Diabetes Care in Community Pharmacy

- Focus on Self-monitoring of Blood Glucose

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In loving memory of my parents Karin Skeide Kjome and Michael Hugh Kjome

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List of papers

I. Kjome, RLS, Sandberg, S and Granas, AG. Diabetes care in Norwegian pharmacies: a descriptive study. Pharm World Sci 2008 30:191-198. DOI 10.1007/s11096-007-9164-5

II. Kjome, RLS, Nerhus, K and Sandberg, S. Implementation of a method for glucose measurements in community pharmacies. Int J Pharm Pract 2010;18(1):13-19. DOI 10.1211/ijpp/18.01.0004

III. Kjome, RLS, Granas, AG, Nerhus, K and Sandberg, S. Quality assessment of patients' self-monitoring of blood glucose in community pharmacies. Pharmacy Practice (internet) 2010; 8(1):62-69.

IV. Kjome, RLS, Granas, AG, Nerhus, K, Roraas, TH and Sandberg, S. The prevalence of self-monitoring of blood glucose and costs of glucometer strips in a nationwide cohort. Submitted to Diabetes Technol Ther March 2010, revision submitted April 2010.

Abstract

Diabetes is a growing concern world wide. Ideal management of the disease requires extensive self-care and broad follow-up by health care professionals. Considerable research has been done on involving the pharmacist in the healthcare of patients with diabetes, arguing that community pharmacists' high availability to patients and specialized medication-focused education makes them a valuable asset to the diabetes team.

This thesis consists of four papers. The work for these papers was performed from 2004 to 2009. Paper I gives an overview over diabetes care provided by Norwegian pharmacies. It is based on a descriptive study where all Norwegian pharmacies were invited to participate by filling out an online questionnaire. We found that most pharmacists were interested in working diabetes services. Some pharmacies offered diabetes patients a wide range of services, but quality control of these services was seldom established. Almost all pharmacies offered practical services related to self-monitoring of blood glucose (SMBG), while giving advice on diet and other lifestyle factors was rarely done. The pharmacists were motivated to work within diabetes care, in particular SMBG. In Paper II we demonstrate how one can assure the quality of a point-of-care test (POCT) at the community pharmacy, in our case a blood glucose test, and show that when given the correct follow-up the pharmacies are able to match the quality of the results achieved at general practitioners' offices. In Paper III we tested a new pharmacy service, where patients brought their own glucometers to the pharmacies where the glucose method was established. Patients had both their performance and their glucometer tested against the pharmacy method. We found that this reduced the number of user errors. It had no effect on the analytical quality of the patients' SMBG results, which was good throughout the study. The patients' trust in their own measurements

increased after their visit to the pharmacy, and the patients expressed a wish for annual pharmacy controls.

In Paper IV we report the sales of SMBG strips to all non-institutionalized patients in Norway in 2008. We found that 96 999 different patients purchased strips that year. This gave a prevalence of 2 % in the Norwegian population, and approximately 70 % among patients being treated pharmacologically for their diabetes. The mean number of strips per day was 1.7, however 53 % of the patients did not purchase enough strips to monitor their blood glucose daily. The one percent of the patients who bought the most strips was responsible for 8 % of the costs. Most patients used only one brand of glucometer, though three percent purchased from 3-7 different types of strips. Use of strips increased with number of different types of strips.

The sum of this work suggests that Norwegian pharmacies can be more actively used in assisting diabetes patients with their SMBG. The employees are motivated, and already involved at a smaller scale. Given correct training and follow-up they are capable of performing services involving POCT of good analytical quality, and patients are happy to receive this type of service from their community pharmacy. A small number of patients use a disproportionate amount of resources spent on SMBG, while a large number of patients rarely perform SMBG, giving room for improvement in the way resources are being spent. Several challenges remain: reaching the patients most in need of SMBG assistance, attaining access for pharmacies to the quality control support from the Norwegian Quality Improvement of Primary Care Laboratories (NOKLUS), and ensuring remuneration for the service.

