 7 participating sites, six in Finland and one in the United Kingdom. The ethics committee of each participating center gave their approval separately. The patients gave written informed consent before entering **Study III**.

5 RESULTS

Study I

The mean age of the patients was 64.2 years (males 61.4, females 66.9 years) with a range in both genders of 40 – 90 years. The diabetes duration averaged 12.8 years (Table 5.). The patients in the group that was treated with insulin alone were somewhat younger, their weight and BMI were lower, their baseline HbA1c was higher and their C-peptide was lower than in the combination treatment groups. These differences indicate that their insulin deficiency was greater and that they therefore were treated with insulin only from the beginning of insulin initiation. The three combination treatment groups did not essentially differ from each other (Table 5.).

The baseline HbA1c value was available for 75% of the patients, the baseline weight for 62% and a recorded height for 80%. Of the participants, 65.5% had their insulin treatment initiated at a hospital (outpatient or ward). General practitioners started 30.2% of the insulin therapies (outpatients 22.0%, health center wards 8.2%). For 4.2% this information had not been recorded; these patients had usually been treated by private practitioners whose records were not available. The number of insulin initiations grew during the years of the study, both in primary and specialized health care (Figure 5.). Insulin monotherapy was popular in the beginning of the study, but decreased with time. In 1991, more than half of the patients started with insulin only and had their OHAs discontinued; in 1996 the frequency was less than 30% (Figure 6.). The number of introductions of metformin in combination with insulin increased rapidly after 1994. During the years after insulin initiation the use of insulin only tended to increase and the use of OHAs to decrease. One year after insulin initiation, 55% of the patients were on combination therapy, at 5 years 36% (Figure 7.).

Insulin was initiated most often as one bedtime injection of intermediate-acting (NPH) insulin. Insulin analogues were not available at that time. Over time, there was a tendency to increase the number of injections, usually to two. The percentage of patients taking two or more injections per day one year after insulin initiation was 47% (Figure 8.). Of all patients, 4.7 % were on multiple daily injections.

Table 5. Baseline characteristics of the patients transferred to insulin therapy (Table 1 Study I). Values are means ± SD. p-values for overall differences (ANOVA) between various therapy regimens (male and female patients combined): age p<0.001, diabetes duration p=0.236, C-peptide p<0.001, body weight p=0.002, BMI p<0.001 and HbA1c p=0.004.

Regimen	Sex	n	Age (y)	Diabetes duration (y)	C-peptide (nmol/l)	Weight (kg)	BMI (kg/m^2)	HbA1c (%)
SU+INS	M	174	63,0±8,3	13,2±4,6	1,01±0,43	88,0±11,7	28,2±4,1	10,1±1,4
	F	186	67,4±7,5	13,0±4,5	0,95±0,41	75,2±10,0	28,9±4,4	10,3±1,4
BI+INS	M	26	61,0±7,4	11,1±4,0	1,10±0,45	91,8±11,5	29,9±4,7	9,8±1,2
	F	27	68,9±7,1	12,2±6,2	1,21±0,48	78,6±9,1	30,2±4,1	10,2±0,9
SU+BI+INS	M	36	65,4±5,8	13,7±5,1	1,21±0,41	92,0±10,8	30,3±3,8	9,8±1,3
	F	49	65,2±7,0	12,1±4,0	1,10±0,46	78,7±10,8	30,0±4,5	9,8±1,0
INS only	M	205	59,1±8,9	11,2±5,7	0,81±0,46	82,5±12,9	27,0±5,1	10,6±1,5
	F	180	66,7±7,7	12,9±5,4	0,90±0,42	70,5±10,7	27,2±5,0	10,6±1,6
All	M	441	61,4±8,5	12,3±5,1	0,95±0,45	85,3±13,6	28,0±4,6	10,2±1,5
	F	442	66,9±7,5	12,8±5,0	0,97±0,43	74,0±13,6	28,5±4,7	10,4±1,4

SU=sulfonylurea, BI=biguanide, INS=insulin

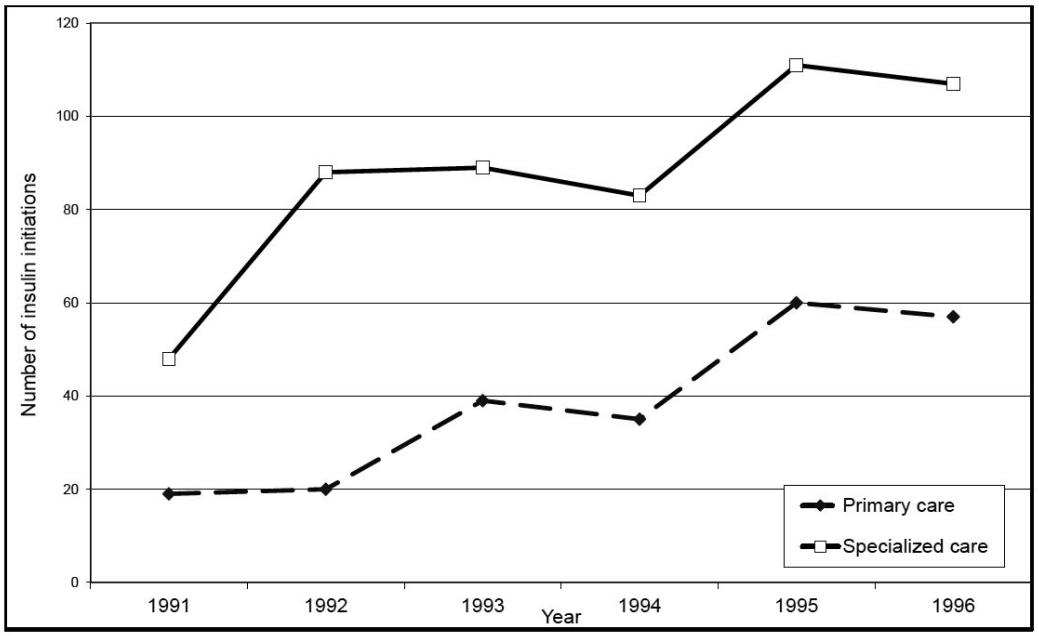

Figure 5. Number of yearly insulin initiations.

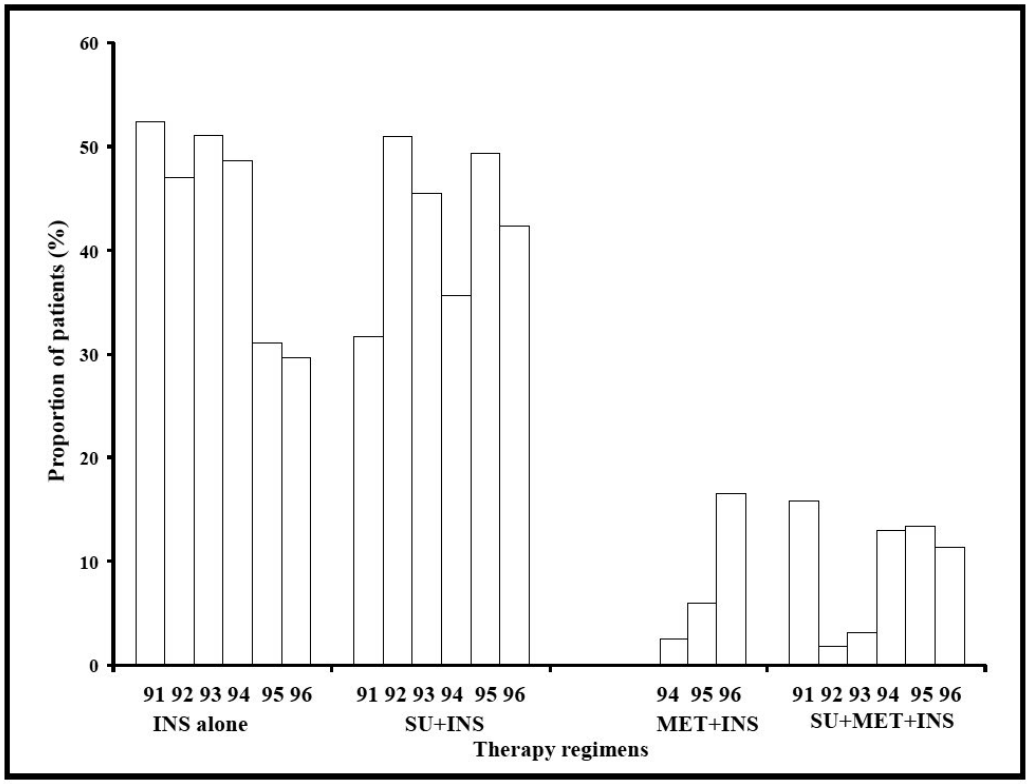

Figure 6. Starting insulin - therapy regimens (years). INS=insulin, SU=sulfonylurea, MET=metformin.

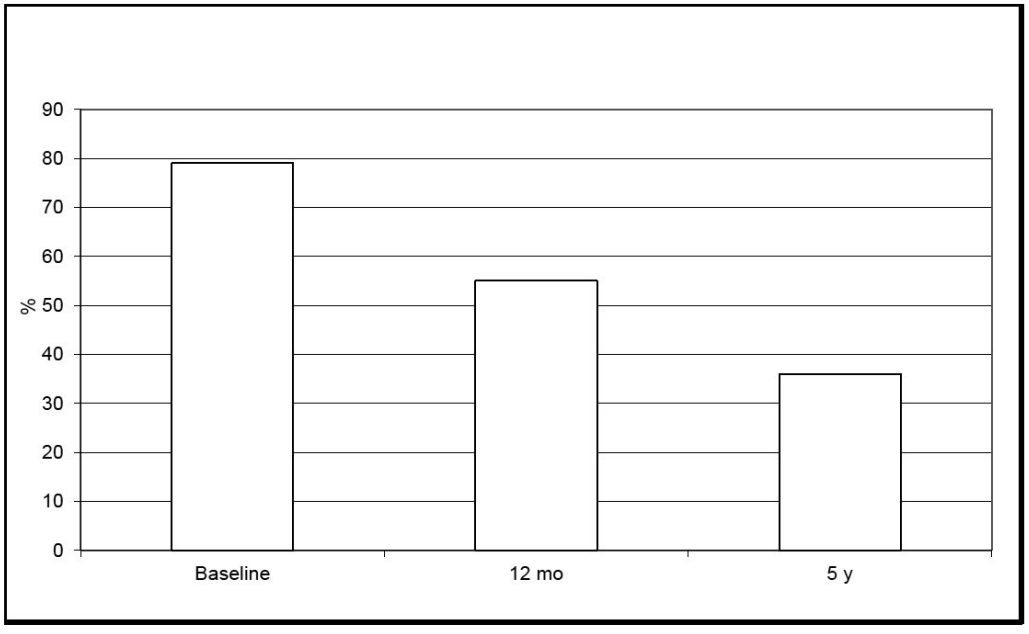

Figure 7. Percentage of patients on combination therapy. mo=months, y=years.

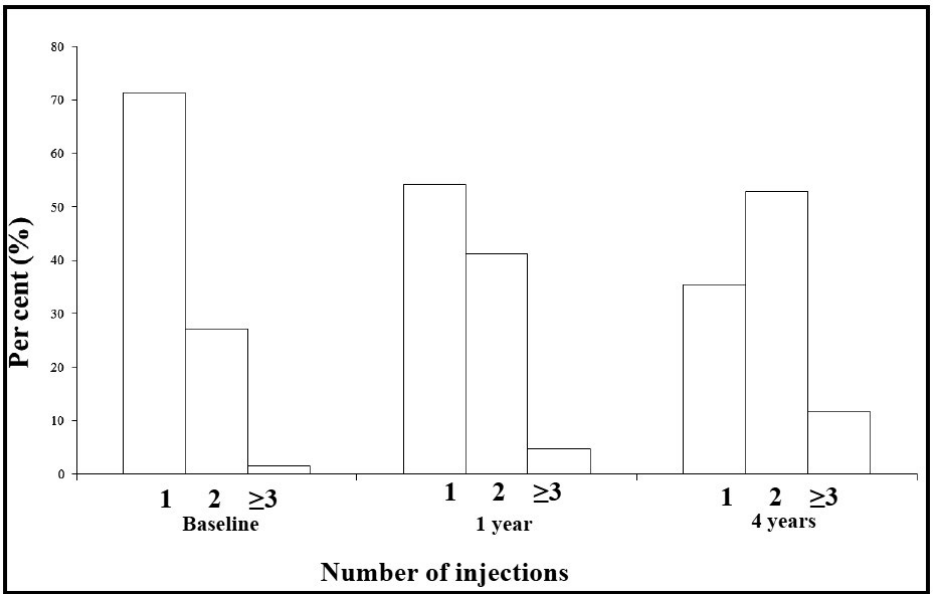

Figure 8. Number of insulin injections.

The daily insulin doses were clearly smaller (average 25 IU) among patients who also used a sulfonylurea than among those who also took metformin but no sulfonylurea (average 38 IU). The insulin dose was clearly highest among those who had insulin monotherapy (average 47 units, Figure 9.).

The variation in the amount of insulin needed by individual patients was very large. The smallest initial doses were 2 – 8 IU/day, the largest final doses 150 – 172 IU/day. The desired reduction in HbA1c, i.e., the target of starting insulin therapy, was attained. The average decline was 2.0 per cent points. In contrast to other studies (UK Prospective Diabetes Study Group, UKPDS 16 1998), the target HbA1c-value was also maintained: at 4 years there was still a mean reduction of almost 2.0% compared to baseline (Figure 10.). The per cent point reductions at one year and four years were highly significant ($p < 0.001$). The HbA1c-value was not significantly different between patients who took insulin only and patients who took combination therapy with sulfonylureas. Since metformin become popular only later, there was not enough data for comparing insulin + metformin treated patients with the other patients.

The results were similar by age group and there was no tendency toward a smaller reduction in HbA1c even in the oldest patient group (Figure 11.).

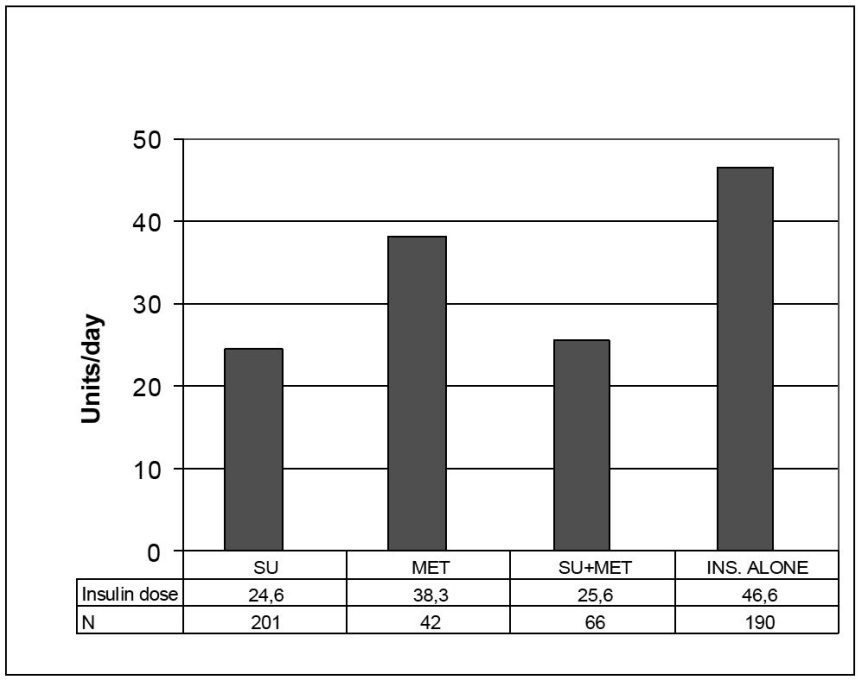

Figure 9. Insulin dose with different therapy regimens at one year from insulin initiation. SU=sulfonylurea, MET=metformin, INS=insulin.

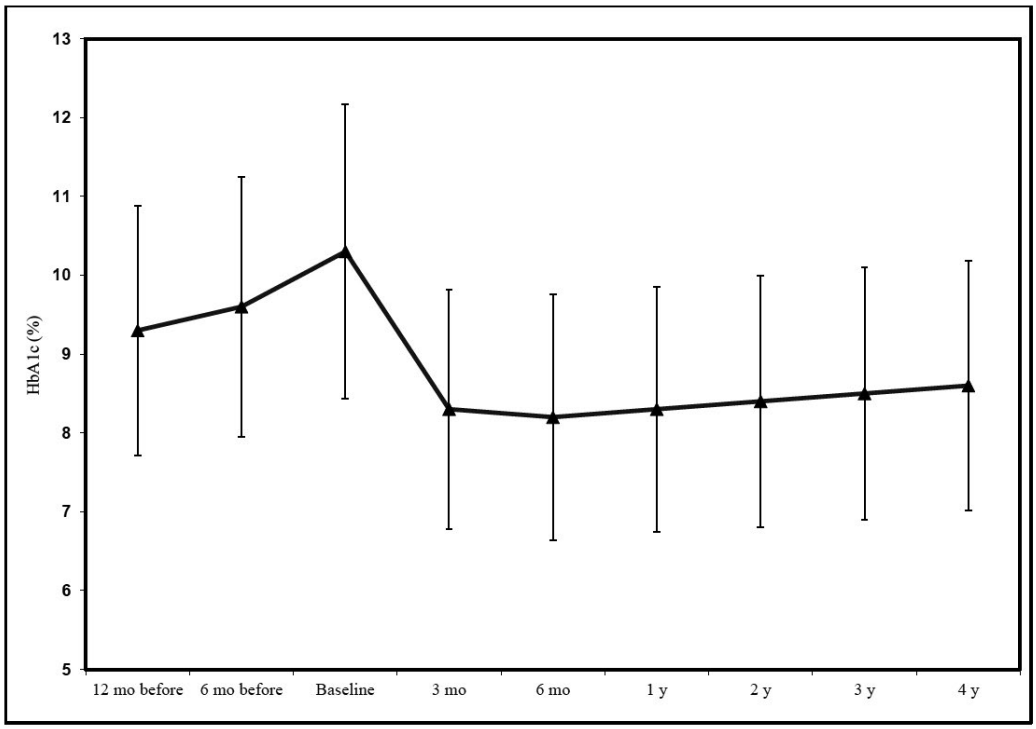

Figure 10. Mean (± SD) HbA1c of all patients before and after insulin initiation. mo=months, y=years.

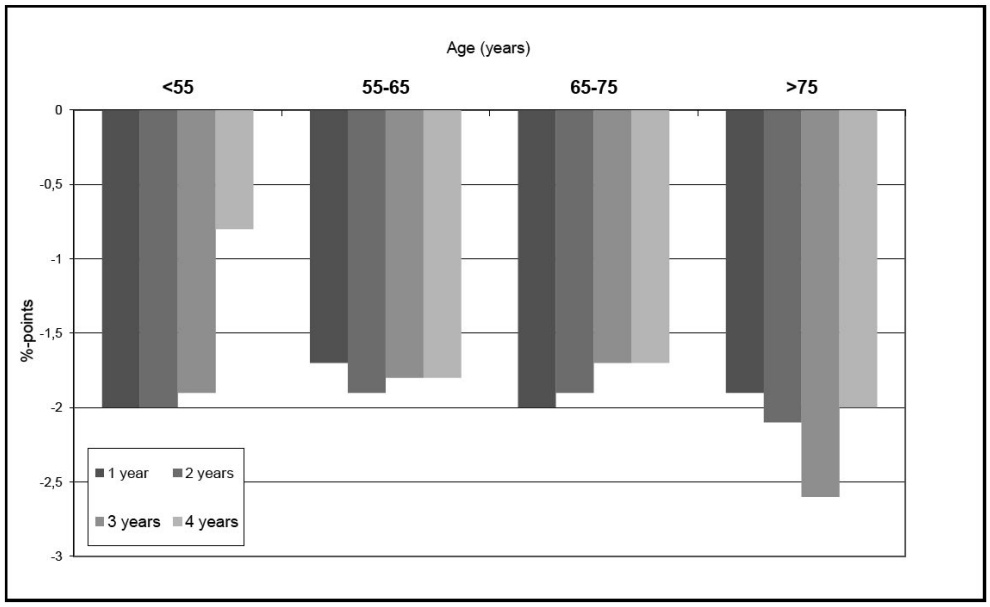

Figure 11. Mean HbA1c decrease by age groups.