Abbreviations

ADA	The American Diabetes Association
DRP	Drug related problem
EGA	Error grid analysis
EQAS	External quality assessment scheme
GDH	Glucose dehydrogenase
GOD	Glucose oxidase
GP	General Practitioner
HbA1c	Glycated hemoglobin
HELFO	The Norwegian Health Economics Administration
IDA	The Interest Group Diabetes in the Pharmacy
NAF	The Norwegian Pharmacy Association
NAV	The National Social Insurance Scheme
NDA	The Norwegian Diabetes Association
NHS	The National Health Service
NOKLUS	Norwegian Quality Improvement of Primary Care Laboratories
NorPD	The Norwegian Prescription database
NSD	The Norwegian Social Science Data Service

OTC	Over-the-counter, non-prescription drugs
POCT	Point of care test
REK	The Regional Ethics Committee
SMBG	Self-monitoring of blood glucose
SPSS	Statistical Package for Social Sciences

Background

Diabetes Mellitus is a disorder of the carbohydrate metabolism, caused by a combination of hereditary and environmental factors and characterized by hyperglycaemia resulting from inadequate secretion and/or utilisation of insulin. The chronic hyperglycaemia of diabetes leads to long term microvascular complications in the form of retinopathy, nephropathy and neuropathy as well as a heightened risk for the macrovascular diseases myocardial infarction, stroke and angina.[1;2] The two main forms of diabetes mellitus are type 1 diabetes, characterized by β-cell destruction leading to total insulin deficiency, and type 2 diabetes, defined by insulin resistance and a relative insulin deficiency. The World Health Organization (WHO) estimates that more than 220 million people worldwide have diabetes[3], 90 % of these have type 2 diabetes.[3] Due to the world wide increase in the proportion of people > 65 years of age combined with a rise in other risk factors such as obesity and sedentary lifestyle this figure is growing fast,[4;5] and is likely to more than double by 2030.[3;5] The Norwegian Diabetes Association (NDA) estimates that 375,000 people, 7.7 % of the population, have diabetes in Norway, and that approximately half of them have yet to be diagnosed.[6] This concurs well with the numbers from the Norwegian national prescription database (NorPD), that registered 131,922 people collecting at least one prescription for antidiabetics during 2007, corresponding to a diagnosed diabetes prevalence of 2.8 %.[7] This number does not include patients with type 2 diabetes treated with diet only. Diabetes mellitus can now be considered a pandemic, and the human and economic costs of the disease will continue to rise.[3]

Management of diabetes

Due to the many possible complications and co-morbidities of diabetes and the complexity of the disease itself, establishing and maintaining an optimal treatment is challenging for both the patients and for the healthcare professionals helping them. Strict glycemic control, aimed at maintaining blood glucose concentrations close to the normal range (preprandial capillary plasma glucose 3.9 – 7.2 mmol/L and postprandial plasma glucose <10 mmol/L[8]) has been considered the optimal treatment goal for patients with both type 1 and type 2 diabetes since the American Diabetes Control and Complications Trial (DCCT, 1993)[9] and the UK Prospective Diabetes Study (UKPDS, 1998)[10-12] showed that this reduces both microvascular and macrovascular complications of diabetes.[9-13] With the exception of the recently published ACCORD study that reported an increased mortality in patients in intensive therapy to target normal glycated haemoglobin levels,[14] later studies have confirmed the benefit of strict glycemic control.[13;15-17] In addition it is recognized that strict blood pressure control and cholesterol lowering treatment with statins reduces microvascular endpoints and diabetes related deaths in patients with type 2 diabetes.[18-20] As a result diabetes patients are often prescribed a long list of drugs, which may introduce new challenges such as drug interactions, adverse effects, contraindications and adherence-issues.[21-25] To avoid serious long-term complications such as blindness and amputations regular controls of eyes and feet are recommended, adding to the management burden of patients and healthcare professionals. Investigating the best way to manage diabetes care has been the focus of many studies. The Cochrane group did a review on this topic in 2000 concluding that "multifaceted professional interventions can enhance the performance of health professionals in managing patients with diabetes".[26] Considering the complex nature of insulin treatment and the complex drug regime of many type 2 diabetes patients, pharmacists, with their specialist knowledge on drugs and drug usage, could be a valuable member of such a multidisciplinary team.[27-30]

Self-monitoring of blood glucose (SMBG)

History and recommendations

As early as 1776 the physician Mathew Dobson documented that both urine and blood from a patient with diabetes contained sugar, and in 1815 the French chemist Chevreul demonstrated that the exact compound was glucose. After this clinical tests for glucose emerged alongside physiological studies, and in 1890 researchers found that removing the pancreas resulted in diabetes. While the early tests for glucose in blood required large volumes, micromethods soon evolved.[31] Self-sampling for blood glucose determination was introduced by Keen and Knight in 1962,[32] a colorimetric method where the sample was obtained by the patient at home, but the analysis was performed at a laboratory. Soon after, in 1964, a method using an enzyme test strip was presented.[33] The first studies to establish the use of self-monitoring of blood glucose (SMBG) and show an effect on glycemic control was published in 1978, when two studies, published in the same volume of Lancet, described the results of 69 and 64 patients respectively, using two different instruments for self-monitoring.[34;35] That SMBG could improve and maintain glycemic control without increasing the frequency of hypoglycaemia lead to the implementation of SMBG in routine care.[31] The role of SMBG in the treatment of diabetes is still widely debated, as it has proved difficult to isolate and measure its effects.[36-44] Monitoring alone does not affect clinical endpoints; improved health outcomes rely on the patients adjusting therapy, diet or exercise based on the results they obtain.[45] While there is a general consensus that SMBG should be used by patients treated with insulin[46] who risk hypoglycaemic incidents and can use their blood glucose results to regulate their treatment,[47;48] there is disagreement on its place in the treatment of patients with type 2 diabetes not being treated with insulin.[39;42;45;49-54] Still, many guidelines recommend the use of SMBG to all diabetes patients as useful in achieving glycemic goals.[8;55-57]

Technology and chemistry of SMBG

The current glucometers are two- part systems, consisting of the meter itself and a test strip. The glucometer is a biosensor, where the enzyme-containing single-use test strip is the biological recognition element where the blood sample is applied and the reaction takes place. The meter itself is the physico-chemical transducer, and is either an electrochemical or an optical device that "reads" the strip and converts its signal to a digital value, which is then shown in a display (see Figure 1).

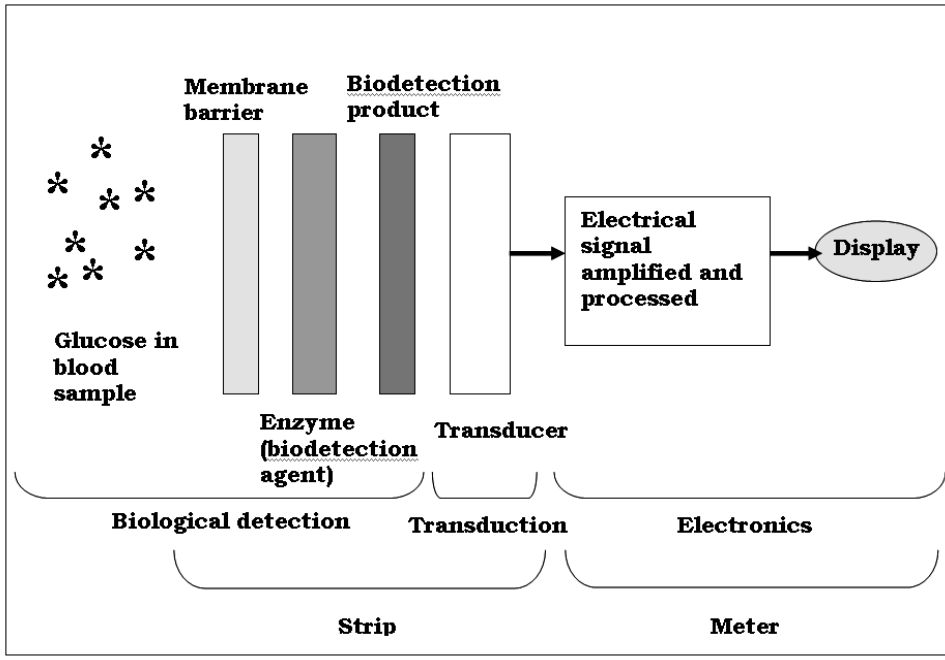

Figure 1. Schematic overview of a glucometer and strip (biosensor). Glucose in the blood sample diffuses through the membrane barrier and reacts with enzymes imbedded in the test strips. The resulting electrons (the biodetection agent) are "read" by the transducer that converts the information into a quantifiable electrical signal. The signal is then displayed in a conventional format (such as mmol/L). (Figure adopted from Rosen[58]).