Weight increased in all patient groups. After 12 months of insulin use, the mean weight had increased with 3.7 kg. In 4 years the increase was 5.6 kg (all patients) (Figure 12.). In the group treated from the beginning with insulin alone, weight gain was greatest, 6.8 kg in 4 years (Table 6.). All patients did not have a recorded weight measurement at the baseline, and their weight change could not be evaluated.

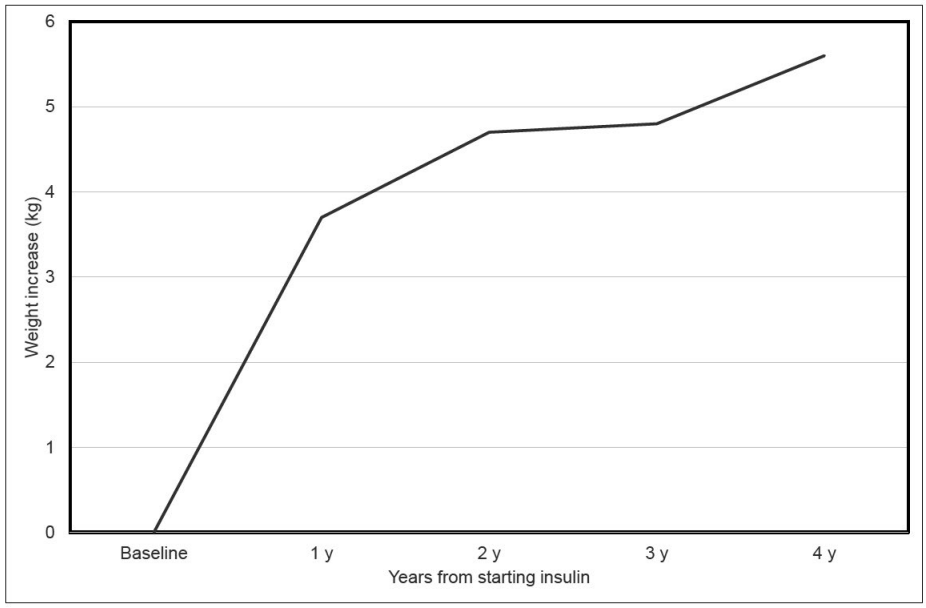

Figure 12. Mean weight change of all patients

When the most obese patients (BMI > 34 kg/m², n=64) were compared to moderately obese (BMI 25 – 28 kg/m², n=125), there was a difference in the glycosylated hemoglobin decline achieved. The most obese group had a decline of 1.5% at one year, while the decline among the moderately obese was 2.4%.

When patients were divided into two groups according to their initial C-peptide value, a lower C-peptide (< 1.0 nmol/l) was associated with a slightly greater HbA1c decrease at 12 months (-2.0%, vs. -1.7%) (Figure 13.). This difference faded with time.

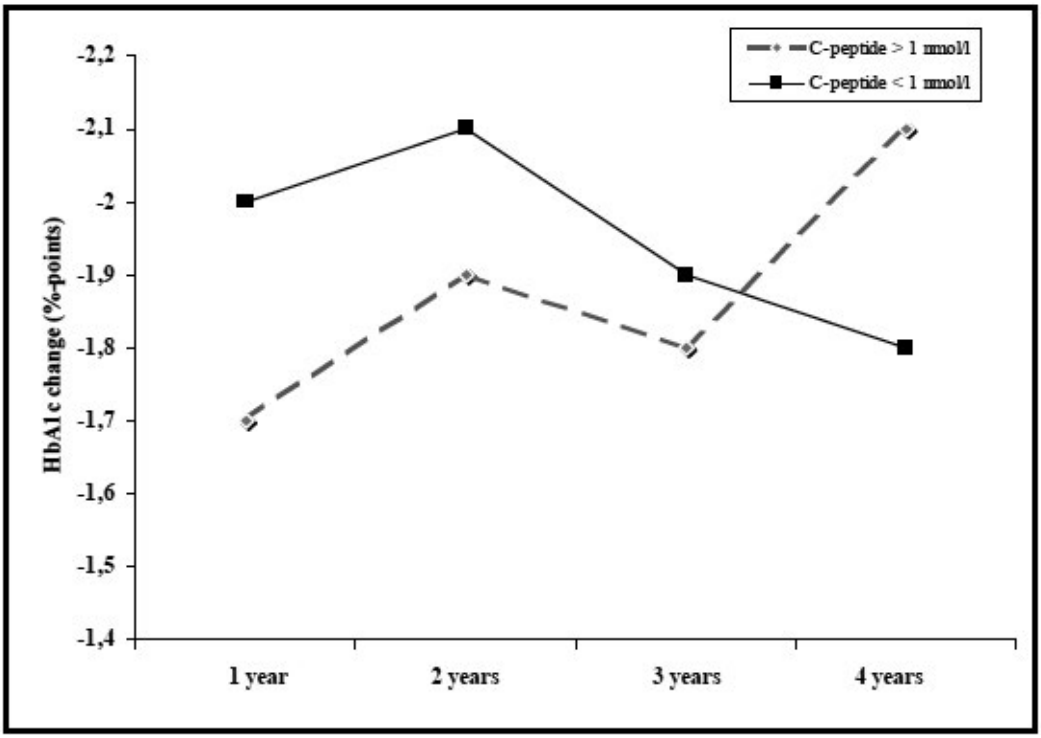

Figure 13. HbA1c values in groups formed according to baseline C-peptide.

There was a difference between the study sites. In specialized care, the diabetic patients had a significantly higher HbA1c at baseline ($p < 0.001$), compared with the patients in primary care. The HbA1c-reduction after insulin initiation was significantly greater in specialized care at one year ($p < 0.01$) and this difference was still significant ($p < 0.01$) at 3 years (Figure 14.).

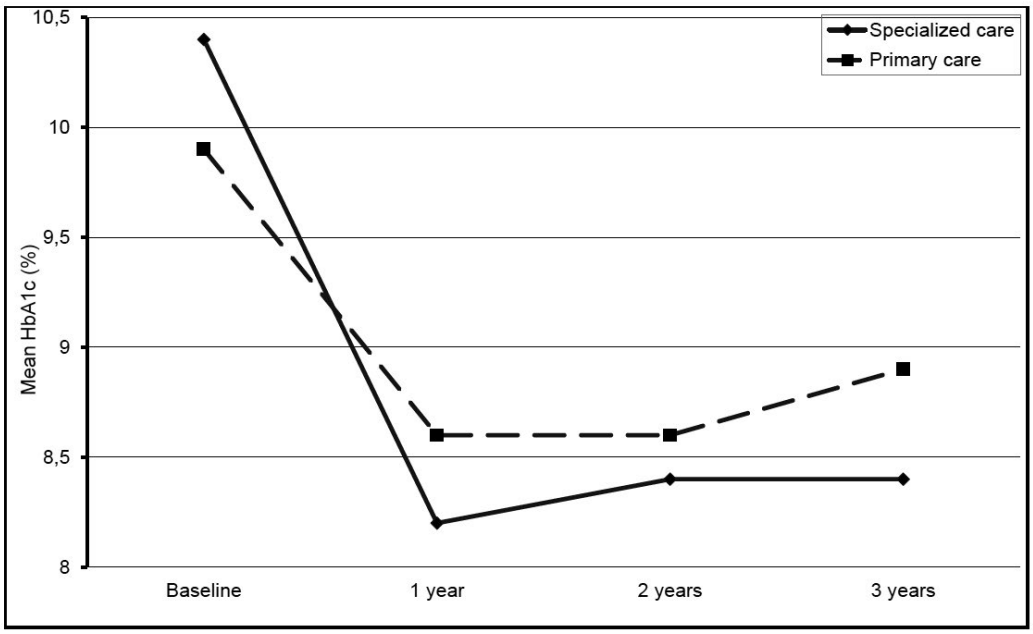

Figure 14. Decline of HbA1c after insulin initiation in specialized care and primary care.

Table 6. Patient data by patient groups with unchanged therapy regimen (Table 2 Study I).

Regimen	INS alone					SU+INS					BI+INS		SU+BI+INS		
Year	0	1	2	3	4	0	1	2	3	4	0	1***	0	1	2***
N	385	197	161	124	91	360	175	123	89	50	53	26	85	41	26
N with measured HbA_{1C}	229	120	93	74	56	241	86	65	52	30	42	20	55	20	18
Mean Hba_{1C} (%)	10,6	8,2	8,4	8,4	8,7	10,2	8,4	8,6	8,7	8,6	10,0	8,2	9,8	8,2	8,9
Mean fasting glucose (mmol/l)	14,7	10,3	10,7	11,0	10,6	14,4	10,4	10,2	10,4	10,2	14,6	9,5	14,6	10,8	10,8
Mean HbA_{1C} reduction (%)		-2,3*	-2,3*	-2,2*	-1,8*		-1,7*	-1,9*	-1,7*	-2,1*		-2,2*		-1,8*	-1,4*
Mean fasting glucose reduction (mmol/l)		-4,6*	-5,1*	-7,7*	-4,2*		-4,1*	-4,9*	-4,7*	-5,4*		-5,5*		-3,9*	-4,2
Mean weight change (kg)		3,7*	6,4*	6,0*	7,6*		1,5*	3,4*	2,7*	3,1*		1,2		1,0*	0,4
Mean insulin dose (IU/day)	38,8**	39,9	41,9	43,4	48,0	17,6**	25,5	27,8	28,4	28,3	22,7**	37,5	13,9**	23,7	24,9

*) $p<0.05$ at least
**) Insulin dose 2 weeks from initiation or at discharge from hospital
***) patient data in BI+INS and SU+BI+INS is not given from later years due to too small number of cases (<10)
SU = sulfonylurea, BI = biguande, INS = insulin

Study II

Altogether 52 patients were randomized (35 male and 17 female). 45 were treated at hospital outpatient clinics and 7 at municipal health centers. The mean BMI was 28.5 kg/m². The range of the fasting plasma glucose was 6.8 – 20.2 mmol/l, mean 12.5 mmol/l. The range of the baseline HbA1c was 7.6 – 11.3%, mean 9.9% (Table 7.).

When insulin was instituted, the mean decrease of HbA1c by 12 months was 1.4 percentage points (Table 7.). Insulin treatment was associated with weight increase, on average over 4 kg and the average BMI increased from 28.5 to 30.1 kg/m². All these changes were statistically significant. There was a significant increase in HDL-cholesterol and an almost significant decrease in triglyceride concentration. Serum total and LDL-cholesterol did not change (Table 7.).

The decline of the mean HbA1c value was significant for all three insulin regimens but smallest for insulin and glipizide (Table 8., Figure 15.).

The patients gained more weight when treated with insulin only (6.3 kg on average) than with insulin and metformin (3.4 kg) or insulin and glipizide (4.7 kg) (Figure 16.). The insulin only group required the highest insulin dose, on average 71 IU/day. The mean insulin dose was approximately half of that (38 IU/day) in the insulin + glipizide group and 33 IU/day in the insulin + metformin group (Table 8.). The dose range of insulin was from 10 IU/day (insulin + metformin) to 160 IU/day (insulin only).

When the patients were divided into two groups according to the hyperglycemia type, the majority (30/52; 58%) had fasting hyperglycemia (FPG/HbA1c ≥ 1.3 mmol/l/%). They formed group A. The group B patients (22/52; 42%) had postprandial hyperglycemia (FPG/HbA1c < 1.3 mmol/l/%) (Table 9.). The fasting plasma glucose declined more in group A. There was no significant difference between the groups regarding the HbA1c-value. When the different therapy regimens were compared, insulin monotherapy tended to be more effective in reducing the HbA1c in the postprandial hyperglycemia group (-2.7 percentage points) than in the fasting hyperglycemia group (- 1.2 percentage points (Table 9.). There was no difference in weight gain between the hyperglycemia types.

Regarding the **initial C-peptide value**, the fasting plasma glucose decline was smaller in the high-C-peptide group, i.e., in the group whose C-peptide at baseline was >1.0 nmol/l. The HbA1c declined significantly in both the high and low C-peptide groups, with the exception of those in the high C-peptide group who were treated with insulin and glipizide and those in the low C-peptide who were treated with insulin alone. There was a decline in HbA1c in these groups but it was non-significant (0.8 and 0.9 per cent points, respectively) (Table 10.).

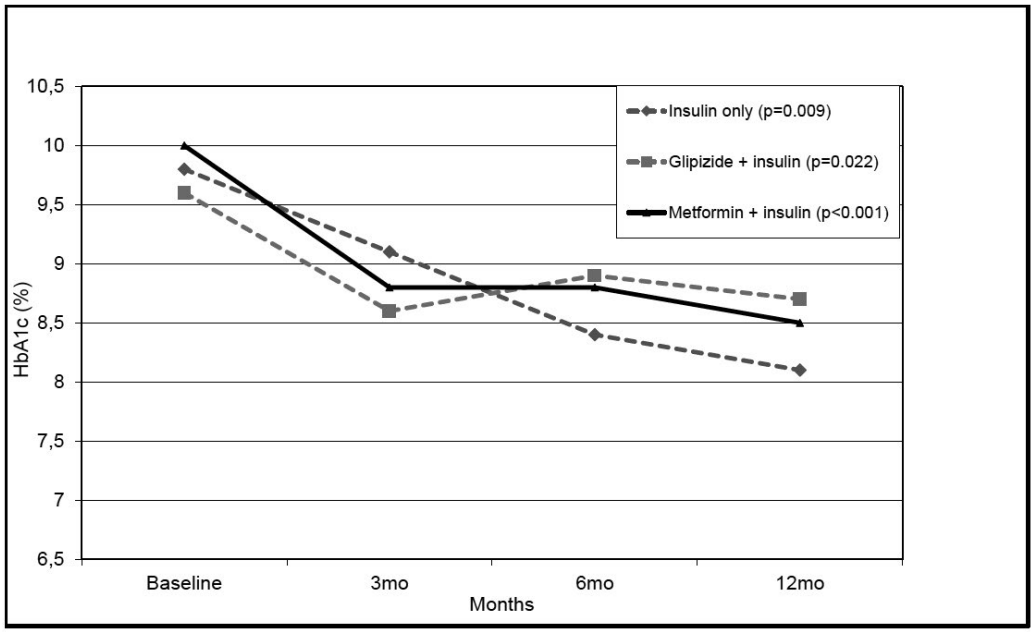

Figure 15. Decline of HbA1c by therapy regimens (p=0.142 between groups).

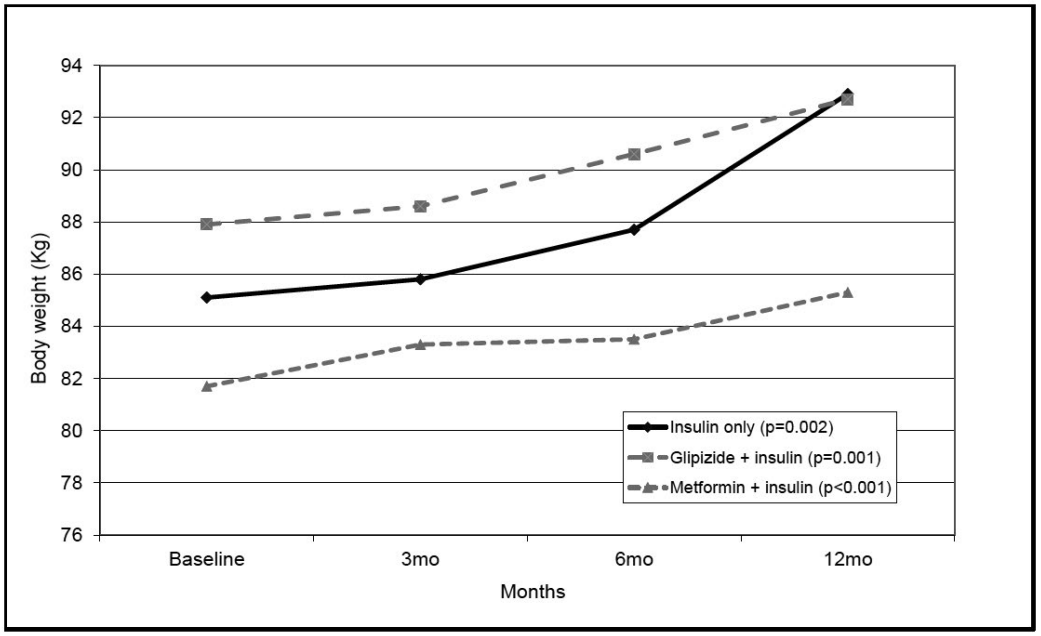

Figure 16. Weight increase by therapy regimens (p=0.468 between groups).

Table 7. Body weight, glucose control, insulin dose and serum lipid values of the whole study population (n=52) (Table 1 Study II).

	Baseline	3 months	6 months	9 months	12 months	Change[1]	CI
Body weight (kg)	84,2	85,3	86,5	86,0	89,1	4,4	3.17,5.59
BMI (kg/m^2)	28,5	28,9	29,3	29,3	30,1	1,5	1.09,1.89
Fasting plasma glucose (mmol/l)	12,5	9,2	9,1	8,8	8,7	-3,8	-5.04,-2.54
HbA1c (%)	9,9	8,8	8,8	8,7	8,5	-1,4	-1.77,-0.98
Insulin dose (IU)	25,1	32,5	37,1	37,9	42,0	16,8	10.87,22.70
Serum cholesterol (mmol/l)	5,5				5,6	0,1	-0.13,0.34
Serum HDL-cholesterol (mmol/l)	1,0				1,2	0,1	0.05,0.20
Serum triglycerides (mmol/l)	2,3				2,1	-0,3	-0.33,-0.01
Serum LDL-cholesterol (mmol/l)	3,5				3,6	0,1	-0.16,0.30

[1]) Baseline vs. 12 months. Values are given as means and 95 % CI.

Table 8. Glucose control, body weight and insulin dose in the three treatment groups (Table 2 Study II).

	Fasting plasma glucose (mmol/l)						HbA1c (%)						Weight (kg)						Insulin dose (U/day)				
Regimen	N	Base-line	3 mo	6 mo	12 mo	Chg	CI	Base-line	3 mo	6 mo	12 mo	Chg	CI	Base-line	3 mo	6 mo	12 mo	Chg	CI	Base-line	3 mo	6 mo	12 mo	Range
Insulin only	11,0	13,3	10,5	8,5	10,2	-4,0	-8.1,-0.1	9,8	9,1	8,4	8,1	-1,8	-3.1,-0.6	85,1	85,8	87,7	92,9	6,3	2.9,9.7	42,7	56,0	63,5	71,1	30-160
Glipizide + insulin	15,0	12,3	9,5	10,0	9,4	-3,1	-5.8,-0.3	9,6	8,6	8,8	8,7	-1,0	-1.8,-0.2	87,9	88,6	90,6	92,7	4,7	2.4,7.0	18,1	25,9	31,3	37,9	18-82
Metformin + insulin	26,0	12,3	8,4	8,2	7,6	-4,2	-5.7,-2.7	10,0	8,8	8,9	8,5	-1,3	-1.9,-1.0	81,7	83,3	83,5	85,3	3,4	1.7,5.1	28,2	26,2	29,3	33,1	10-103

mo=months, chg=change between baseline and 12 months, CI= 95 % confidence interval.

Table 9. Glucose control, body weight and C-peptide by type of hyperglycemia (Table 3 Study II).