Biosensors are simple to use devices that do not require sample preparation but can be used directly on native test material, in this instance whole blood. The strips rely on enzymatic processes were glucose is oxidized, and the resulting electrons used to reduce a mediator molecule, typically a small organic or inorganic compound capable of existing in both a reduced and an oxidized form. The mediator molecule then delivers the electrons to either an electrode (in an electrochemical method) or to an indicator molecule that forms colour and can be read by a photometer.[58-60]

Different systems use different oxidoreductases to oxidize glucose. The most common are glucose oxidase (GOD) and different types of glucose dehydrogenase (GDH). All enzymes use coenzymes such as flavin adenine dinucleotide, pyrrolo quinoline quinine or nicotinamide adenine dinuclotide, and some processes may also rely on additional enzymes such as peroxidase where the overall reaction involves intermediate steps. The method used in many laboratories, a combination of hexokinase and glucose-6-phosphate dehydrogenase, is not used in current test strips.[61]

Accuracy and precision of SMBG

Accuracy is defined as "closeness of agreement between a measured quantity value and a true quantity value of a measurand."[62] The term "accuracy", when applied to a set of test results, involves a combination of random error components and a common systematic error or bias component.[63] If one measures the closeness of agreement between the average value obtained from a large series of test results and an accepted reference value, thereby eliminating the contribution of random error, the term used is *trueness*.[62] Trueness is usually expressed in terms of its inverse, *bias*.[63] Bias is caused by systematic error, for example wrong calibration, wrong storage of reagents, and lack of user education.[64] *Precision* of measurement is "closeness of agreement between (…) measured quantity values obtained by replicate

measurements on the same or similar objects under specified conditions. The degree of precision is expressed numerically by the statistical measures of imprecision of measurements, such as standard deviation and coefficient of variation, that are inversely related to precision".[62;63] Imprecision is the result of random error, such as varying quality of the equipment, varying measurement technique (test preparation, timing), or lack of user education.[64] Figure 2 shows the relationships between the different types of error, qualitative performance characteristics and their quantitative expression.[65]

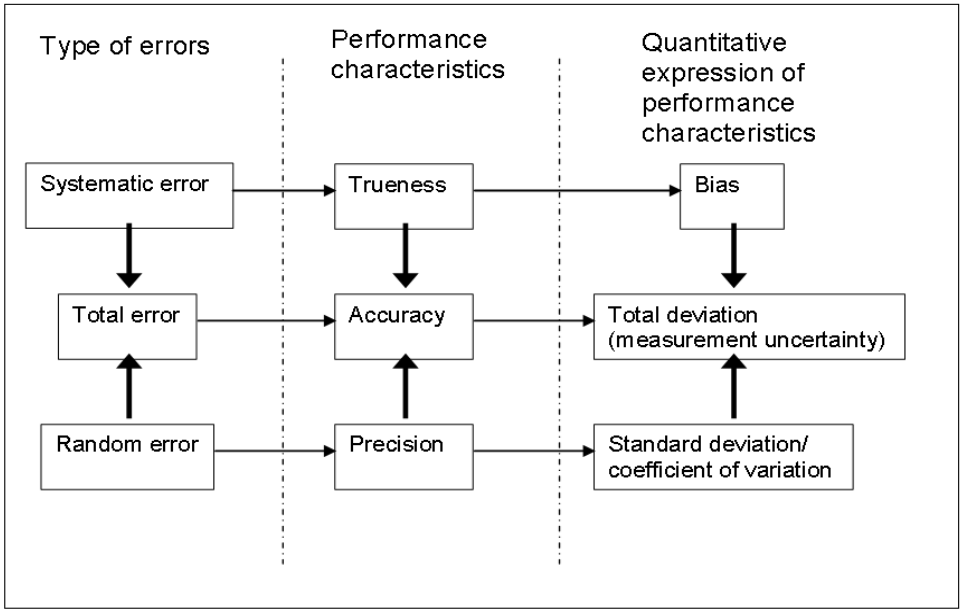

Figure 2. Relationships between types of error, qualitative performance characteristics and their quantitative expression. (Figure adopted from Menditto[65]).

There is no standardized approach for evaluating the analytical performance of SMBG instruments, though several professional recommendations exist.[55;63;66;67] Two commonly used quality specifications for SMBG devices are the Clarke error grid analysis (EGA), published by Clarke et al in 1987,[68] and ISO 15197, published by the International Organization for Standardization.[63] The EGA is used to assess the clinical significance of

differences between the glucometer in question and a reference measurement, often described as the glucometers clinical accuracy,[68] though actually it describes potential consequence of the patient's actions based on his results.[69] Measurements of the glucometer in question are compared to a reference value, by plotting the results of each measurement into different zones drawn on the grid (Figure 3).

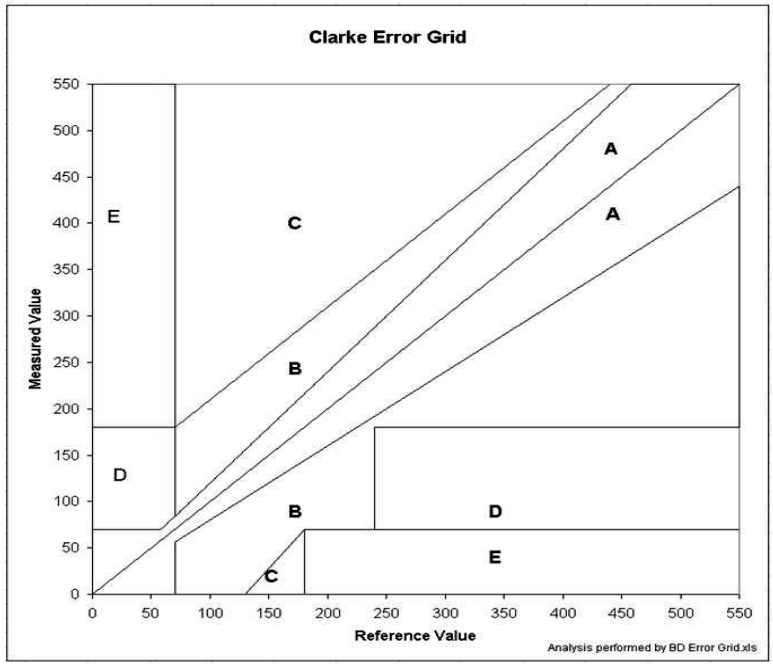

Figure 3. The Clarke Error Grid. Region A are values within 20% of the reference sensor, Region B contains points that are outside of 20% but would not lead to inappropriate treatment, Region C are points leading to unnecessary treatment, Region D are points indicating a potentially dangerous failure to detect hypo- or hyperglycemia, and Region E are points that would confuse treatment of hypoglycemia for hyperglycemia and vice-versa. (Clarke[68]).

The grid breaks down a scatterplot of a reference method and an evaluated glucometer into five regions. Critics of the method have claimed that the grid has "arbitrary" regions that should be updated,[69;70] (and this has been done by Parkes in the Parkes Error Grid, also known as the Consensus Error Grid or the Becton Dickinson (BD) Error Grid [70]) and that it is not precise enough due to the use of broad regions.[69] Both critics and authors agree that the grid should not be used alone, but rather as an addition to other statistical methods of assessing accuracy.[69;71]

ISO 15197, the specification used in this thesis, states that 95 % of the individual glucose results shall fall within ± 0.83 mmol/L of the results of a reference glucose method at glucose concentrations < 4.2 mmol/L and within ± 20 % at glucose concentrations ≥ 4.2 mmol/L.[63] While this standard dictates a procedure for quality evaluation for manufacturers, there are no standard procedures for how to perform quality control of SMBG devices that are in use by patients.[72] To obtain realistic measures of accuracy and precision it is important to test devices in the hands of the patients[8;72] as these results may often differ from results of measurements performed by professionals.[73;74] We know very little about the accuracy of measurements performed by patients in daily life, and throughout the lifetime of the device.[72] Control material, a "specimen, or solution, which is analyzed solely for quality control purposes",[75] is sold by many manufacturers to be used with their instruments, though few patients use this regularly.[73] However it is important to be aware of the limitations of control material. The material does not come with a "true value", but rather a glucose interval that the result should lie within. This means that the control material may be suited for an internal control of instrument precision; however it does not give an accurate representation of the instruments trueness. An additional problem is that instrument performance using control material is not necessarily transferrable to the performance of the instrument when measuring blood.[76-78]