		Fasting plasma glucose (mmol/l)				HbA1c (%)				Body weight (kg)				Baseline C-peptide (nmol/l)	Insulin dose (U/day)		
	n	Base-line	12 mo	Chg	CI	Base-line	12 mo	Chg	CI	Base-line	12 mo	Chg	CI	CI	12 mo	CI	Range
A. (Fasting hyperglycemia)																	
Insulin only	6	15,4	10,5	-4,9	-10.6,0.8	9,7	8,5	-1,2	-2.9,0.4	89,6	95,9	6,3	0.7,11.9	1,1,2.0	58,5	41.0,75.1	40-82
Glipizide + insulin	11	13,7	8,9	-4,8	-7.7,-1.8	9,4	8,7	-0,8	-1.7,0.2	88,9	93,6	4,7	2.1,7.2	1,1,2.0	38,6	24.8,52.5	18-82
Metformin + insulin	13	15	8,4	-6,5	-8.5,-4.6	10.1	8,6	-1,5	-2.0,-1.0	86,2	90,1	4	1.4,6.6	0.9,1.4	37,7	25.6,49.8	14-82
All patients	30	14,6	9,1	-5,5	-7.1,-3,9	9.8	8,6	-1,2	-1.0,-0.8	87,9	92,6	4,6	3.0,6.3	1,2,1.5	42,2	34.5,49.9	14-82
B. (Postprandial hyperglycemia)																	
Insulin only	5	10,9	9,4	-1,4	-9.0,6.2	9,9	7,5	-2,7	-5.6,0.2	79,7	88,4	6,3	-0.5,13.0	0.8,2.4	90	-10.3,190.3	30-160
Glipizide + insulin	4	9,3	10,5	1,2	-4.5,6.9	10,2	8,7	-1,5	-3.8,0.8	85,2	90,1	4,9	-4.2,13.9	0.5,1.3	36	15.4,56.6	22-48
Metformin + insulin	13	9,5	6,8	-2,3	-4.0,-1.1	9,7	8,3	-1,3	-4.0,-1.1	77,2	79,7	2,4	0.2,4.7	0.9,1.5	28,5	14.0,42.9	10-103
All patients	22	9,5	8	-1,3	-3.0,-0.7	9,9	8,2	-1,6	-3.0,-0.7	79,9	83,8	3,9	1.9,5.9	1.0,1.4	41,6	23.7,59.6	10-160

A= fasting plasma glucose/HbA1c ≥ 1.3 B = fasting plasma glucose/HbA1c < 1.3, mo = months, Change (Chg) = Baseline vs. 12 months, CI = 95 % confidence interval

Table 10. Subjects stratified by treatment-specific* baseline C-peptide levels in the three insulin treatment groups (Table 4 Study II).

		Fasting glucose (mmol/l)				HbA1c (%)				Body weight (kg)			
	n	Base-line	12 mo	Chg	CI	Base-line	12 mo	Chg	CI	Base-line	12 mo	Chg	CI
Low C-peptide													
Insulin only	5	13,5	11,2	-3,3	-10.9,4.4	9,1	8,5	-0,9	-2.6,0.9	82,9	91,6	5,9	-0.1,11.9
Glipizide + insulin	9	12,9	8,6	-3,7	-7.7,0.4	9,9	8,4	-1,5	-2.3,-0.8	83,0	87,8	5,4	1.4,9.4
Metformin + insulin	17	12,4	7,9	-4,1	-5.9,-2.4	9,9	8,6	-1,4	-1.9,-0.8	81,6	85,0	3,4	1.3,5.4
All patients	31	12,6	8,3	-4,5	-5.4,-2.3	9,8	8,5	-1,3	-1.7,-0.9	82,1	86,4	3,9	2.7,6.0
High C-peptide													
Insulin only	5	13,2	9,9	-4,7	-13.5,2.0	10,2	7,0	-2,8	-4.8,-0.8	86,4	93,5	6,7	0.4,13.0
Glipizide + insulin	6	11,7	10,4	-1,9	-6.9,3.0	9,4	9,0	-0,8	-1.8,1.7	93,6	98,3	3,7	2.1,5.3
Metformin + insulin	7	12,5	7,1	-4,8	-7.6,-1.9	10,3	8,1	-1,7	-2.9,-0.5	81,9	86,5	3,5	-0.3,7.3
All patients	18	12,3	9,2	-3,1	-6.1,-1.3	9,9	8,3	-1,4	-2.4,-0.5	87,3	93,1	5,2	2.6,6.4

*Stratification by median value: insulin only; low C-peptide < 1.8 nmol/l, glipizide+insulin and metformin+insulin, low C-peptide < 1.3 nmol/l. The number of patients may vary slightly at different time points. mo = months. Change (Chg) = baseline vs. 12 months. CI = 95 % confidence interval.

Study III

Patients were divided in groups based on the hyperglycemia type and insulin preparation (NPH or glargine) (Table 11.). Fasting plasma glucose values were, by definition, higher in the fasting hyperglycemia group than in the postprandial hyperglycemia group, but the baseline HbA1c-values were not significantly different. Also the metformin doses were similar, as was the percentage of previous sulfonylurea users.

There were, however, some differences at baseline between the groups: patients with fasting type hyperglycemia had a significantly higher BMI and significantly higher plasma triglyceride, hsCRP and ALT concentrations and hypertension tended to be more prevalent (p=0.063).

Among the patients using glargine the reduction of HbA1c was significantly greater (p=0.034) in the postprandial hyperglycemia group than in the fasting hyperglycemia group. This difference disappeared, when the groups were adjusted for baseline HbA1c (p=0.489) and baseline BMI (p=0.493). When the same adjustments were applied in the two fasting hyperglycemia groups, there was a tendency toward a greater HbA1c decline in those using NPH than in those using insulin glargine (p=0.075) (Figure 17.).

When the groups of fasting hyperglycemia using NPH insulin and postprandial hyperglycemia using glargine were combined and compared with the two other groups (fasting hyperglycemia using glargine and postprandial hyperglycemia using NPH), the former combined group had a significantly greater decline of HbA1c (p=0.046), also after adjustment for baseline HbA1c (p=0.052). However, this statistical significance disappeared after further adjustment for baseline BMI (p=0.813).

The patients in the fasting hyperglycemia group were more obese than the patients in the postprandial hyperglycemia group; the BMI difference was 2.1 kg/m² (p=0.044). The patients in the fasting hyperglycemia group gained also more weight during insulin treatment; the weight gained was, on average, 2.0 kg greater compared to the postprandial hyperglycemia group (p=0.020). After adjustment for baseline BMI, the difference was still significant (p=0.035) (Figure 18.). There was no difference in weight gain between glargine and NPH users.

The fasting plasma glucose decreased more in the fasting hyperglycemia than in the postprandial hyperglycemia group (p<0.001). When glargine and NPH were compared, there was no difference (p=0.667) in either of the hyperglycemia type groups.

The final insulin doses differed significantly (p<0.001) between the hyperglycemia types. Patients with fasting hyperglycemia needed more insulin to achieve the good metabolic control (0.77 IU/kg versus 0.57 IU/kg, p<0.001) (Table 12.).

NHP insulin use was associated with more hypoglycemic events in both the fasting hyperglycemia and the postprandial hyperglycemia groups during the first three months of the study compared to insulin glargine. After three months the difference

disappeared. Postprandial hyperglycemia had an initial tendency to associate with more frequent hypoglycemias than fasting hyperglycemia (p=0.055), independent of insulin preparation. This tendency disappeared with time.

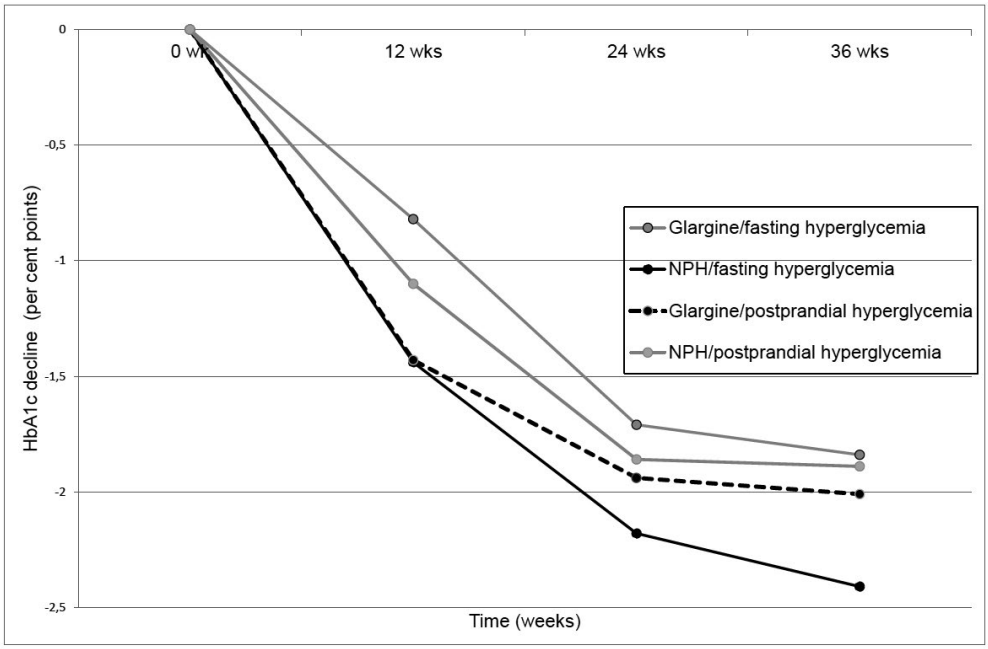

Figure 17. HbA1c decline with various therapy regimens.

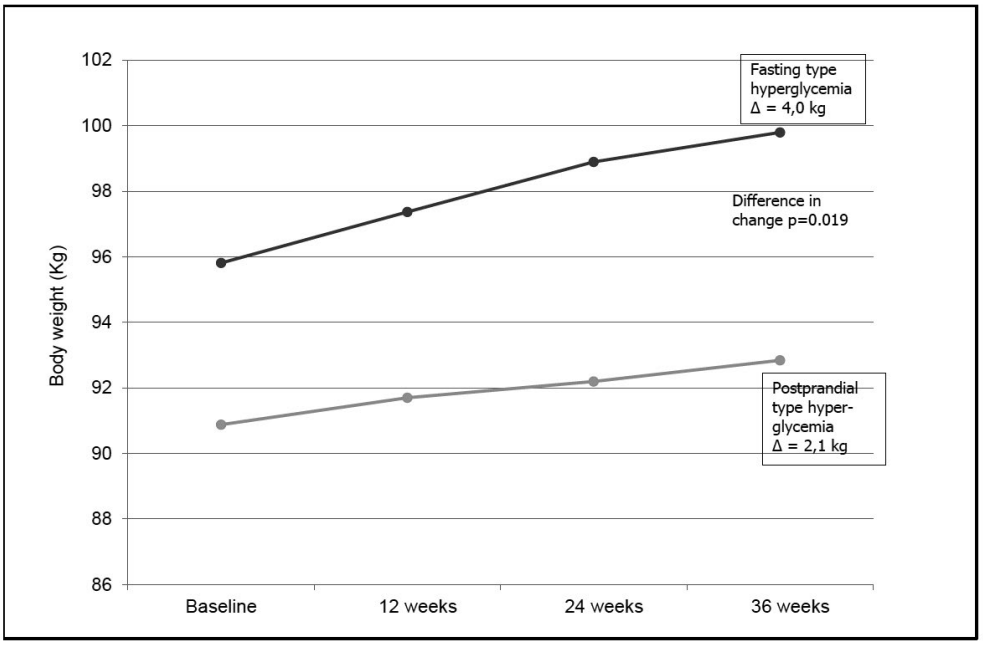

Figure 18. Hyperglycemia type and body weight.

Table 11. Baseline data stratified by insulin and hyperglycemia type (Table 1 Study III).

	Fasting type hyperglycemia						Postprandial type hyperglycemia						
	Glargine (n=35)		NPH (n=22)		Glargine+NPH (n=57)		Glargine (n=25)		NPH (n=27)		Glargine+NPH (n=52)		*p* value*
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Sex (%, M/F)	54/46		64/36		58/42		76/24		67/33		71/29		n.s.
Age (years)	55,9	8,7	57,0	7,7	58,3	8,3	56,6	10,6	57,9	9,2	57,3	9,8	n.s.
BMI (kg/m^2)	32,1	4,7	33,5	6,3	32,7	5,4	30,1	5,8	30,7	4,2	30,6	5,0	0,044
Fasting plasma glucose (mmol/l)	13,8	2,4	14,1	1,8	13,9	2,2	10,6	1,7	10,6	1,6	10,6	1,7	<0,001
HbA1c (%)	9,0	1,2	9,4	1,0	9,1	1,1	9,2	1,0	9,2	1,3	9,2	1,0	n.s.
fP-Gluc/HbA1c (mmol/l/%)	1,6	0,3	1,5	0,2	1,5	0,2	1,2	0,1	1,2	0,1	1,2	0,1	<0,001
Metformin dose (g)	2,3	0,5	2,2	0,4	2,2	0,4	2,3	0,4	2,1	0,3	2,2	0,4	n.s.
Sulfonylurea users (%)	77,1		86,4		80,7		80,8		85,2		82,7		n.s.

*) *p* values show the significance of differences between combined groups (Glargine + NPH) in fasting and postprandial hyperglycemia

Table 12. Body weight, glucose control and insulin dose during the trial (Table 2 Study III).

	Fasting type hyperglycemia						Postprandial type hyperglycemia						p value*
	Glargine (n=35)		NPH (n=22)		Glargine+NPH (n=57)		Glargine (n=25)		NPH (n=27)		Glargine+NPH (n=52)		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Body weight (kg)													
0 wk	94,0	18,1	98,6	22,2	95,8	19,7	90,8	19,5	90,9	13,6	90,9	15,9	n.s.
12 wks	95,6	18,5	100,2	22,2	97,4	19,9	91,2	19,5	92,2	14,4	92,7	16,4	n.s.
24 wks	96,7	18,5	102,3	24,1	98,9	20,8	91,8	20,1	92,6	15,1	92,2	16,9	0,069
36 wks	97,5	19,3	103,5	24,4	99,8	21,4	92,3	18,8	93,3	15,1	92,8	16,8	0,064
Δ 0 vs 36 wks	3,4	4,9	4,9	5,0	4,0	4,9	1,5	3,4	2,4	4,3	2,0	3,9	0,020
Fasting blood glucose (mmol/l)													
0 wk	13,8	2,4	14,1	1,8	13,9	2,2	10,7	1,8	10,6	1,5	10,6	1,7	<0,001
12 wks	6,5	1,4	7,1	2,1	6,7	1,7	6,3	1,6	6,6	2,0	6,4	1,8	n.s.
24 wks	6,2	1,7	6,7	2,2	6,4	1,9	6,6	1,5	6	1,3	6,3	1,4	n.s.
36 wks	6,4	1,6	5,9	1,6	6,2	1,6	6,4	2,6	5,9	1,6	6,2	2,2	n.s.
Δ 0 vs 36 wks	-7,4	2,9	-8,2	2,2	-7,7	2,6	-4,2	2,8	-4,7	2,5	-4,5	2,7	<0,001
HbA1c (%)													
0 wk	9,0	1,2	9,4	1,0	9,1	1,1	9,4	1,1	9,2	1,1	9,2	1,0	n.s.
12 wks	8,1	1,2	7,9	1,1	8,0	1,1	7,8	1	8,2	1,0	7,9	0,9	n.s.
24 wks	7,3	1,0	7,2	0,9	7,2	1,0	7,3	1	7,4	0,8	7,3	0,9	n.s.
36 wks	7,2	0,9	6,9	0,8	7,1	0,9	7,1	1	7,3	1,1	7,2	1,0	n.s.
Δ 0 vs 36 wks	-1,8	1,1	-2,4	0,7	-2,1	1,0	-2,1	1,3	-1,9	1,3	-2,0	1,3	n.s.
Insulin dose (U/kg)													
36 wks	0,77	0,40	0,78	0,26	0,78	0,36	0,56	0,29	0,58	0,30	0,57	0.25	0,001
Hypoglycemic events per patient													
0-12 wks	0,6		1,4		1,0		1,2		2,6		2,0		0,055
13-24 wks	0,9		1,4		1,1		1,4		2,1		1,8		0,100
25-36 wks	1,2		1,8		1,5		2,2		1,7		1,9		n.s.
0-36 wks	2,8		4,6		3,5		4,6		6,3		5,7		0,061

*) p values show the significance of differences between combined groups (Glargine+NPH) in fasting and postprandial hyperglycemia types

6 DISCUSSION

6.1 Methodological considerations, strengths and limitations of the study

Study I was a retrospective and descriptive study that examined insulin initiation of unselected diabetic patients in 1991 - 1997. A strength of the study is that practically all diabetic patients in Southwestern Finland were identified on the basis of use of insulin injection supplies and therefore, the patient population is highly representative. A limitation was that some of these patients might have had LADA, which was then not known, and should have been excluded. At that time, national recommendations specially focused on the treatment of type 2 diabetes were available (Groop et al. 1989). Understandably, there was a considerable lack of organization in many places where patients were treated. Finding the appropriate data was not always easy, and some data could be missing only due to misplacement, since the patient records were still solely on paper. The recording practice varied between hospitals and health centers, and there was no electronic medical chart prompting the necessary data. In particular, important data was often not recorded in the patient records, since it was customary that a patient had a personal logbook where body weight, blood pressure etc. were entered, but these data were not transferred to the patient files in the health center. Thus, the body weight at the insulin initiation visit could be traced for only 62% of the patients. The height of the patient could, on the other hand, often be found recorded in x-ray referrals and similar entries. At the beginning of the study (in 1991) HbA1c was still considered expensive and was measured only irregularly. HbA1c testing clearly increased during the seven years of the study.

It was neither rational not possible to retrospectively collect data on hypoglycemic events, since minor hypoglycemias are frequent and only seldom recorded in the patient files. Severe hypoglycemias requiring assistance from medical personnel are usually recorded in the files, but this is by no means *always* the case, because severe hypoglycemic events are often treated by the patients' relatives or paramedics at the patient's home or at emergency departments and will not always be reported to the responsible clinician. Thus, retrospectively collected data on hypoglycemic events would be neither comprehensive nor feasible.

Study II was a prospective randomized trial, performed in the years 1994 - 1998. It was an investigator-initiated study with no external funding and the routines of the study were performed in connection with regular clinical visits. This might have induced reluctance of the doctors to recruit patients to the study and thus the number of randomized patients was lower than expected (the original target was 100 patients). Therefore it was appropriate to analyze the data by combining the groups using lente insulin or

NPH insulin with glipizide into one group, and the groups using lente insulin or NPH insulin with metformin into another group. A preliminary analysis of the lente and NPH groups had shown that there was no difference in the outcomes. In spite of this, the low number of patients in some subgroup analyses may have hindered identification of all differences that could have been significant had the number of patients been larger.

Study III was a post hoc analysis of data collected in a randomized, multicenter study, originally aimed to compare NPH and glargine insulin in type 2 diabetes treatment. The HbA1c specimens were analyzed in a central laboratory. The study was designed to test the hypothesis, arisen from **Study II**, that the type of hyperglycemia affects the efficacy of insulin initiation differently when using NPH insulin or insulin glargine. The number of patients recruited in the study was double the number of patients in **Study II**. When the patients were divided into two groups by the hyperglycemia type and further into two groups by the insulin used, the number of patients in the four subgroups may be regarded sufficient (22 – 35 patients per group) to detect differences between the effects of NPH and glargine insulins in patients with the two types of hyperglycemia (fasting or postprandial hyperglycemia).

6.2 How to start insulin therapy (a historical perspective)

Until the end of 1980's it was customary to start insulin therapy in type 2 diabetic patients always in hospital wards (Seppälä et al. 1989, Rönnemaa 1995). In the 1990's it became widely accepted to start insulin in open care and municipal health centers where the family physicians were responsible for the management of diabetes patients. The previous Finnish therapy recommendation (Aro and Uusitupa 1981) advised against combination therapy and the recommendations published before the study (Groop et al. 1989) still emphasized the lack of long-term experience of combining oral drugs with insulin and recommended insulin monotherapy (Gries and Alberti 1987). Due to a more active approach to treating diabetes and to the great number of diabetic patients in poor metabolic control, health centers had to take on a more active role, and this called for also insulin therapy. When general practitioners treating outpatients started insulin they probably felt safer using relatively small insulin doses and discontinuing the OHAs. Patients with more severe hyperglycemia were referred to hospitals. Glucagon-stimulated C-peptide determination was used to detect patients prone to insulin deficiency. If the C-peptide response was poor, OHAs were considered futile and therapy started with insulin only. As starting insulin within open care became more common, the percentage of patients starting with "insulin only" sank. The rise in the use of metformin was observed in **Study I**, although the combination became more widely used only by the end of the study period, after 1995. Starting metformin with insulin was boosted by well-known Finnish diabetes studies, like the FINMIS study (Yki-Järvinen et al. 1992).

The stimulus for moving into insulin therapy for individual patients came often from diabetes nurses. They have played an important role in Finnish diabetes care for decades. The professional diabetes nurse association (Diabeteshoitajat ry.) was founded in 1985 and has currently some 1,800 members. In health centers the follow-up of diabetics, especially of those with type 2 diabetes, is to a large extent entrusted to diabetes nurses. Health center physicians seldom specialize in diabetes care. There used to be, however, close cooperation between the diabetes nurses and health center doctors. In many health centers they formed a team that took care of most diabetic patients. - At the time of the study, most health centers in Finland applied a care system based on what is called **local population responsibility** (Mäkelä et al. 1995): a doctor in charge of all inhabitants of a certain area was responsible for treating all diseases of those patients. This, not surprisingly, resulted in difficulties to train physicians sufficiently in treating a manifold of diseases. Especially type 1 diabetes treatment suffered, because the patients were too few per single physician to maintain the necessary skills and experience of the physician. Type 2 diabetes patients, on the other hand, were so numerous that every physician had to update his/her skills to be able to provide diabetes care at least with oral medication and, when necessary, to refer patients for insulin initiation to colleagues with experience in insulin treatment.

The quality of diabetes care improved with time, as shown by the changes in HbA1c values over the years. (Valle et al. 1993, Valle and Tuomilehto 2004, Valle et al. 2010) Usually diabetes patients whose insulin therapy had been initiated in a hospital ward or in a hospital outpatient clinic were transferred to the ambulatory care of health centers one year after initiation of insulin treatment, if the metabolic control was stable. In those days, there was some uncertainty concerning the skills of health center physicians in managing insulin therapy. The results of this study show, however, that the metabolic control achieved after the start of insulin was maintained for at least 4 years. This is probably due to extensive education of physicians working in health centers in Finland. Nowadays starting insulin is routine in health centers.

The decline in the HbA1c value was on average around 2 percentage points. The HbA1c level achieved was 8.2%, which still exceeded the recommended target value in the 1990's which was 7.5%. The group on insulin only already from the beginning had a higher baseline HbA1c and also a greater decline, and reached at 1 year the same level as the other treatment groups.

In a Finnish study (Valle et al. 1997) the metabolic control of diabetic patients was examined. The mean HbA1c of patients that had become diabetic at an age above 40 years (presumed to be type 2 diabetic patients) was 8.0% for men and 8.6% for women. At the time the study data was collected (1993), HbA1c was not determined for all patients: among the patients who were treated with diet only the median HbA1c was 6.3% (31% measured), with OHAs 8.0% (52% had a HbA1c determination during the year), with combination therapy 9.4% (73% recorded) and insulin only 8.8% (91% had a determination). A similar study was performed during 2000 – 2001 (Valle and

Tuomilehto 2004). At that time the coverage of HbA1c measurements was better, 97% of OHA-treated, 99.7% of combination therapy patients and 99% of those using insulin only had HbA1c taken at least once a year. Patients on diet therapy had a mean HbA1c of 6.4%, on OHAs 7.4%, on OHAs and insulin 8.4% and on insulin only 8.3%. In a later survey in 2010, the mean metabolic control improved, and the corresponding figures were 7.7% for patients on combination therapy and 7.8% for insulin only users (Valle et al. 2010).

Table 13. Metabolic control of type 2 diabetics in Finland in various years (mean HbA1c, %) (OHA=Oral Hypoglycemic Agent).

Year(s)	Diet	OHAs	Combination OHAs+Insulin	Insulin only	Men	Women	All
1993	6.3	8.0	9.4	8.8	8.0	8.6	8.4
2000 - 2001	6.4	7.4	8.4	8.3	7.6	7.7	7.6
2009 - 2010	6.1	6.4	7.7	7.8	6.7	6.6	6.7

In Imatra, a Finnish town with 31 549 inhabitants in 1999, a similar study as **Study I** was carried out (Miettinen et al. 2001). Type 2 diabetics were treated in the health center of Imatra by teams formed by their responsible health center doctor and a nurse who gave the diabetes education. Type 1 diabetics were treated at hospital outpatient clinics by specialists, but the care of type 2 diabetics was organized according to the local population responsibility system (LPR) (Mäkelä et al. 1995). The greater number of type 2 diabetics allowed the doctors to gain more experience in diabetes treatment. The mean HbA1c of all 935 type 2 diabetic patients was 7.6%; 200 were treated on diet only (mean HbA1c 6.9%) and 735 patients had some antihyperglycemic medication (mean HbA1c 7.8%). In the decentralized system of Imatra, 58% of diabetic patients were in good metabolic control. At that time the recommendation was <7.5%, which was reached by 32% in a nationwide study at that time (Valle et al. 1997).

Arterial disease

It is known that the risk of arterial disease is threefold in the type 2 diabetes population compared to the non-diabetic population. The relative risk is higher for women than men (Juutilainen et al. 2004, 2005), i.e., diabetic women loose the protective effect of estrogen against CVD. In contrast, diabetes is associated with a higher increase in the risk for stroke for men than women (Hyvärinen 2009). A diabetic patient has an equal risk of myocardial infarction as a non-diabetic patient who has sustained a myocardial infarction previously (Haffner et al. 1998). It has been shown that patients in poor diabetic control have an increased risk of coronary events (Stratton et al. 2000). Therefore, one might suppose that intensive treatment could prevent CVD events. However, the ACCORD, ADVANCE and VADT trials, where the goal of HbA1c was set at 6%, failed to show any expected benefit and, in fact, the strict glycemic goal was

associated with even increased mortality in the ACCORD trial (Heller 2000, The ACCORD study group 2008, Duckworth et al. 2009).

In the UKPDS study (UK Prospective Diabetes Study Group UKPDS 33 1998), a decline of 1 percentage point of the HbA1c resulted in a 25% reduction of microvascular complications. This was translated into fewer cases of retinopathy needing treatment. By extrapolation, a reduction of 2 percentage points of the HbA1c-value could reduce the occurrence of microvascular complications by 50%. A 10-year follow-up study of the UKPDS study showed also a beneficial effect on myocardial infarction (- 15%) and death from any diabetes-related cause (-13%) (Holman et al. 2008). This effect was called the *legacy effect*, since it suggested that good metabolic control immediately after diabetes has been diagnosed prevents diabetic complications even if the control deteriorates somewhat in the long term.

Hypoglycemia

Hypoglycemia is an important side effect of the pharmacologic therapy of diabetes, particularly in the elderly. Unfortunately, in the retrospective study (**Study I**) it was not possible to collect data on the occurrence of hypoglycemias. In terms of achieved HbA1c values, the study showed that elderly people may well be treated with insulin, since the results were as good as in younger age groups. Health centers can provide senior citizens with help in taking injections and measuring blood glucose. Health care personnel may visit the patient several times a day, if necessary, to ascertain safe insulin therapy. At that time the therapy recommendations did not take into account the special detrimental effects hypoglycemia has on elderly people. After publication of more recent studies, like VADT, ACCORD and ADVANCE, we now know that these patients should be treated by an individual care plan that allows higher HbA1c values particularly for frail, insulin-sensitive patients (Diabetes. Current Care Guidelines 2013).

Body weight increase

The weight increase in this study was significantly greater for patients that were treated with insulin alone (on average 5.5 kg, i.e., almost 10% in 4 years) than with combinations of insulin + OHA. The weight increase with insulin + sulfonylurea combination averaged 3.1 kg, i.e., only 50% of the weight increase in insulin monotherapy. (When insulin + metformin or insulin + metformin + sulfonylurea were used, data is available only for 1 or 2 years.) The insulin-associated weight increase is due to prevention of loss of glucose calories in the urine and partially due to the anabolic effect of insulin, and seems to be dose-related (Russell-Jones and Khan 2007). The data from metformin users in this study supports the observation of a smaller weight gain with insulin + metformin than with insulin monotherapy (Yki-Järvinen et al. 1992). The conclusion is that combination therapies should be preferred, because the amount of insulin needed to reach the target HbA1c level is smaller.

The weight gain is hard to prevent. Energy restriction is the natural choice, but it is well known that it is difficult to maintain in the long run. Diabetes education needs to point out that lowering glucose with insulin does not permit excessive eating. The fear of hypoglycemia may be a reason for the patient to eat prophylactically (Carver 2006). It is, therefore, important to react if the patient's symptoms or SMBG results suggest repeated hypoglycemia (even minor) without a logical cause. Increased exercise may also prevent weight gain and has other health benefits. Exercise plays, unfortunately, only a small role in consumption of calories and usually cannot compensate for excessive eating (Klein et al. 2004). Many type 2 diabetic patients are elderly and have disabilities that prevent effective physical exercise. Some diabetes drugs contribute to weight gain, insulin the most. Sulfonylureas, as other insulin secretagogues, may also cause weight gain by the same mechanism, although the second-generation sulfonylureas maybe less so. The thiazolidinediones are also associated with weight gain due to increase in subcutaneous fat and fluid retention, especially in combination with insulin (Yki-Järvinen 2004). Metformin is the only "traditional" diabetes drug that is not associated with weight gain.

Can unwanted effects be avoided with new diabetes drugs?

New diabetes drugs not available at the time **Study I** raise therapeutic optimism. In principle, they can all be used together with insulin. The DPP-4-inhibitors are weight neutral and the GLP-1-analogues can cause marked weight reduction (Drucker and Nauck 2006, Thornberry and Gallwitz 2009). Nor do these drugs cause hypoglycemia and thus they eliminate the need to eat prophylactically to prevent hypoglycemia. Combination of GLP-1 analogs with insulin decreases the risk of hypoglycemia compared with insulin alone and the insulin doses are reduced (Balena et al. 2013). Also the SGLT2-inhibitors lower plasma glucose and reduce weight by inducing excessive urinary glucose excretion (Chao and Henry 2010). This weight reduction is not due to decreased caloric intake but an increased caloric loss in the urine. The SGLT2-inhibitors do not cause hypoglycemia, either.

There is another factor affecting the use of diabetes drugs. In Europe, every country has its own reimbursement policy. For instance, long-acting insulin analogues are not reimbursed in Germany and therefore NPH insulin plays a major role in diabetes treatment in Germany. In contrast, in Finland insulin analogues have been 100% reimbursed for type 2 diabetics for several years, and most new insulin treatments have been started with either glargine or detemir insulin since the start of the reimbursement. Reimbursement policies also affect the use of the GLP-1-analogues. They have only recently become 100% reimbursed in Finland but only for patients with severe obesity (BMI > 35 kg/m^2), a limitation mainly dictated by economic rather than medical reasons.

Role of C-peptide test in selecting diabetes treatment

The C-peptide test has been widely used when considering insulin treatment for type 2 diabetes. At the time of **Study I**, the recommendation was to perform the test either after a postprandial challenge or under stimulation with an intravenous dose of 1 mg of glucagon, 6 minutes after which a blood sample for C-peptide determination was drawn with a concurrent plasma glucose concentration of at least 7 mmol/l. However, in **Study I** the test was performed without stimulation in the fasting state. The main idea was to exclude type 1 diabetic patients that needed insulin therapy and who would not benefit from a combination with OHAs. In addition, patients with high concentrations of C-peptide in their plasma were considered more insulin resistant than patients with a low concentration (Jones and Hattersley 2013). Thus, patients with a lower value would have a better response to insulin therapy. In accordance with this, **Study I** patients in the low C-peptide group (<1.0 nmol/l) seemed to respond slightly better to insulin treatment at 12 months than patients in the high C-peptide group. This difference faded off after 12 months, most probably because insulin doses were increased to a sufficiently high level also in insulin resistant patients. A recent review (Jones and Hattersley 2013) agrees on the usefulness of C-peptide testing in detecting type 1 diabetes, but states that there is limited evidence that this test is useful for predicting therapy response in type 2 diabetes.

6.3 Prospective comparison of different therapy regimens

Study II included 52 patients who were treated with insulin only or with combination therapies of insulin + glipizide or insulin + metformin. The study was performed in 1994 – 1998. The study duration was 52 weeks to ensure that the stabilization period was reached. After insulin initiation, the stabilization took usually up to 6 months. In this study there was no algorithm for increasing the insulin dose. The dosage was adjusted at each open care visit by the treating physician according to the physician's judgment. Many published insulin initiation studies are 24 – 36 weeks long (see Tables 2 to 4 in Review of the literature), but the insulin dose is usually decided centrally or there is a clear algorithm according to which the insulin dose is raised or reduced. The situation in this study mimicked everyday clinical practice. Most physicians who carried out the study did not have long experience in insulin dose titration and the dose was usually raised carefully.

The mean HbA1c of the patients was 9.9% at baseline, i.e., glucose control was poor. In 3 months the HbA1c had declined with no less than 1.1 percentage points. There was further improvement over time, and the final average HbA1c at 12 months was the lowest, 8.5%. The fasting plasma glucose improved also at every visit and was lowest at the final visit. This suggests that reaching the final metabolic balance takes time, and that a shorter study would have given inaccurate results. An even longer study may

have been useful, as in **Study I** the decline in HbA1c continued after one year from insulin initiation and was approximately 2 per cent points in 3 years.

Insulin therapy proved to be efficient, since the HbA1c was reduced, on average, by 1.4 percentage points. The achieved mean HbA1c 8.5% was far from the recommendation in Finland, which at that time was extremely low 4.0 – 6.0%, i.e., in the range of non-diabetic subjects (Uusitupa et al. 1994) and also markedly higher than the general goal 7.0% in the present recommendations (Inzucchi et al. 2012, Diabetes. Current Care Guidelines 2013).

In all these studies (**Study I, II and III**) the main outcome measure was to decrease HbA1c. After three years of treatment, insulin alone caused decrease of HbA1c of 2.2 per cent points (**Study I**). In **Study II**, insulin monotherapy was the best of the three compared therapy regimens, generating a decline of HbA1c of 1.8 per cent points. In **Study III** there was no insulin monotherapy group. In other studies with insulin monotherapy, the HbA1c decrease has been -1.9% points (Yki-Järvinen et al. 1999) or -2.4% points (Taylor et al. 2000). The results of the substudies of this thesis were comparable with these studies.

According to this thesis combination therapy with sulfonylureas was less efficient: in **Study I** the decline was 1.7% points (at 3 years). In **Study II**, combination of insulin and glipizide resulted in a mean decline of 1.0 per cent points. In **Study III** only metformin was used in combination therapy. In the literature, a decline of 2.4 per cent points with insulin plus sulfonylurea combination was found in a single study (Wolffenbuttel et al. 1996) and in another study a decrease of 1.8 per cent points was observed (Yki-Järvinen et al. 1999). A meta-analysis from year 1992 (17 studies from years 1966 to 1991) found sulfonylurea combined with insulin to be more effective than insulin alone, but having only modest effect on HbA1c, a decline of 0.8 per cent points (Pugh et al. 1992, Stehouwer et al. 2003). The studies that were analyzed were criticized for not reaching the fasting plasma glucose normalization with aggressive insulin dose titration. This was also the case in the two first substudies of this thesis.

The use of metformin with insulin in type 2 diabetes started in Finland in the middle of the 1990´s. In **Study I**, the mean reduction of HbA1c was 2.2 per cent points after one year of metformin – insulin combination therapy. In **Study II** the corresponding change after one year was -1.5 per cent points. There was no significant difference between patients with fasting type hyperglycemia (-1.5 per cent points) or those with postprandial type hyperglycemia (-1.3 per cent points). In **Study III** the mean decline of HbA1c was 2.1 per cent points (-2.1 per cent points in fasting type hyperglycemia patients and 2.0 in postprandial type hyperglycemia patients). Thus the combination of metformin and insulin was equally effective in both hyperglycemia types. In other studies, the insulin-metformin combination caused a decline of HbA1c of 2.5 per cent points (Yki-Järvinen et al. 1999) and 1.8 per cent points (Strowig et al. 2002). The results of the thesis were comparable with them. In a meta-analysis of 26 randomized trials,

metformin caused an extra reduction of HbA1c of 0.5 per cent points when compared with insulin alone. The mean weight gain was 1 kg less and the final insulin dose 5 IU less when metformin plus insulin was used (Hemmingsen et al. 2012).

The weight gain associated with insulin therapy is dose-dependent (Rosenstock et al. 2008). In the present study, the need for insulin was almost double when insulin was used alone compared to the insulin + OHA-combination. As one may expect, the weight increase was also greater in the insulin monotherapy group. There was less weight gain with the insulin + glipizide combination, and the least with the insulin + metformin combination. Because insulin alone and both combination therapies yielded similar HbA1c-reductions, combination therapy is preferable. Metformin is the best combination OHA, as has also been shown in earlier studies (Mäkimattila et al. 1999).

6.4 Hyperglycemia type and selection of therapy

A special aim of **Study II** was to examine whether the diurnal variation in glucose levels, i.e., the hyperglycemia type affects the efficacy of insulin initiation and to examine which regimen gives the best results in patients with various hyperglycemia types. Type 2 diabetic patients can be divided into two groups, the *fasting* and the *postprandial* hyperglycemia type. Postprandial hyperglycemia reflects mainly a defect in early phase insulin secretion, typical for diabetes with a short duration, whereas fasting hyperglycemia reflects a combination of insulin resistance, deficient overall insulin secretion and inappropriate glucagon secretion (Pratley and Weyer 2001). In practice, there should be a simple way to define the hyperglycemia type. It is easier to define the type by using fasting plasma glucose and HbA1c, rather than performing postprandial plasma glucose measurements. Obtaining comparable fasting plasma glucose measurements requires less standardization than postprandial measurements, where one must keep track of the time of the measurement after the meal has been started, and also of the amount and quality of the carbohydrates of the meal. HbA1c reflects the overall diurnal glycemia including fasting, preprandial as well as postprandial glucose levels. Monnier and coworkers have shown that fasting and postprandial glucose levels contribute differently to the HbA1c level in good and poor metabolic control (Monnier et al. 2003). When the metabolic control is poor, like in **Study I**, postprandial glucose contributes by 30% and fasting glucose by 70% of the HbA1c level, whereas in good metabolic control the relative contributions of postprandial and fasting values are vice versa, i.e., 70% and 30%, respectively. If the FPG/HbA1c ratio is high, the diabetic patient has fasting hyperglycemia. A low value suggests that the patient has postprandial type hyperglycemia. In **Study II** HbA1c was equally high in fasting and postprandial hyperglycemia groups although there was a 5.1 mmol/l difference in fasting glucose. This is in contrast to the findings of Monnier et al. and suggests that postprandial values contribute greatly to HbA1c also in poor metabolic control.

Determination of the hyperglycemia type may help in the selection of the insulin initiation regimen. **Study II** showed that for patients with the postprandial type of hyperglycemia two daily insulin injections gives a greater HbA1c reduction than combination therapy of one dose of insulin at bedtime (-2.7 percentage points vs. -1.5/-1.3 percentage points). A similar effect is not seen in fasting hyperglycemia patients. Postprandial hyperglycemia patients have high blood glucose after meals, and thus it is logical to assume that they benefit from a second insulin dose in the morning, particularly since the insulin used was NPH insulin which has a duration of action clearly below 24 hours. The results of **Study II** are in accordance with previous studies suggesting that SU drugs combined with basal insulin are not sufficiently effective in lowering postprandial glucose values in the afternoon (Stehouwer et al. 2003). Patients with the fasting type of hyperglycemia have a tendency to benefit more from metformin than glipizide because metformin decreases effectively hepatic glucose output during the night by suppressing gluconeogenesis (Bailey and Turner 1996). In general, metformin improves the metabolic control as effectively as glipizide. Metformin has other advantages over the sulfonylureas: it is weight-neutral, increases insulin sensitivity (Klip and Leiter 1990) and does not cause hypoglycemia. Thus, if a patient tolerates metformin and there are no other contraindications, metformin is the drug of choice for combination with insulin in type 2 diabetes.

Patients with postprandial hyperglycemia treated with insulin alone required a considerably higher insulin dose for a similar decline in HbA1c than those with fasting hyperglycemia (90 IU vs. 59 IU), but, interestingly, they did not gain more weight in spite of the higher insulin dose (+6.3 kg vs. + 6.3 kg). Bedtime insulin and OHAs did not provide adequate control of postprandial hyperglycemia. Managing postprandial hyperglycemia is important, as shown in two major studies (Ohkubo et al. 1995, The DECODE Study Group 1999).

At the time of **Studies I** and **II** no long-acting insulin analogues were available. NPH insulin was used in these studies and is still widely used in European countries due to lower price and reimbursement policies. Because of its action profile, NPH insulin twice daily is preferable for many type 2 diabetics, particularly those with postprandial hyperglycemia. Bedtime insulin should thus not automatically be the first or only choice in selection of insulin regimen when OHAs fail.

6.5 NPH and insulin analogues: effect of hyperglycemia type on HbA1c and weight

The results of **Study II** suggest that patients with high glucose values both at fasting state and postprandially benefit more from a regimen of long-acting insulin twice daily than from a regimen of bedtime insulin combined with oral agents, metformin or SU. There were no such differences between the regimens among patients with a preponderance

of high fasting glucose values. The results led to a concept of two hyperglycemia types, fasting and postprandial (then called "overall"). There are obviously no previous studies that have taken the hyperglycemia type into account in connection with insulin initiation. **Study III** was conducted to test the hypothesis that bedtime NPH insulin, by virtue of its action profile, might be more efficient in treating patients with high morning plasma glucose than insulin glargine whereas glargine, the action profile of which is more even and its duration of action longer, would be better suited for patients with a tendency toward high plasma glucose after meals. Unadjusted analyses showed that NPH insulin was indeed better for fasting hyperglycemia and glargine insulin was better for postprandial hyperglycemia than vice versa. However, adjustment for baseline HbA1c and BMI eliminated these differences. It would be necessary to test the same hypothesis by randomizing patients to a similar study by taking into account baseline HbA1c and BMI in order to determine the true significance of the hyperglycemia type for selection of the basal insulin when initiating insulin treatment.

Weight increase is common when insulin is started. In **Study III** the group with the fasting type of hyperglycemia had a significantly higher baseline mean BMI (32.7 ± 5.4 kg/m^2) than the group with the postprandial type of hyperglycemia (30.6 ± 5.0 kg/m^2). Fasting type hyperglycemia was also associated with significantly higher weight gain (4.0 kg vs. 2.0 kg) during insulin therapy (p=0.020, after adjusting for the initial BMI p=0.035) and a higher insulin requirement (0.77 IU/kg vs. 0.57 IU/kg, p=0.001).

Fasting hyperglycemia patients exhibited more components of the metabolic syndrome: they had higher fasting plasma triglycerides (p=0.018) and tended to have higher blood pressure. The metabolic syndrome is associated with insulin resistance and low-grade inflammation (van Greevenbroek and Schalkwijk 2013). Low-grade inflammation is associated with the western lifestyle involving central obesity and intake of refined foods (Kolb and Mandrup-Poulsen 2010). Fasting hyperglycemia patients had also a significantly higher hsCRP value (p=0.010) and ALT activity (p=0.019). Higher ALT is a marker of excess liver fat and is also associated with insulin resistance, even within the reference range (Kotronen et al. 2008). Not surprising, then, that patients with fasting hyperglycemia needed much more insulin than patients with postprandial hyperglycemia to overcome their strong hepatic insulin resistance (Ryysy 2000).

According to **Study III** the determination of the hyperglycemia type of a diabetic patient is worthwhile and may be easily done by calculating the FPG/HbA1c-ratio. This ratio, if high, predicts a greater weight gain with insulin therapy compared to the situation that the ratio is low. When treating a patient with fasting hyperglycemia, this should be kept in mind. Insulin detemir, which causes less weight gain than insulin glargine or NPH insulin, may be a better choice, but this question should be addressed in a separate clinical study. The strong marketing efforts directed toward insulin analogues must not obscure NPH insulin from the field of view. It is an effective and less expensive alternative than the long-acting insulin analogues. However, biosimilar long-acting insulin analogs may change the financial aspect in near future (Heinemann 2012).

6.6 HbA1c targets

The early recommendations for a HbA1c target in type 2 diabetes in Europe were set by The European NIDDM Policy Group in 1986 (-Gries and Alberti 1987). The target was set to < mean + 2 SD of nondiabetic individuals. This was justified by the very variable reference ranges of HbA1c in European countries (IDF Bulletin 1987). A WHO recommendation in 1994 gave a target of < 110% of upper reference range (WHO 1994). The Consensus Conference of the American Diabetes Association in 1995 recommended < 7% as the target (ADA 1996).

In Finland, the first recommendation for treatment of type 2 diabetes was issued in 1989 (Groop et al. 1989). Metabolic control was considered good, if the HbA1c value was below the upper reference range value + 1 per cent unit. By the time of the next recommendation (Uusitupa et al. 1994), a more stringent goal was given: HbA1c should be within 4 – 6%.

In the light of current knowledge, one may ask whether the target in 1994 was realistic. At that time, there was only one target HbA1c for all diabetics regardless of age, weight and profession, and the reasoning was that only a normal glucose level (i.e., the same as a non-diabetic person has) can prevent diabetic complications. Later on, studies like ACCORD (The ACCORD Study Group, 2008) and ADVANCE (Heller, 2009) have shown that therapeutic efforts that bring the HbA1c close to non-diabetic levels may not be beneficial for all patients at all. In these studies, patients used typically insulin plus several OHAs. The patients that were intensively treated had more myocardial infarctions and strokes and their all-cause mortality rate was higher than in the conventionally treated group. Thus, very low HbA1c targets (in the range 4.0 – 6.0%) may not only be very difficult to reach but they may be harmful to the patients. An important cause for these undesired effects may be hypoglycemia. The most important culprits are the sulfonylureas and insulin. Most of the new diabetes drugs (DPP-4-inhibitors, GLP-analogs and SGLT2-inhibitors) cause little or no hypoglycemia. The important consequence of the findings in the ACCORD and ADVANCE studies has been a new emphasis on individually planned therapies, which has led to allowing higher HbA1c targets for elderly diabetic patients, especially those that have cardiac conditions or are frail. The use of sulfonylureas has decreased in Finland, particularly to the favor of DPP-4-inhibitors. Insulin will be needed, since many type 2 diabetics will become insulin-deficient, but institution of insulin can be postponed with new regimens, particularly the GLP-1-analogs. Using insulin in combination with these new drugs will enhance safety in achieving good metabolic control in insulin therapy (Eng et al. 2014).

6.7 Considerations for the future

Despite the ongoing surge of new medications, insulin will always be an important option for treating type 2 diabetes. Most type 2 diabetes patients become insulin-deficient in

the long run, and then insulin is obligatory. Insulin has no absolute contraindications, and it can be used by patients with comorbidities that would contraindicate other medications. Some diabetic patients have little or no response to other medications than insulin.

Insulin has some disadvantages that need to be coped with. Hypoglycemia and weight increase remain as problems, although there has been some progress, as insulin analogues cause less hypoglycemia than NPH or the lente insulins, and insulin detemir causes less weight increase than the other insulins, but these are only partial solutions. The advent of degludec insulin may cause less hypoglycemia (Aye and Atkin 2014), but there is so far no evidence on an effect on weight that would be different from that of other insulins.

The aspect of hyperglycemia type in insulin initiation needs further and thorough study. The hypothesis was set in **Study II**. The best way to confirm this hypothesis is to study a larger patient population where baseline BMI and HbA1c are taken into account in the randomization phase. The choice of antidiabetic therapy for an individual patient is also affected by its influence on weight gain – a piece of information that would be useful in advance.

As to combination therapies with insulin, combination with GLP-1 analogs seems to provide more advantages than any of the oral agents (Buse et al. 2011). GLP-1 analogs are easy to use and result in less weight gain and lower insulin doses and no increase in hypoglycemias compared with insulin alone (Balena et al. 2013). Due to reimbursement policies very expensive drugs are usually best avoided, but especially in patients with very high needs of insulin, combination with GLP-1 analogs may result in even decreased total treatment costs.

Bariatric surgery will also have a growing role in future. It has – in addition to several positive outcomes due to extensive weight loss – been shown to have an almost curative role in management of type 2 diabetes (Sjöström et al. 2004), which could be due to resolution of accumulated fat in the liver and pancreas (Camastra et al. 2007, Taylor 2013, Brethauer et al. 2013). Bariatric surgery is, however, a complex procedure. The patients suitable for this therapy must be carefully selected and they need to be followed-up for a long time. Therefore this effective treatment cannot be a solution to the great numbers of type 2 diabetics.

7 CONCLUSIONS

1 The practices of insulin initiation in Finland in the 1990's were changing from hospital-based to open care based. Previously, insulin had been started as the only hypoglycemic drug, but with the shift to open care, combination therapies with OHAs became more common. The use of the insulin + metformin combination started in the middle of 1990's.

2 Insulin initiation was successful also in open care, but the results were better when insulin was started in specialized care. Initiation in open care was probably more cautious, which led to too slow up-titration of the insulin dose.

3 In a retrospective study, initiation of insulin as monotherapy and in combination with sulfonylurea or metformin resulted in similar decline, approximately 2 per cent points, in HbA1c. In a prospective study combination of insulin with sulfonylurea was less effective compared to insulin monotherapy or a combination of insulin and metformin. The body weight increased most with insulin only. Serum HDL-cholesterol increased significantly and triglycerides tended to decrease slightly with insulin initiation, probably due to the stimulating effect of insulin on lipoprotein lipase.

4 By hyperglycemia type, NPH insulin monotherapy twice daily was the best choice for patients with the postprandial type of hyperglycemia, while patients with the fasting type of hyperglycemia benefited least from insulin and glipizide.

5 NPH insulin and the insulin analogue glargine were equally effective in reducing hyperglycemia, irrespective of the type of hyperglycemia.

6 Compared with patients characterized by the postprandial type of hyperglycemia, patients with the fasting type of hyperglycemia were more obese and gained significantly more weight after insulin initiation. Special effort should be made on the prevention of excess weight gain in this subset of patients.

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9 REFERENCES

Abdul-Ghani M, DeFronzo R. Inhibition of renal glucose reabsorption: a novel strategy for achieving glucose control in type 2 diabetes mellitus. *Endocr Pract* 2008; 14: 782-90.

ADA. Consultation statement. The Pharmacological Treatment of Hyperglycemia in NIDDM. *Diabetes Care* 1995; 18: 1510-8.

ADA. Insulin Administration. *Diabetes Care* 2004; 27: 1065–107.

ADA. Nutrition Recommendations and Interventions for Diabetes. Position Statement. *Diabetes Care 2008;* 31 (Suppl. 1): S61–S78.

ADA. Position statement. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2010; 33(Suppl. 1): S62–9.

ADA. Standards of Medical Care in Diabetes - 2010 Position Statement. *Diabetes Care* 2010; 33(Suppl. 1), S13–S61.

ADA. Standards of Medical Care in Diabetes - 2013 Position Statement. *Diabetes Care* 2013; 36(Suppl. 1), S31.

ADA. Standards of Medical Care in Diabetes - 2015 Position Statement. *Diabetes Care* 2015; 38(Suppl. 1), S49.

Adeghate E , Schattner P, Dunn E. An update on the etiology and epidemiology of diabetes mellitus. *Ann N Y Acad Sci* 2006; 1084: 1–29.

Ahmann A, Riddle M. Insulin therapy in type 2 diabetes mellitus. *Insulin Therapy*, Cefalu W, ed. USA, Marcel Dekker Publishing 2002: 108–16.

Ahrén B, Foley, J. The islet enhancer vildagliptin: mechanisms of improved glucose metabolism. *Int J Clin Pract* 2008; 62: 8–14.

Ahrén B, Landin-Olsson M, Jansson P-A, Svensson M, Holmes D, Schweizer A. Inhibition of dipeptidyl peptidase-4 reduces glycemia, sustains insulin levels, and reduces glucagon levels in type 2 diabetes. *J Clin Endocrinol Metab* 2004; 89: 2078–84.

Albers J, Pop-Busui R. Diabetic neuropathy: mechanisms , emerging treatments and subtypes. *Curr Neurol Neurosci Rep* 2014; 14: 473–5.

Alberti K, Aschner P, Assal J-P, Groop L. Guidelines for definition, diagnosis and classification pf diabetes mellitus and its complications. A report of a WHO consultation 1999; (pp. 1–60).

Ampudia-Blasco F, Rossetti P, Ascaso J. (2011). Basal plus basal-bolus approach in type 2 diabetes. *Diabetes Technol Ther* 2011; 13(Suppl. 1): S75–S83.

Aro A, Uusitupa M. Diabeteksen lääkehoito. [Pharmacotherapy of diabetes] *Kapseli 11 (Lääkintöhallituksen julkaisu)* 1981; pp. 1-38. (In Finnish)

Aschner P, Kipnes M, Lunceford J, Sanchez M, Mickel C, Williamson-Herman D. Effect of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy on glycemic control in patients with type 2 diabetes. *Diabetes Care* 2006; 29: 2632-7.

Astrup A, Finer N. Redefining Type 2 diabetes: 'Diabesity' or 'Obesity Dependent Diabetes Mellitus'? *Obesity Reviews* 2000; 1: 57-9.

Awa, W. Fach E, Krakow D, Welp R, Kunder J, Voll A et al. Type 2 diabetes from pediatric to geriatric age: analysis of gender and obesity among 120,183 patients from the German/Austrian DPV database. *Eur J Endocrinol* 2012; 167: 245–54.

Aye M, Atkin S. Patient safety and minimizing risk with insulin administration - role of insulin degludec. *Drug Healthc Patient Saf* 2014; 30: 55-67.

Bailey C, Turner R. Drug Therapy - Metformin (review). *N Engl J Med 1996;* 334: 574–9.

Bajaj M, Suraamornkul S, Piper P, Hardies L, Glass L, Cersosimo E et al. (2004). Decreased plasma adiponectin concentrations are closely related to hepatic fat content and hepatic insulin resistance in pioglitazone-treated type 2 diabetic patients. *J Clin Endocrinol Metab* 2004; 89*:* 200–6.

Balena R, Hensley I, Miller S, Barnett A. Combination therapy with GLP-1 receptor agonists and basal insulin: a systematic review of the literature. *Diabetes Obes Metab* 2013; 15: 485-502.

Balford J, Faulds D. Repaglinide. *Drugs Aging* 1998; 13: 173-80.

Barach J. Lower fat diet in diabetes. *JAMA* 1932; 98: 1265-8.

Barbalat Y, Dombrowskiy V, Weiss R. Association between pioglitazone and urothelial bladder cancer. *Urology* 2012; 80: 1-4.

Bartnik M, Rydén L, Ferrari R, Malmberg K, Pyörälä K, Simoons O et al. The prevalence of abnormal glucose regulation in patients with coronary artery disease across Europe. The Euro Heart Survey on diabetes and the heart. *Eur Heart J* 2004; 25: 1880-90.

Basit A, Musarrat R, Fawwad A. Glimepiride: evidence-based facts, trends, and observations. *Vasc Health Risk Manag* 2012; 8: 463–72.

Basu R, Chandramouli V, Dicke B, Landau B, Rizza R. Obesity and type 2 diabetes impair insulin-

induced suppression of glycogenolysis as well as gluconeogenesis. *Diabetes* 2005; 54*:* 1942–8.

Becker R, Frick A, Burger F, Potgieter J, Scholtz H. Insulin glulisine, a new rapid-acting insulin analogueue, displays a rapid time-action profile in obese non-diabetic subjects. *Exp Clin Endocrinol Diabetes* 2005; 113: 435–43.

Belfort R, Harrison S, Brown K, Darland C, Finch J, Hardies J et al. A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. *N Engl J Med* 2006; 355: 2297–307.

Berberoglu Z, Yazici A, Demirag N. Effects of rosiglitazone on bone mineral density and remodelling parameters in postmenopausal diabetic women: a 2-year follow-up study. *Clin Endocrinol* 2010; 73: 305–12.

Bergenstal R, Johnson M, Powers M, Wynne A. Adjust to target in type 2 diabetes. *Diabetes Care* 2008; 31: 1305–10.

Bergenstal R, Wysham C, Macconell L, Malloy J, Walsh B, Yan P et al. Efficacy and safety of exenatide once weekly versus sitagliptin or pioglitazone as an adjunct to metformin for treatment of type 2 diabetes (DURATION-2): a randomised trial. *Lancet* 2010; 376: 431–9.

Bonds D, Miller M, Bergenstal R. The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study. *BMJ* 2010; 340: b4909.

Brandenburg D. History and diagnostic significance of C-peptide. *Exp Diabetes Res* 2008; 576862: 1–8.

Brange J, Owens D, Kang S, Vølund A. Monomeric insulins and their experimental and clinical implications. *Diabetes Care* 1990; 13: 923–54.

Brethauer S, Aminian A, Romero-Talamas H, Batayyah E, Mackey J, Kennedy L et al. *Ann Surg* 2013; 258: 628-37.

Buchanan T, Xiang A, Peters R, Kjos S, Marroquin A, Goico J et al. Preservation of pancreatic β-cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk Hispanic women. *Diabetes* 2002; 51: 2796-803.

Buse J, Bergenstal R, Glass L, Heilmann C, Lewis M, Kwan A et al. Use of twice-daily exenatide in basal insulin-treated patients with type 2 diabetes: a randomized, controlled trial. *Ann Intern Med* 2011; 154: 103-112.

Buse J, Rosenstock J, Sesti G, Schmidt W, Montanya E, Brett J et al. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). *Lancet* 2009; 374: 39–47.

Callaghan B, Cheng H, Stables C, Smith A, Feldman E. Diabetic neuropathy: clinical manifestations and current treatments. *Lancet Neurol* 2012; 11: 521–34.

Camastra S, Manco M, Mari A, Greco A, Frascerra S, Mingrone G et al. Beta-cell function in severely obese type 2 diabetic patients: long-term effects of bariatric surgery. *Diabetes Care* 2007; 30: 1002-4.

Carlson M, Campbell P. Intensive insulin therapy and weight gain in IDDM. *Diabetes* 1993; 42: 1700–7.

Carlsson S, Midthjell K, Grill V. Smoking is associated with an increased risk of type 2 diabetes but a decreased risk of autoimmune diabetes in adults: an 11-year follow-up of incidence of diabetes in the Nord-Trøndelag study. *Diabetologia* 2004; 47: 1953-6.

Carver C. Insulin treatment and the problem of weight gain in type 2 diabetes. *Diabetes Educ* 2006; 32: 910–7.

Célia R, de Andrade G, de Figueiredo R, Foss-Freitas M, Pace A, Lelis, A. et al. Prevalence of diabetes mellitus in the Japanese-Brazilian community of Mombuca, Guatapará. *Arch Bras Endocrinol Metabol* 2011; 55: 127–33.

Centers for Disease Control and Prevention. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011. Atlanta, GA, U.S.

Chan J, Rimm E, Colditz G, Stampfer M, Willett W. Obesity, fat distribution and weight gain as risk factors for clinical diabetes in men. *Diabetes Care* 1994; 17: 961-9.

Chao E, Henry R. SGLT2 inhibition - a novel strategy for diabetes treatment. *Nat Rev Drug Discov* 2010; 9: 551–9.

Church T, Cheng Y, Earnest C, Barlow C, Gibbons L, Priest E et al. (2004). Exercise capacity and body composition as predictors of mortality among men with diabetes. *Diabetes Care* 2004; 27: 83–8.

Cnop M, Landchild M, Vidal J, Havel P, Knowles N, Carr D wt al. (2002). The concurrent accumulation of intra-abdominal and subcutaneous fat explains the association between insulin resistance and plasma leptin concentrations : distinct metabolic effects of two fat compartments. *Diabetes* 2002; 51: 1005–15.

Colberg S, Sigal R, Fernhall B, Regensteiner J, Blissmer B, Rubin R, et al. (2010). Exercise and type 2 diabetes: the American College of Sports Medicine and the American Diabetes Association: joint position statement. *Diabetes Care* 2010*;* 33: 147–67.

Colditz G, Willett W, Rotnizky A, Manson J. Weight gain as a risk factor for clinical diabetes mellitus in women. *Ann Intern Med* 1995; 122: 481-6.

Colhoun H, Betteridge D, Durrington P, Hitman G, Neil H, Livigstone S et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 2004; 384: 685-96.

Covic A, Schelling J, Constantiner M, Iyengar S, Sedor J. Serum C-peptide concentrations poorly phenotype type 2 diabetic end-stage renal disease patients. *Kidney Int* 2000; 58: 1742–50.

Cryer P. Minireview: Glucagon in the pathogenesis of hypoglycemia and hyperglycemia in diabetes. *Endocrinology* 2012; 153: 1039–48.

Dailey G, Rosenstock J. Insulin glulisine provides improved glycemic control in patients with type 2 diabetes. *Diabetes Care* 2004; 27: 2263-8.

Damsbo P, Clauson P, Marbury T, Windfeld K. A double-blind randomized comparison of meal-related glycemic control by repaglinide and glyburide in well-controlled type 2 diabetic patients. *Diabetes Care* 1999; 22: 789–94.

Danaei G, Finucane M, Lu Y, Singh G, Cowan M, Paciorek C et al. National , regional , and global trends in fasting plasma glucose and diabetes prevalence since 1980 : systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2,7 million participants. *Lancet* 2011; 378: 31–40.

Daneman D. Type 1 diabetes. *Lancet* 2006; 367: 847–58.

Davies M, Storms F, Shutler S, Bianchi-Biscay M, Gomis R. Improvement of glycemic control in subjects with poorly controlled type 2 diabetes: comparison of two treatment algorithms using insulin glargine, *Diabetes Care* 2005; 28: 1282-8.

DeFronzo R, Goodman A, the Multicenter Metformin Study Group. Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. *N Engl J Med* 1995; 333: 541-9.

DeFronzo R, Ratner R, Han J, Kim D, Fineman M, Baron A. Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. *Diabetes Care* 2005; 28: 1092–100.

De Leeuw I, Vague P, Selam J, Skeie S, Lang H, Draeger E et al. Insulin detemir used in basal-bolus therapy in people with type 1 diabetes is associated with a lower risk of nocturnal hypoglycaemia and less weight gain over 12 months in comparison to NPH insulin. *Diabetes, Obes Metab* 2005; 7: 73–82.

Del Prato S, Bianchi C, Dardano A, Miccoli R. Insulin as an early treatment for type 2 diabetes: ORIGIN or end of an old question? *Diabetes Care* 2013; 36(Suppl. 2): S198–204.

Diabetes (online). Current Care Guidelines. Working group set up by the Finnish Medical Society Duodecim and the Finnish Cardiac Society. Helsinki: *The Finnish Medical Society Duodecim*, 2014 (referred October 24, 2014). Available online at: www.kaypahoito.fi. (In Finnish)

Dixit S, Maiya A, Shastry B. Effect of aerobic exercise on peripheral nerve functions of population with diabetic peripheral neuropathy in type 2 diabetes: A single blind, parallel group randomized controlled trial. *J Diabetes Complications* 2014; 28: 2–9.

Donner T, Muñoz M. Update on insulin therapy for type 2 diabetes. *J Clin Endocrinol Metab* 2012; 97: 1405–13.

Dornhorst A. Insulinotropic meglitinide analogues. *Lancet* 2001; *358*: 1709–16.

Drucker J, Nauck M. (2006). The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. *Lancet* 2006; 368: 1696–705.

Drygas W, Kostka T, Jegier A, Kuński H. Long-term effects of different physical activity levels on coronary heart disease risk factors in middle-aged men. *Int J Sports Med* 2000; 21: 235–41.

Duckworth C, Abraira W, Moritz T, Reda D, Emanuele N, Reaven P et al. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med* 2009; 360: 129-39.

Dungan K, Dagrilla C, Abdel-Rasoul M, Osei K. Prandial insulin dosing using the carbohydrate counting technique in hospitalized patients with type 2 diabetes. *Diabetes Care* 2013; 36: 3476–82.

Duttaroy A, Voelker F, Merriam K, Zhang X, Ren X, Subramanian K et al. The DPP-4 inhibitor vildagliptin increases pancreatic beta cell mass in neonatal rats. *Eur J Pharmacol* 2011; 650: 703–7.

Dyslipidaemias (online). Current Care Guidelines. Working group set up by the Finnish Medical Society Duodecim and the Finnish Cardiac Society. Helsinki: *The Finnish Medical Society Duodecim*, 2014 (referred October 24, 2014). Available online at: www.kaypahoito.fi. (In Finnish)

Eliaschewitz F, Calvo C, Valbuena H. Therapy in type 2 diabetes: Insulin glargine vs. NPH insulin both in combination with glimepiride. *Arch Med Res* 2006; 37: 496-501.

Elrick H, Stimmler L, Hlad C, Arai Y. Plasma insulin response to oral and intravenous glucose administration. *J Clin Endocrinol Metab* 1964; 24: 1076–82.

Eng C, Kramer C, Zinman B, Retnakaran R. Glucagon-like peptide-1 receptor agonist and basal insulin combination treatment for the management of type 2 diabetes: a systematic review and meta-analysis.

Lancet 2014; S0140-6736(14)61335-0 (Epub ahead of print).

Evert A, Boucher J, Cypress M, Dunbar S, Franz M, Mayer-Davis E et al. Nutrition therapy recommendations for the management of adults with diabetes. *Diabetes Care* 2014; 37 (Suppl. 1): S120-43.

Fajans S, Bell G. MODY: history, genetics, pathophysiology, and clinical decision making. *Diabetes Care* 2011; 34: 1878–84.

Ferrannini E, Ramos Jimenez S, Salsali A, Tang W, List J. Dapagliflozine monotherapy in type 2 diabetic patients with inadequate glycemic control by diet and exercise. *Diabetes Care* 2010; 33: 2217–24.

Festa A, Williams K, d'Agostino R, Wagenknecht L, Haffner S. The natural course of beta-cell function in nondiabetic and diabetic indiviuals. The insulin resistance atherosclerosis study. *Diabetes* 2006; 55: 1114–20.

Friedewald W, Lewy R, Fredrickson D. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 1972; 18: 499-502.

Frier, B, Russell-Jones D, Heise T. A comparison of insulin detemir and neutral protamine Hagedorn (isophane) insulin in the treatment of diabetes: a systematic review. *Diabetes Obes Metab* 2013; 15: 978–86.

Fritsche A, Schweitzer M, Haring H-U. Glimepiride combined with morning insulin glargine, bedtime neutral protamine hagedorn insulin, or bedtime insulin glargine in patients with type 2 diabetes. *Ann Intern Med* 2003; 138: 952-9.

Fujimoto W, Leonetti, D, Kinyoun J, Newell-Morris L, Shuman W, Stolov W et al. Prevalence of diabetes mellitus and impaired glucose tolerance among second-generation Japanese-American men. *Diabetes* 1987; 36: 721–9.

Gæde P, Lund-Andersen H, Parving H-H, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. *New Engl J Med* 2008; 358: 580-91.

Gæde P, Vedel P, Larsen N, Jensen G, Parving H-H. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *New Engl J Med* 2003; 348: 383-93.

Gallwitz, B. Emerging DPP-4 inhibitors: focus on linagliptin for type 2 diabetes. *Diabetes Metab Syndr Obes* 2013; 6: 1–9.

Garber A, King A, Del Prato S, Sreenan S, Balci M, Muñoz-Torres M et al. Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 2 diabetes (BEGIN Basal-Bolus Type 2): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. *Lancet* 2012; 379: 1498–507.

Gastaldelli A, Basta G. Ectopic fat and cardiovascular disease. What is the link? *Nutr Metab Cardiovasc Dis* 2010; 20: 481-90.

Gedulin B, Smith P, Prickett K, Tryon M. Dose–response for glycaemic and metabolic changes 28 days after single injection of long-acting release exenatide in diabetic fatty Zucker rats. *Diabetologia* 2005; 48: 1380–5.

Gerich J. DPP-4 inhibitors: What may be the clinical differentiators? *Diabetes Res Clin Pract* 2010; 90: 133-40.

Gerstein H, Yale J-F, Harris S, Issa M, Stewart J, Dempsey E. A randomized trial of adding insulin glargine vs. avoidance of insulin in people with Type 2 diabetes on either no oral glucose-lowering agents or submaximal doses of metformin and/or sulphonylureas.The Canadian INSIGHT (Implementing new strategies with insulin glargine for hyperglycaemia treatment) study. *Diabet Med* 2006; 23: 736–42.

Giorda C, Sacerdote C, Nada E, Marafetti L, Baldi I, Gnavi R. Incretin-based therapies and acute pancreatitis risk: a systematic review and meta-analysis of observational studies. *Endocrine* 2014; [Epub ahead of print].

Giugliano D, Maiorino M, Bellastella G, Chiodini P, Esposito K. Treatment regimens with insulin analogues and haemoglobin A1c target of <7% in type 2 diabetes: a systematic review. *Diabetes Res Clin Pract* 2011; 92: 1–10.

Go A, Mozaffarian D, Roger V, Benjamin E, Berry J, Borden W et al. Heart disease and stroke statistics--2013 update: a report from the American Heart Association. *Circulation* 2013; 127; 143-52.

Goergen S, Rumbold G, Compton G, Harris C. Systematic review of current guidelines, and their evidence base, on risk of lactic acidosis after administration of contrast medium for patients receiving metformin. *Radiology* 2009; 254: 261–9.

Gough S, Harris S, Woo V, Davies M. Insulin degludec: overview of a novel ultra long-acting basal insulin. *Diabetes Obes Metab* 2013; 15: 301–9.

Grant S, Thorleifsson G, Reynisdottir I, Benediktsson R, Manolescu A, Sainz J et al. Variant of transcription factor 7-like 2 (TCF7L2) gene confers risk of type 2 diabetes. *Nature Genetics* 2006; 38: 320-3.

Graham G, Punt J, Arora M, Day R, Doogue M, Duong J. et al. Clinical pharmacokinetics of metformin. *Clin Pharmacokin* 2011; 50: 81–98.

Greenwood D, Threapleton D, Evans C, Cleghorn C, Nykjaer C, Woodhead C et al. Glycemic index, glycemic load, carbohydrates, and type 2 diabetes: systematic review and dose-response meta-analysis of prospective studies. *Diabetes Care* 2013; 36: 4166–71.

van Greevenbroek M, Schalkwijk C, Stehouwer C. Obesity-associated low-grade inflammation in type 2 diabetes mellitus: causes and consequences. *Neth J Med* 2013; 71: 174-87.

Gries F, Alberti K. Management of non-insulin-dependent diabetes mellitus in Europe: A consensus statement. *International Diabetes Federation Bulletin* 1987; 11: 5-11.

Groop L. Sulfonylureas in NIDDM. *Diabetes Care* 1992; 15: 737–54.

Groop L, Nissén M, Salo S, Taskinen M-R, Uusitupa M. Aikuistyypin diabeteksen hoitosuositus (Recommendation of treatment of maturity onset diabetes). *Finnish Diabetes Association* 1989. Helsinki, Finland pp. 1-54.

Groop L, Tuomi T, Rowley M, Zimmet P, Mackay I. Latent autoimmune diabetes in adults (LADA) -- more than a name. *Diabetologia* 2006; 49: 1996-8.

de Groot-Kamphuis D, van Dijk R, Groenier K, Houweling S, Bilo H. Vitamin B 12 deficiency and the lack of its consequences in type 2 diabetes patients using metformin. *Neth J Med* 2013; 71: 386–90.

Guide to Diabetes Education for Health Professionals. Topic 14. Gestational diabetes. http://www.nursesreg.health.nsw.gov.au. Accessed 24.10.2014.

Haak T, Tiengo A, Draeger E, Suntum M, Waldha W. Lower within-subject variability of fasting blood glucose and reduced weight gain with insulin detemir compared to NPH insulin in patients with type 2 diabetes. *Diabetes Obes Metab 2005; 7*: 56–64.

Haffner S, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med* 1998; 339: 229–34.

Hamaty M. Insulin treatment for type 2 diabetes: when to start, which to use. *Cleve Clin J Med* 2011; 78: 332–42.

Hanefeld M, Bramlage P. Insulin use early in the course of type 2 diabetes mellitus: the ORIGIN trial. *Curr Diab Rep* 2013; *13*: 342–9.

Hawley J, Lessard S. Exercise training-induced improvements in insulin action. *Acta Physiol* 2008; 192: 127-35.

Heine R, van Gaal L, Johns D, Mihm M, Widel M, Brodows R. Exenatide versus insulin glargine in patients with suboptimally controlled type 2 diabetes: a randomized trial. *Ann Intern Med* 2005; 143: 559-69.

Heinemann L. Biosimilar insulins: how will this story evolve? *Diabetes Technol Ther* 2012; 14: 986-8.

van Heiningen P, Hatorp V, Kramer Nielsen K, Hansen K, van Lier J, De Merbel, N et al. Absorption, metabolism and excretion of a single oral dose of (14)C-repaglinide during repaglinide multiple dosing. *Eur J Clin Pharmacol* 1999; 55: 521–5.

Heinzerling L, Raile K, Rochlitz M, Zuberbier T, Worm M. Insulin allergy: clinical manifestations and management strategies. *Allergy* 2008; 63: 148–55.

Heise T, Hermanski L, Nosek L, Feldman A, Rasmussen S, Haahr H. Insulin degludec: four times lower pharmacodynamic variability than insulin glargine under steady-state conditions in type 1 diabetes. *Diabetes Obes Metab* 2012; 14: 859–64.

Heller S. A summary of the ADVANCE trial. *Diabetes Care* 2009; 32(Suppl. 2): S357–61.

Hemmingsen B, Christensen L, Wettersley J, Waag A, Gluud C, Lund S et al. Comparison of metformin and insulin versus insulin alone for type 2 diabetes: systematic review of randomised clinical trials with meta-analyses and trial sequential analyses. *BMJ* 2012; 344: e1771.

Herder C, Roden M. Genetics of type 2 diabetes: pathophysiologic and clinical relevance. *Diabetes Care* 2010; 33 (Suppl. 1): S82-9.

Hermansen K, Davies M, Derezinski T, Martinez Ravn G, Clauson P, Home P. A 26-week, randomized, parallel, treat-to-target trial comparing insulin detemir with NPH insulin as add-on therapy to oral glucose-lowering drugs in insulin-naive people with type 2 diabetes. *Diabetes Care* 2006; 29: 1269–74.

Holman R, Farmer A, Davies M, Levy J, Darbyshire J, Keenan J et al. Three-year efficacy of complex insulin regimens in type 2 diabetes. *N Engl J Med* 2009; 361: 1736–47.

Holman R, Paul S, Bethel M, Matthews D, Neil H. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008; 359: 1577–89.

Holman R, Thorne K, Farmer A, Davies M, Keenan J, Paul S et al. Addition of biphasic, prandial, or basal insulin to oral therapy in type 2 diabetes. *N Engl J Med* 2007; 357: 1716–30.

Holst J. Enteroendocrine secretion of gut hormones in diabetes, obesity and after bariatric surgery. *Curr Opin Pharmacol* 2013; 12: 983-8.

Hyvärinen M, Tuomilehto J, Laatikainen T, Söderberg S, Eliasson M, Nilsson P et al. The impact of diabetes on coronary heart disease differs from that on ischaemic stroke with regard to the gender. *Cardiovasc Diabetol* 2009; 8: 1-5.

Ilonen J, Reijonen H, Herva E, Sjöroos M, Iitiä A, Lövgren T et al. Rapid HLA-DQB1 genotyping for four alleles in the assesment of risk for IDDM in the Finnish population. *Diabetes Care* 1996; 19: 795-800.

International Diabetes Feberation Guideline Development Group. Global guideline for type 2 diabetes. *Diabetes Res Clin Pract 2014*; 104: 1-52.

Inzucchi S, Bergenstal R, Buse J, Diamant M. Management of hyperglycemia in type 2; a patient-centered approach. *Diabetes Care* 2012; 35: 1364–79.

Inzucchi S, Maggs D, Spollett G, Page S, Rife F, Walton W et al. Efficacy and metabolic effects of metformin and troglitazone in type II diabetes mellitus. *N Engl J Med* 1998; 338: 867-72.

Janka H, Plewe G, Riddle M, Kliebe-Frisch C, Schweitzer M, Yki-Järvinen, H. Comparison of basal insulin added to oral agents versus twice-daily premixed insulin as initial insulin therapy for type 2 diabetes. *Diabetes Care* 2005; 28: 254–9.

Jebb S, Lovegrove J, Griffin B, Frost G, Moore C, Chatfield M et al. Effect of changing the amount and type of fat and carbohydrate on insulin sensitivity and cardiovascular risk: the RISCK (Reading, Imperial, Surrey, Cambridge, and Kings) trial. *Am J Clin Nutr* 2010; 92: 748-58.

Johnsson K, Ptaszynska A, Schmitz B, Sugg J, Parikh S, List J. Vulvovaginitis and balanitis in patients with diabetes treated with dapagliflozin. *J Diabetes Complications* 2013; 27: 479–84.

Jonassen I, Havelund S, Hoeg-Jensen T, Steensgaard D, Wahlund P-O, Ribel U. Design of the novel protraction mechanism of insulin degludec, an ultra-long-acting basal insulin. *Pharm Res* 2012; 29: 2104–14.

Jones A, Hattersley A. The clinical utility of C-peptide measurement in the care of patients with diabetes. *Diab Med 2013; 30*: 803–17.

Jude E, Oyibo S, Chalmers N, Boulton A. Peripheral arterial disease in diabetic and nondiabetic patients. *Diabetes Care* 2001; 24: 1433–37.

Jurgens C. Toukatly M, Fligner C, Udayasankar J, Subramanian S, Zraika S et al. (2011). Beta-cell loss and beta-cell apoptosis in human type 2 diabetes are related to islet amyloid deposition. *Am J Path* 2011; 178: 2632–40.

Juutilainen A, Kortelainen S, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Gender difference in the impact of type 2 diabetes on coronary heart disease risk. *Diabetes Care* 2004; 27: 2898-904.

Juutilainen A, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Type 2 Diabetes as a "Coronary Heart

Disease Equivalent": an 18-year prospective population-based study in Finnish subjects. *Diabetes Care* 2005; 28: 2901-7.

Kahn S, Cooper M, Del Prato S. Pathophysiology and treatment of type 2 diabetes: perspectives on the past, present, and future. *Lancet* 2013; 383: 1068–83.

Kahn S, Hull R, Utzschneider K. Mechanisms linking obesity to insulin resistance and type 2 diabetes. *Nature* 2006; 444: 840–6.

Kangas T. Miten insuliinit valmistetaan? [How insulins are being prepared?] 2003. In Ilanne-Parikka P, Kangas T, Kaprio E, Rönnemaa T (Eds.), *Diabetes.* 3rd ed., pp. 73-5. Helsinki, Finland. Kustannus Oy Duodecim and Finnish Diabetes Association. (In Finnish)

Kanoski S, Rupprecht L, Fortin S, De Jonghe B,Hayes, M. The role of nausea in food intake and body weight suppression by peripheral GLP-1 receptor agonists, exendin-4 and liraglutide. *Neuropharmacology* 2012; 62: 1916–27.

Kansallinen liikuntatutkimus 2009-2010 [National survey on physical activity 2009-2010] 2013. *Kuntoliikuntaliitto* (pp. 1-72). (In Finnish)

Karasik A, Aschner P, Davies M, Stein P. Sitagliptin, a DPP−4 inhibitor for the treatment of patients with type 2 diabetes: a review of recent clinical trials. *Curr Med Res Opin* 2008; 24: 489-96.

Kasalová Z, Prázný M, Skrha J. Relationship between peripheral diabetic neuropathy and microvascular reactivity in patients with type 1 and type 2 diabetes mellitus -- neuropathy and microcirculation in diabetes. *Exp Clin Endocrinol Diabetes* 2006; 114: 52–7.

Kawahito S, Kitahata H, Oshita S. Problems associated with glucose toxicity : Role of hyperglycemia-induced oxidative stress. *World J Gastroenterol* 2009; 15: 4137–42.

Kearney M, Blackwell L, Collins R, Keech A, Simes J, Peto R et al. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. *Lancet* 2008; 371: 117-25.

Kela. Voimassaolevat, alkaneet ja päättyneet lääkekorvausoikeudet 2012. [Started, pending and finished rights for reimbursement of medications 2012.] Kelasto-raportit 2013; http://raportit.kela.fi/ibi_apps/WFServlet. Accessed 27.10.2014. (In Finnish)

Kennedy L, Herman W, Strange P, Harris A. Impact of active versus usual algorithmic titration of basal insulin and point-of-care versus laboratory measurement of HbA1c on glycemic control in patients with type 2 diabetes: the Glycemic Optimization with Algorithms and Labs at Point of Care (GOAL A1C) trial. *Diabetes Care* 2006; 29: 1-5.

Kenny S, Aubert R, Geiss L. Prevalence and incidence of non-insulin-dependent diabetes. 1995. *Diabetes in America, 2nd edition*, NIH Publication No. 95-1468; pp. 47-67.

Klein S, Sheard N, Pi-Sunyer X, Daly A, Wylie-Rosett J, Kulkarni K et al. Weight management through lifestyle modification for the prevention and management of type 2 diabetes: rationale and strategies. *Diabetes Care* 2004; 27: 2067-73.

Klem M, Wing R. McGuire M, Seagle H, Hill J. A descriptive study of individuals successful at long-term maintenance of substantial weight loss. *Am J Clin Nutr* 1997; 66: 239–46.

Klip A, Leiter, L. Cellular mechanism of action of metformin. *Diabetes Care* 1990; 13: 696–704.

Knip M, Simell O. Environmental triggers of type 1 diabetes. *Cold Spring Harb Perspect Med* 2012*; 2*: a007690 pp. 1-15.

Kocova M, Trucco M, Konstantinova M, Dorman J. A cold spot of IDDM incidence Macedonia. *Diabetes Care* 1993; 16*:* 1236–40.

Kolb H, Mandrup-Poulsen T. The global diabetes epidemic as a consequence of lifestyle-induced low-grade inflammation. *Diabetologia* 2010; *53*: 10–20.

Koski S. Diabetesbarometri [Diabetes barometer]2010*, Finnish Diabetes Federation,* (pp. 1–58) (in Finnish).

Kotronen A, Juurinen L, Hakkakainen A, Westerbacka J, Cornér A, Bergholm R et al. Liver fat is increased in type 2 diabetic patients and underestimated by serum alanine aminotransferase compared with equally obese nondiabetic subjects. *Diabetes Care* 2008, 31: 165.9.

Krepinsky J, Ingram A, Clase C. Prolonged sulfonylurea-induced hypoglycemia in diabetic patients with end-stage renal disease. *Am J Kidney Dis* 2000; *35*: 500–5.

Kumar P, Clark M. Diabetes mellitus and other disorders of metabolism (1999). In Kumar P and Clark M (Eds.) *Clinical Medicine*, 4th ed., pp. 959–1005. Sounders, London.

Kurtzhals P. Engineering predictability and protraction in a basal insulin analogue: the pharmacology of insulin detemir. *Int J Obes Relat Metab Disord* 2004; 28(Suppl 2): S23–8.

Laakso M. Hyperglycemia and cardiovascular disease in type 2 diabetes. *Diabetes* 1999; 48: 937–42.

Laakso M. Onko diabeteksen geenidiagnostiikasta hyötyä potilastyössä? [Clinical value of DNA diagnostics] *Suom Lääkäril* 2011; 66: 37–42. (In Finnish, English summary)

Laakso M, Cederberg H. Glucose control in diabetes: Which target level to aim for? *J Intern Med* 2012; 272*:* 1–12.

Laakso M, Groop L. Yksi, kaksi vai monta diabetesta? [One, two or many diabeteses?] *Duodecim* 2001; 123: 1423-6. (In Finnish)

Laakso M, Kuusisto J. Cerebrovascular disease in type 2 diabetes. *Int Congr Ser* 2007; 1303: 65–69.

Larger E. Weight gain and insulin treatment. *Diabetes Metab* 2005; 31: 4S51–4S56.

Lavernia F. What options are available when considering starting insulin: premix or basal? *Diabetes Technol Ther* 2011; 13(Suppl. 1): S85-92.

Lee A, Morley J. Metformin decreases food consumption and induces weight loss in subjects with obesity with type II non-insulin-dependent diabetes. *Obes Res* 1998; 6: 47-53.

Lindström J, Tuomilehto J. The diabetes risk score. *Diabetes Care* 2003; 26: 725-21.

Lipska K, Bailey C, Inzucchi S. Use of metformin in the setting of mild-to-moderate renal insufficiency. *Diabetes Care* 2011; 34: 1431–7.

List J, Woo V, Morales E, Tang W, Fiedorek, F. Sodium-glucose cotransport inhibition with dapagliflozin in type 2 diabetes. *Diabetes Care* 2009; 32: 650–7.

Little S, Shaw J, Home P. Hypoglycemia rates with basal insulin analogues. *Diabetes Technol Ther* 2011; 13(Suppl. 1): S53–64.

Loke Y, Singh S, Furberg C. Long-term use of thiazolidinediones and fractures in type 2diabetes: a meta-analysis. *CMAJ* 2008; 180: 32-9.

Lyseng-Williamson K. Sitagliptin. *Drugs* 2007; 67: 587–97.

Maassen J, Hart L, van Essen E, Heine R, Nijpels G, Roshan, S et al. Mitochondrial Diabetes. *Diabetes* 2004; 53(Suppl 1): S103–S109.

Madsbad S, Krarup T, McNair P, Christiansen C, Faber O, Transbøl I et al. Practical clinical value of the C-peptide response to glucagon stimulation in the choice of treatment in diabetes mellitus. *Acta Med Scand* 1981; 210: 153–6.

Maggard M, Shugarman L, Suttorp M, Maglione M, Sugarman H, Livingston E et al. Surgical treatment of obesity (meta-analysis). *Ann Intern Med* 2005; 142: 547–60.

Malmberg K, Norrhammar A, Wedel H, Rydén L. Glycometabolic state at admission: important risk marker of mortality in conventionally treated patients with diabetes mellitus and acute myocardial infarction: long-term results from the Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study. *Circulation* 1999; 99: 2626-32.

Mannucci E, Monami M, Marchionni N. Short-acting insulin analogues vs. regular human insulin in type 2 diabetes: a meta-analysis. *Diabetes Obes Metab* 2009; 11: 53–9.

Martikainen, M. Mitochondrial disease in Southwestern Finland. Population-based molecular

genetic and clinical studies. *Annales Universitatis Turkuensis*, Ser. D. 2012. P. 47.

Martin-Castillo B, Vazquez-Martin A, Oliveras-Ferraros C, Menendez J. Metformin and cancer. *Cell Cycle* 2010; 9: 1057–64.

Mayfield J, White R. Insulin therapy for type 2 diabetes: rescue, augmentation, and replacement of beta-cell function. *Am Fam Physician* 2004; 70: 489–500.

Meigs J, Shrader P, Sullivan L, McAteer J, Fox C., Dupuis J et al. Genotype score in addition to common risk factors for prediction of type 2 diabetes. *N Engl J Med* 2008; 359: 2208–19.

Meneghini L, Kesavadejev J, Demissie M, Nazeri A, Hollander P. Once daily initiation of basal insulin as add-on to metformin: a 26-week, randomized, treat-to-target trial comparing insulin detemir with insulin glargine in patients with type 2 diabetes. *Diabetes Obes Metab* 2013; 15: 729-36.

Meneghini L, Traylor R, Schwartz S. Improved glycemic control with insulin glargine versus pioglitazone as add-on therapy to sulfonylurea or metformin in patients with uncontrolled type 2 diabetes mellitus. *Endocr Pract* 2010; 16: 588-99.

Miettinen J, Friman A, Vanhala M. Miten väestövastuinen terveyskeskus vastaa tyypin 2 diabeteksen hoidon haasteisiin? [How does a health centre with local population responsibility system respond to the challenge of type 2 diabetes treatment?] *Suom Lääkäril* 2001; 56: 515-9. (In Finnish)

Miettinen P, Tuomi T. MODY-diabetes – yksigeeninen haiman beetasolujen kehitys- ja toimintahäiriö [MODY - monogenic disorder in development and function of pancreatic beta-cells]. *Duodecim 2012*, *128*, 1989–98. (In Finnish)

Mihaylova B, Briggs A, Armitage J, Parish S, Gray A, Collins R. Lifetime cost effectiveness of simvastatin in a range of risk groups and age groups derived from a randomised trial of 20,536 people. *BMJ* 2006; 333: 1145-9.

Mingrone G, Panunzi S, De Gaetano A, Guidone C, Iaconelli A, Leccesi L et al. Bariatric surgery versus conventional medical therapy for type 2 diabetes. *N Engl J Med* 2012; 366: 1577–85.

Mirouze J, Monnier L, Richard J, Gancel A, Soua K. Comparative study of NPH Human Insulin (recombinant DNA) and pork insulin in diabetic subjects: Preliminary report. *Diabetes Care* 1982; Suppl. 2: 60-62.

Miyazaki Y, Glass L, Triplitt C, Matsuda M, Cusi K, Mahankali A et al. Effect of rosiglitazone on glucose and non-esterified fatty acid metabolism in type II diabetic patients. *Diabetologia* 2001; 44: 2210–9.

Mokdad A, Ford E, Bowman B. Diabetes trends in the US: 1990-1998. *Diabetes Care* 2000; 23: 1278–83.

Monnier L, Lapinski H, Colette C. Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients: variations with increasing levels of HbA(1c). *Diabetes Care 2003; 26*: 881–5.

Montani J-P, Carroll J, Dwyer T, Antic V, Yang Z, Dulloo A. Ectopic fat storage in heart, blood vessels and kidneys in the pathogenesis of cardiovascular diseases. *Int J Obes Relat Metab Disord* 2004; 28 (Suppl. 4): S58-65.

Mori Y, Murakawa Y, Okada K, Horikoshi H, Yokoyama J, Tajima N et al. Effect of troglitazone on body fat distribution in type 2 diabetic patients. *Diabetes Care* 1999; 22: 908–12.

Moura B, Amorim P, Silva B, Franceschini S, Reis J, Marins J. Effect of a short-term exercise program on glycemic control measured by fructosamine test in type 2 diabetes patients. *Diabetol Metab Syndr* 2014; 6: 1-6.

Mulherin A, Oh A, Kim H, Grieco A, Lauffer L, Brubaker P. Mechanisms underlying metformin-induced secretion of glucagon-like peptide-1 from the intestinal L cell. *Endocrinology* 2011; 152: 4610–9.

Muntoni S, Stabilini L, Stabilini M, Mancosu G. Steadily high IDDM incidence over 4 years in Sardinia. *Diabetes Care* 1995; 18: 1600–1.

Mäkelä M, Sainio S, Åström M, Bergström M. Local population responsibility in Finnish health centres in 1989–1993. *Eur J Pub Health* 1998; 8: 313-8.

Mäkimattila S, Nikkilä K, Yki-Järvinen H. Causes of weight gain during insulin therapy with and without metformin in patients with type II diabetes mellitus. *Diabetologia* 1999; 42: 406–12.

Nathan D, Buse J, Davidson M, Heine R, Holman R, Sherwin R et al. Management of hyperglycemia in type 2 diabetes : a consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2006; 29: 1963–72.

National Diabetes Data Group. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. *Diabetes* 1979; 28: 1039–57.

Nielsen S, Siega-Riz A, Popkin B. Trends in energy intake in U.S. between 1977 and 1996: similar shifts seen across age groups. *Obes Res* 2002; 10: 370–8.

Niemi M, Winell K. *Diabetes Suomessa. Esiintyvyys ja hoidon laadun vaihtelu* [Diabetes in Finland. Prevalence and variety of care quality], STAKES, Finland 2005; pp. 1–81. (In Finnish)

Nishizawa H, Shimomura I, Kishida K, Maeda N, Kuriyama H, Nagaretani H et al. Androgens decrease plasma adiponectin, an insulin-sensitizing adipocyte-derived protein. *Diabetes* 2002; 51: 2734–41.

Ogden C, Carroll M, Kit B, Flegal K. Prevalence of childhood and adult obesity in the United States, 2011-2012. *JAMA* 2012; 311: 806–14.

Ohkubo Y, Kishikawa H, Araki E, Miyata T. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependdent diabetes mellitus. *Diabetes Res Clin Pract* 1995; 28: 103–17.

Owens D. Insulin preparations with prolonged effect. *Diabetes Technol Ther* 2011; 13 (Suppl. 1): S5-14.

Owens D, Zinman B, Bolli G. Insulins today and beyond. *Lancet* 2001; 358: 739–46.

Paffenbarger R, Hyde R, Wing A. The association of changes in physical-activity level and other lifestyle characteristics with mortality among men. *N Engl J Med* 1993; 328: 538–45.

Pala L, Mannucci E, Dicembrini I, Rotella C. A comparison of mealtime insulin aspart and human insulin in combination with metformin in type 2 diabetes patients. *Diabetes Res Clin Pract* 2007; 78: 132–5.

Palmer J, Hampe C, Chiu H, Goel A, Brooks-Worrell B. Is latent autoimmune diabetes in adults distinct from type 1 diabetes or just type 1 diabetes at an older age? *Diabetes* 2005; 54 (Suppl. 2): S62-67.

Pan C, Sinnassamy P, Chung K, Kim K. Insulin glargine versus NPH insulin therapy In Asian type 2 diabetic patients. *Diabetes Res Clin Pract* 2007; 76: 111-6.

Paoli A. Ketogenic diet for obesity : friend or foe? *Int J Environ Res Public Health* 2014; 11: 2092–107.

Peltonen M, Oksa H, Puolijoki H, Saltevo J, Vanhala M, Saaristo T et al. Lihavuuden, diabeteksen ja muiden glukoosiaineenvaihdunnan häiriöiden esiintyvyys suomalaisessa aikuisväestössä [Prevalence of obesity, type 2 diabetes, and other disturbances in glucose metabolism in Finnish adult population – the FIN-D2D survey]. *Suom Lääkäril* 2006; 3: 163–70. (In Finnish, English summary)

Philis-Tsimikas A, Charpentier G, Clauson P, Ravn G, Roberts V, Thorsteinsson B. Comparison of once-daily insulin detemir with NPH insulin added to a regimen of oral antidiabetic drugs in poorly controlled type 2 diabetes. *Clin Ther* 2006; 28: 1569–81.

Pillai O, Panchagnula R. Insulin therapies - past, present and future. *Drug Discov Today* 2001; 6: 1056–61.

Poitout V, Robertson R. Glucolipotoxicity: fuel excess and beta-cell dysfunction. *Endocr Rev* 2008; 29: 351–66.

Polonsky K. The past 200 years in diabetes. *N Engl Med* 2012; 367: 1332–40.

Porcellati F, Rossetti P, Ricci Busciantella N, Marzotti S, Lucidi P, Lizio S. Comparison of pharmacokinetics and dynamics of the long-acting insulin analogues glargine and detemir at steady state in type 1 diabetes. *Diabetes Care* 2007; 30: 2447–52.

Poulsen P, Kyvik K, Vaag A, Beck-Nielsen H. Heritability of type II (non-insulin-dependent) diabetes mellitus and abnormal glucose tolerance - a population-based twin study. *Diabetologia* 1999; 42: 139–45.

Pratley R, Weyer C. The role of impaired early insulin secretion in the pathogenesis of Type II diabetes mellitus. *Diabetologia* 2001; 44: 929-45.

Pridjian G, Benjamin T. Update on gestational diabetes. *Obstet Gynecol Clin North Am* 2010; 37: 255–67.

Pugh J, Wagner M, Sawyer J, Ramirez G, Tuley M, Fredberg S. Is combination sulfonylurea and insulin therapy useful in NIDDM patients? A metaanalysis. *Diabetes Care* 1992; 18: 953-9.

Quianzon C, Cheikh I. History of current non-insulin medications for diabetes mellitus. *J Community Hosp Intern Med Perspect* 2012; 2: 2–5.

Rahmoune H, Thompson P, Ward J, Smith C, Hong G, Brown J. Glucose transporters in human renal proximal tubular cells isolated from the urine of patients with non-insulin-dependent diabetes. *Diabetes* 2005; 54: 3427–34.

Rajpar S, Foulds I, Abdullah A, Maneshwari M. Severe adverse cutaneous reaction to insulin due to cresol sensitivity. *Contact Dermatitis* 2006; 55: 113–25.

Rana J, Li T, Manson J, Hu F. Adiposity compared with physical inactivity and risk of type 2 diabetes in women. *Diabetes Care* 2007; 30: 53-8.

Raskin P, Allen E, Hollander P, Lewen A. Initiating insulin therapy in type 2 diabetes; a comparison of biphasic and basal insulin analogues. *Diabetes Care* 2005; 28: 260–5.

Rauramaa, R. Relationship of physical activity , glucose and weight management. *Prev Med* 1984; 13: 37–46.

Reusch, J. Diabetes, microvascular complications, and cardiovascular complications : what is it about glucose? *J Clin Invest 2003; 112*: 986–8.

Richter B, Bandeira-Echtler E, Berghoff K, Lerch C. Dipeptidyl peptidase-4 (DPP-4) inhibitors for type 2 diabetes mellitus (Review). *The Cochrane Library* 2008, 2: 1-74.

Riddle M, Henry R. Exenatide elicits sustained glycaemic control and progressive reduction of body weight in patients with type 2 diabetes inadequately controlled by sulphonylureas with. *Diabetes Metab Res Rev 2006;* 22: 483–91.

Riddle M, Rosenstock J, Gerinch J. The treat-to-target trial. *Diabetes Care* 2003; 26: 3080–6.

Ritz E, Ogata H, Orth S. Smoking: a factor promoting onset and progression of diabetic nephropathy. *Diabetes Metab* 2000; 26: 54-63.

Rizza R. Pathogenesis of fasting and postprandial hyperglycemia in type 2 diabetes: implications for therapy. *Diabetes* 2010; 59: 2697–707.

Robbins J, Vaccarino V, Zhang H, Kasl S. Socioeconomic status and diagnosed diabetes incidence. *Diabetes Res Clin Pract* 2005; 68: 230–6.

Robinson L, Holt T, Rees K, Randeva H, O'Hare J. Effects of exenatide and liraglutide on heart rate, blood pressure and body weight: systematic review and meta-analysis. *BMJ Open* 2013; 3: e001986.

Romualdi D. Selective effects of pioglitazone on insulin and androgen abnormalities in normo- and hyperinsulinaemic obese patients with polycystic ovary syndrome. *Hum Reprod* 2003; 18: 1210–18.

Rosenfeld, L. Insulin: discovery and controversy. *Clin Chem* 2002; 48: 2270–88.

Rosenstock J, Dailey G, Massi-Benedetti M, Fritsche A. Reduced hypoglycemia risk with insulin glargine. *Diabetes Care* 2005; 28: 950–5.

Rosenstock J, Davies M, Home P. A randomised, 52-week, treat-to-target trial comparing insulin detemir with insulin glargine when administered as add-on to glucose-lowering drugs in insulin-naïve type 2 diabetics. *Diabetologia* 2008; 51: 408–16.

Rosenstock J, Sugimoto D, Strange P, Stewart J, Soltes-Rak E, Dailey S. Triple therapy in type 2 diabetes: insulin glargine or rosiglitazone added to combination therapy of sulfonylurea plus metformin in insulin-naive patients. *Diabetes Care* 2006; 29: 554-9.

Russell-Jones D, Khan R. Insulin-associated weight gain in diabetes--causes, effects and coping strategies. *Diabetes Obes Metab* 2007; 9: 799–812.

Rydén L, Grant P, Anker S, Berne C, Cosentino F, Danchin N et al. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J* 2013; 34: 3035-87.

Ryysy L, Häkkinen A, Goto T, Vehkavaara S, Westerbacka J, Halavaara J et al. Hepatic fat content and insulin action on free fatty acids and glucose metabolism rather than insulinabsorption are associated with insulin requirements during insulin therapy in type 2 diabetic patients. *Diabetes* 2000; 48: 749-58.

Rönnemaa T. Aikuistyypin diabeteksen insuliinihoito. [Insulin treatment of maturity onset diabetes.] *Diabetes ja lääkäri* 1995; 23: 13-6. (In Finnish)

Rönnemaa T, Marniemi J, Puukka P, Kuusi T. Effects of long-term physical exercise on serum lipids, lipoproteins and lipid metabolizing enzymes in type 2 (non-insulin-dependent) diabetic patienst. *Diabetes Res* 1988; 7: 79-84.

Rönnemaa T, Ilanne-Parikka P. Insuliinivalmisteiden kehitys [The development of insulin preparations]. 2015. In Ilanne-Parikka P, Rönnemaa T, Saha M-T, Sane T (Eds.), *Diabetes.* 8th ed., pp. 239-40. Helsinki, Finland. Kustannus Oy Duodecim and Finnish Diabetes Association. (In Finnish)

Rönnemaa T, Viikari J. Reducing snacks when switching from conventional soluble to lispro insulin treatment: effects on glycaemic control and hypoglycaemia. *Diabet Med* 1998; 15: 601-7.

Sacks D, John W. Interpretation of hemoglobin A1c values. *JAMA* 2014;311: 2271–2.

Salinari S, Bertuzzi A, Asnaghi S, Guideone C, Manco M, Mingrone G. First-phase insulin secretion restoration and differential response to glucose load depending on the route of administration in type 2 diabetic subjects after bariatric surgery. *Diabetes Care* 2009; 32: 375-80.

Saraheimo M, Sane T. Diabeteksen alamuodot [Subtypes of diabetes.]. 2015. In Ilanne-Parikka P, Rönnemaa T, Saha M-T, Sane, T. (Eds.), *Diabetes.* 8th ed., pp. 14-15. Helsinki, Finland. Kustannus Oy Duodecim and Finnish Diabetes Association. (In Finnish)

Saris W, Blair S, van Baak M, Eaton S, Davies P, Di Pietro L et al. How much physical activity is enough to prevent unhealthy weight gain? Outcome of the IASO 1st stock conference and consensus statement. *Obes Rev 2003; 4*: 101–14.

Schauer P, Bhatt D, Kirwan J, Wolski K, Brethauer S, Navaneethan S et al. Bariatric surgery versus intensive medical therapy for diabetes — 3-year outcomes. *N Engl J Med* 2014; 370: 2002–13.

Schmid-Antomarchi H, De Weille J, Fosset M, Lazdunski M. The receptor for antidiabetic sulfonylureas controls the activity of the ATP-modulated K+ channel in insulin-secreting cells. *J Biol Chem* 1987; 262: 15840–4.

Schneider D, von Herrath M. Viruses and type 1 diabetes: a dynamic labile equilibrium. *Diabetes Manag* 2013; 3: 217–23.

Schreuder T, Maessen M, Tack C, Thijssen D, Hopman M. Life long physical activity restores metabolic and cardiovascular function in type 2 diabetes. *Eur J Appl Physiol* 2014; 114: 619–27.

Schrier R, Estacio R, Mehler P, Hiatt W. Appropriate blood pressure control in hypertensive and normotensive type 2 diabetes mellitus: a summary of the ABCD trial. *Nat Clin Pract Nephrol* 2007; 3: 428-38.

Schwartz M, Porte D. Diabetes, obesity, and the brain. *Science* 2005; 307: 375–9.

Scott L. Repaglinide a review of its use in type 2 diabetes mellitus. *Drugs* 2012; 72: 249–72.

Seppälä P, Rönnemaa T, Laakso M, Kallio V, Pyörälä K. Aikuisiässä sairastuneiden diabeetikkojen hoitokäytänto KYKS- ja TYKS-piirissä. [The current practice of treating adult-onset diabetic patients in the hospital districts of Kuopio and Turku.] *Suom Lääkäril* 1989; 44: 1416-22. (In Finnish)

Shah P, Vella A, Basu A, Basu R, Schwenk W, Rizza R. Lack of suppression of glucagon contributes to postprandial hyperglycemia in subjects with type 2 diabetes mellitus. *J Clin Endocrinol Metab* 2000; 85: 4053–9.

Shaw R, Lamia K, Vasquez D, Koo S, Bardeesy N, Depinho R et al.The kinase LKB1 mediates glucose homeostasis in liver and therapeutic effects of metformin. *Science* 2005; 9: 1642–6.

Short K, Vittone J, Bigelow M, Proctor D, Rizza R, Coenen-Schimke J et al. Impact of aerobic exercise training on age-related changes in insulin sensitivity and muscle oxidative capacity. *Diabetes* 2003; 52: 1888-96.

Shulman G. Ectopic fat in insulin resistance, dyslipidemia and cardiometabolic disease. *New Engl J Med* 2014; 371: 1131-41.

Sinclair A, Paolisso G, Castro M, Bourdel-Marchasson I, Gadsby R, Rodriguez Mañas L. European diabetes working party for older people 2011 clinical guidelines for type 2 diabetes mellitus. Executive summary. *Diabetes Metab* 2011; 37(Suppl 3): S27–38.

Sjöström L, Lindroos A. Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. *New Engl J Med* 2004; 351: 2683–93.

Sjöström L, Narbro K, Sjöström C, Karason K, Larsson B, Wedel H et al. Effects of bariatric surgery on mortality in Swedish obese subjects. *N Engl J Med* 2007; 357: 741-52.

Skyler J, Bergenstal R, Bonow R, Buse J, Deedwania P, Gale, E et al. Intensive glycemic control and the prevention of cardiovascular events: Implications of the ACCORD, ADVANCE, and VA Diabetes Trials. *J Am Coll Cardiol* 2009; 53: 298-304.

Snel M, Jonker J, Schoones J, Lamb H, de Roos A, Pijl H et al. Ectopic fat and insulin resistance: pathophysiology and effect of diet and lifestyle interventions. *Int J Endocrinol* 2012 Article ID 983814, 18 pages, 2012.

Søeborg T, Hove Rasmussen C, Mosekilde E, Colding-Jørgensen M. Absorption kinetics of insulin after subcutaneous injection. *Eur J Pharm Sci* 2009; 36: 78-90.

Stamler J, Vaccaro O, Neaton J, Wentwoth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the multiple risk factor intervention trial. *Diabetes Care* 1993; 16: 434-44.

Stehouwer M, DeWries J, Lumell J, Ader H, Engbers A, Iberen A et al. Combined bedtime insulin--daytime sulphonylurea regimen compared with two different daily insulin regimens in type 2 diabetes: effects on HbA1c and hypoglycaemia rate - a randomised trial. *Diabetes Metab Res Rev* 2003; 19: 148-52.

Stevens G, Singh G, Lu Y, Danaei G, Lin J, Finucane M et al. National, regional, and global trends in adult overweight and obesity prevalences. *Popul Health Metr* 2012; 10: 22.

Stout, D, Fugate S. Thiazolidinediones for treatment of polycystic ovary syndrome. *Pharmacotherapy* 2005; 25: 244–52.

Strange P. Treat-to-target insulin titration algorithms when initiating long or intermediate acting insulin in type 2 diabetes. *J Diabetes Sci Technol* 2007; 1: 540–8.

Stratton I, Adler A, Neil A, Matthews D, Manley S, Cull C et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): a prospective observational study *BMJ* 2000; 321: 405-12.

Stringhini S, Batty G, Bovet P, Shipley M, Marmot M, Kumari M et al. Association of lifecourse socioeconomic status with chronic inflammation and type 2 diabetes risk: the Whitehall II prospective cohort study. *PLoS Medicine* 2013; 10: e1001479.

Strowig, S, Raskin P. Combination therapy using metformin or thiazolidinediones and insulin in the treatment of diabetes mellitus. *Diabetes Obes Metab* 2005; 7: 633–41.

Stumvoll M. Thiazolidinediones -- some recent developments. *Expert Opin Invest Drugs* 2003; 12: 1179–87.

Sugerman H, Wolfe L, Sica D, Clore J. Diabetes and hypertension in severe obesity and effects of gastric bypass-induced weight loss. *Ann Surg* 2003; 237: 751–6.

Suh S, Paik I, Jacobs. Regulation of blood glucose homeostasis during prolonged exercise. *Mol Cells* 2007; 23: 272–9.

Sullivan P, Morrato E, Ghuschyan V, Wyatt H, Hill J. Obesity, inactivity, and the prevalence of diabetes and diabetes-related cardiovascular comorbidities in the U.S., 2000–2002. *Diabetes Care* 2005; 28: 1599-603.

Sund R, Koski S. On the register-based measurement of the prevalence and incidence of diabetes and its long-term complications. *Finnish Diabetes Association* 2009; Tampere, Finland, pp. 1–21.

Suomen Diabetesliitto [Finnish Diabetes Association]. Diabeteksen historia [History of diabetes]. Accessed

29.10.2014. http://www.diabetes.fi/diabetestietoa/yleista_diabeteksesta/diabeteksen_historia. (In Finnish)

Suomen lääketilasto - Finnish Statistics on Medicines 2012. *Fimea Finnish Medicines Agency and Kela Social Insurance Institution* 2012, Helsinki, Finland, pp. 1-326. (In Finnish)

Syvänne M, Taskinen M-R. Lipids and lipoproteins as coronary risk factors in non-insulin-dependent diabetes mellitus. *Lancet* 1997; 350 (Suppl. 1): 20-3.

Taylor R. Type 2 diabetes; etiology and reversibility (review article). *Diabetes Care* 2013; 36: 1047–55.

Taylor R, Davies R, Fox C, Sampson M, Weaver J, Wood L. Appropriate insulin regimes for type 2 diabetes: a multicenter randomized crossover study. *Diabetes Care* 2000; 23: 1612-8.

Tertti K, Ekblad U, Koskinen P, Vahlberg T, Rönnemaa T. Metformin vs. insulin in gestational diabetes. A randomized study characterizing metformin patients needing additional insulin. *Diabetes Obes Metab* 2013; 15: 246-51.

Teuscher A. The history of insulin. In *Insulin - A Voice for Choice* 2007; Karger AG, Basel, Switzerland, pp. 10–13.

The ACCORD Study Group Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008; 368: 2545–59.

The DCCT Research Group. Weight gain associated with intensive therapy in the diabetes control and complications trial. *Diabetes Care* 1988; 11: 567–73.

The DECODE Study Group. Glucose tolerance and mortality: comparison of WHO and American Diabetic Association diagnostic criteria. *Lancet* 1999; 354: 617–21.

The Diabetes Prevention Program (DPP) Research Group. The Diabetes Prevention Program (DPP). *Diabetes Care* 2002, 25: 2165–71.

Thornberry N, Gallwitz B. Mechanism of action of inhibitors of dipeptidyl-peptidase-4 (DPP-4). *Best Pract Res Clinl Endocrinol Metab* 2009; 23: 479–86.

Thunander M, Törn C, Petersson C, Ossiansson B, Fornander J, Landin-Olsson M.Levels of C-peptide, body mass index and age, and their usefulness in classification of diabetes in relation to autoimmunity, in adults with newly diagnosed diabetes in Kronoberg, Sweden. *Eur J Endocrinol* 2012; 166: 1021–9.

Tonstad S. Cigarette smoking, smoking cessation and diabetes. *Diabetes Res Clin Pract* 2009; 85: 4-13.

Tuomilehto J, Lindström J, Eriksson J, Valle T, Hämäläinen H. Prevention of tyoe 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *New Engl J Med* 2001; 344: 1343–50.

UK Prospective Diabetes Study (UKPDS) Group. Overview of 6 years' therapy of type II diabetes: a progressive disease (UKPDS 16). *Diabetes* 1998; 44: 1249–58.

UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998; 352: 837–53.

UK Prospective Diabetes Study (UKPDS) Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes (UKPDS 38). *BMJ 1*998; 317: 703–13.

U.S. Department of Health and Human Services. Health, United States 2012. *DHHS Publication No. 2013-1232* 2013; pp. 1-489.

Uusitupa M, Groop L, Nissén M, Salo S, Taskinen M-R. Aikuistyypin diabeteksen hoitosuositus. [Recommendation for therapy of maturity onset diabetes]. *Finnish Diabetes Association* 1994; Tampere, Finland pp. 1-55. (In Finnish)

Wake N, Hisashige A, Katayama T, Kishikawa H, Ohkubo Y, Sakai M et al. Cost-effectiveness of intensive insulin therapy for type 2 diabetes: a 10-year follow-up of the Kumamoto study. *Diabetes Res Clin Pract 2000*; *48*: 201–10.

Valle T and working group. Diabeetikkojen hoitotasapaino Suomessa vuosina 2009-2010 [The metabolic control of diabetic patients in Finland in the years 2009-2010]. *Finnish Diabetes Association* 2010; Tampere, Finland pp. 1-18.

Valle T, Koivisto V, Reunanen A, Kangas T, Rissanen A. Glycemic control in patients with diabetes in Finland. *Diabetes Care* 1999; 22: 575-9.

Valle T, Reunanen A, Koivisto V, Kangas T, Rissanen A. Suomalaisen diabeetikon hoitotasapaino [The metabolic control of Finnish diabetic patients]. *Duodecim* 1997; 113: 1903-09. (in Finnish)

Walter Y, Spratt D, Garreffa S, McLeod J. Mealtime glucose regulation by nateglinide in type-2 diabetes mellitus. *Eur J Clin Pharmacol* 2000; 56: 129–33.

Vauhkonen I, Niskanen L, Vanninen E, Kainulainen S, Uusitupa M, Laakso M. Defects in insulin secretion and insulin action in non-insulin-dependent diabetes mellitus are inherited. Metabolic studies on offspring of diabetic probands. *J Clin Invest* 1998; 101: 86–96.

Vepsäläinen, T. Factors predicting mortality in type 2 diabetes with special reference to physical exercise, blood pressure, proteinuria, inflammation and p wave duration. *Annales Universitatis Turkuensis* 2013, Turku, Finland (pp. 1–84).

Vessby B, Uusitupa M, Hermansen K, Riccardi G, Rivellese A, Tapsell L et al. Substituting dietary saturated for monounsaturated fat impairs insulin

sensitivity in healthy men and women: The KANWU Study. *Diabetologia* 2001; 44: 312-9.

WHO. Diabetes mellitus. Report of a WHO expert committee. *World Health Organization Technical Report Series* 1965; Geneva, Switzerland, pp. 1-44.

WHO. Expert committee on diabetes mellitus. Second report. *World Health Organization Technical Report Series* 1980; 646. Geneva, Switzerland, pp 1-80.

WHO. Diabetes mellitus. Report of a WHO study group. *World Health Organization Technical Report Series* 1985; 727. Geneva, Switzerland, pp 1-113.

WHO. Management of diabetes mellitus. Standards of care and clinical practice guidelines. *WHO-EM/DIN6/E/G* 1994. Alexandria, Egypt, pp 1-35.

WHO. Use of glycated haemoglobin (HbA1c) in the diagnosis of diabetes mellitus. Abbreviated report of a WHO consultation. *WHO* 2011; pp. 1–25.

Willms B, Werner J, Juul Hiolst J, Ørskov C, Creutzfeldt W, Nauck M. Gastric emptying, glucose responses, and insulin secretion after a liquid test meal: effects of exogenous glucagon-like peptide-1. *J Clin Endocrinol Metab* 1996; 81: 327–32.

Vilsbøll T, Christensen, M, Junker A, Knop F, Gluud L. Effects of glucagon-like peptide-1 receptor agonists on weight loss: systematic review and meta-analyses. *BMJ* 2012; 344: 1–11.

Vilsbøll T, Rosenstock J, Yki-Järvinen H, Cefalu W, Chen Y, Luo E. et al. Efficacy and safety of sitagliptin when added to insulin therapy in patients with Type 2 Diabetes. *Diabetes Obes Metab* 2010; 12: 167–77.

Virtanen S, Aro E, Keskinen P, Lindström J, Rautavirta M, Ventola A-L et al. Diabeetikon ruokavaliosuositus 2008. [Dietary recommendations for diabetic patients]. *Finnish Diabetes Association* 2008; Finland, pp. 1-24. (in Finnish)

Wolffenbuttel B, Sels J, Rondas-Colbers G, Menheere P, Nieuwenhuijzen-Kruseman A. Comparison of different insulin regimens in elderly patients with NIDDM. *Diabetes Care* 1996; 19: 1326-32.

Wood I, Trayhurn P. Glucose transporters (GLUT and SGLT): expanded families of sugar transport proteins. *Br J Nutr* 2003; 89: 3–9.

Vora J. Combining incretin-based therapies with insulin. *Diabetes Care* 2013; 36 (Suppl. 2): S226-32.

Wu M, Johnston P, Sheu W, Hollenbeck C, Jeng C, Goldfine I et al. Effect of metformin on carbohydrate and lipoprotein metabolism in NIDDM patients. *Diabetes Care* 1990; 13: 1–8.

Xie X, Liu Q, Wu J, Wakui M. Impact of cigarette smoking in type 2 diabetes development. *Acta Pharmacol Sin* 2009; 30: 784-7.

Yale J-F. Oral antihyperglycemic agents and renal disease: new agents, new concepts. *J Am Soc Nephrol 2005; 16*(Suppl 1): S7–S10.

Yki-Järvinen, H. Insulin therapy in type 2 diabetes: role of the long-acting insulin glargine analogueue. *Eur J Clin Invest* 2004; 34: 410–16.

Yki-Järvinen, H. Thiazolidinediones (review article). *N Engl J Med* 2004; 351: 1106–18.

Yki-Järvinen H, Dressler A, Ziemen M. Less nocturnal hypoglycemia and better post-dinner glucose control with bedtime NPH insulin during insulin combination therapy in type 2 diabetes. *Diabetes Care* 2000; 23: 1130-6.

Yki-Järvinen H, Juurinen L, Alvarsson M, Bystedt T, Caldwell I, Davies M et al. Initiate Insulin by Aggressive Titration and Education (INITIATE): a randomized study to compare initiation of insulin combination therapy in type 2 diabetic patients individually and in groups. *Diabetes Care* 2007; 30: 1374-9.

Yki-Järvinen H, Kauppila M, Kujansuu E, Lahti J, Marjanen T., Niskanen L et al. Comparison of insulin regimens in patients with non-insulindependent diabetes mellitus. *N Engl J Med* 1992; 327: 1426-33.

Yki-Järvinen H, Kauppinen-Mäkelin R, Tiikkainen M, Vähätalo M, Virtamo H, Nikkilä K et al. Insulin glargine or NPH combined with metformin in type 2 diabetes: the LANMET study. *Diabetologia* 2006, 49: 442–51.

Yki-Järvinen H, Ryysy L, Nikkilä K, Tulokas T, Vanamo R, Heikkilä M. Comparison of bedtime insulin regimens in patients with type 2 diabetes mellitus. *Ann Intern Med* 1999; 130: 389-96.

Yoon N, Cavaghan M, Brunelle R, Roach P. Exenatide added to insulin therapy: a retrospective review of clinical practice over two years in an academic endocrinology outpatient setting. *Clin Ther* 2009; 31: 1511-23.

Zoungas S, Patel A, Chalmers J, de Galan B, Li Q, Billot L et al. Severe hypoglycemia and risks of vascular events and death. *N Engl J Med* 2010; 363: 1410–8.

Åkerblom H, Vaarala O, Hyöty H, Ilonen J, Knip M. Environmental factors in the etiology of type 1 diabetes. *Am J Med Genet* 2002; 115: 18–29.