External quality assessment (EQA) can be used to evaluate the quality of glucose measurements, both those performed by health personnel and SMBG performed by patients. In an EQA the patient or professional receives control material, preferably of the same origin as patient samples, analyses it and returns the result to the EQA agency. As SMBG and POCT devices for glucose utilize whole blood, this is the preferred control material. However in such a sample ongoing glycolysis will reduce the glucose concentration by 5-7 % per hour at room temperature, and as EQA material is not analysed immediately, the control material must be stabilized. As the preservatives added to the sample may affect different instruments in different ways, a method specific target value is assigned to the control material based on a median of all participants using a certain instrument. Each participant is then given feedback on how they performed compared to the target value and other participants; however this means that only relative trueness, the deviation from the method specific target value, is assessed.

Another method for quality control of SMBG is using a split sample design[79-82] where the patients' performance is monitored and the results are compared to a "true value" ideally obtained by a "reference method". This method has advantages compared to conventional EQA since the patients' performances can be observed and it is therefore possible to detect user errors. Also, the use of native blood makes it possible to compare the performance of different instruments.

Many patients, and perhaps also health professionals, are not aware that the digital number provided by their glucometer might not be the exact value.[72] However knowledge of the uncertainty imbedded in the value, e.g. that a displayed value of 4 mmol/L may in fact imply a true result lying between 3.2 and 4.8 mmol/L, is important in order to achieve a realistic understanding of SMBG and its uses.

Sources of error of SMBG

User error

Among patients and healthcare workers alike many may consider SMBG a mundane task; however there are many steps that must be performed correctly in order to obtain a reliable result. These are sequential in nature, meaning that each step is reliant on the success of the previous step. When investigating the user-friendliness of a SMBG system that advertised that it "measured blood glucose in three easy steps", Rogers et al identified 52 sub-steps that the user must perform, from the set up of the meter (6 steps) and checking the system (22 steps), to testing of blood glucose (24 steps).[83] Manufacturers strive to make devices increasingly user-friendly through eliminating the necessity of manual coding, reducing the required amount of blood and outfitting the devices with alarms that warn the user of under-filled strips. Still user error is among the most common reasons for faulty results.[72;73;84] In an evaluation of 9 different SMBG instruments 2 % to 34 % of patients (depending on the instrument) responded that they had technical difficulties with the instrument.[85]

Müller et al[86] classifies potential errors in 5 categories according to their potential effect on the patient or the results of the measurement (Table 1). Table 2 shows a list of possible sources of user error categorized in Müller's 5 error codes.[86] Not all user errors will necessarily lead to erroneous results, but may instead make it difficult to utilize the results optimally (for example not saving/documenting the results of a measurement), or may lead to a more painful measurement for the patient, thereby lessening compliance (for example not changing the lancet with every measurement). Assessing user technique is therefore important also when the analytical quality of the measurement seems satisfactory.

Table 1. Classification of potential errors in conducting blood glucose tests. (Müller et al.[86])

Error Code	Error Category	Evaluation
F1	Errors that make a reading useless (due to the error, it is not possible to anticipate whether the measured blood glucose level is higher or lower than the true value and how great the deviation is).	If only one of these errors is made, the result cannot be interpreted. The test must be repeated (correctly).
F2	Errors that can lead to a false reading (or a false interpretation) in individual cases.	The significance is dependent on the exact situation or the consequence that is drawn.
F3	Errors that can have a negative effect on compliance.	These errors have no impact on the measuring results, but possibly affect the willingness of the patient to perform the self-monitoring.[72]
F4	Errors that can make conducting the test more difficult or prevent it entirely (device components).	Either the handling is unsatisfactory or the functionality is impaired.
F5	Errors which make a consequential action / interpretation (by the patient, doctor, or pharmacist) more difficult.	Readings not available for evaluation over the middle term.

Table 2. **Potential sources of user-error. (Müller et al.[86])**

	Potential sources of error	**Error code**
Blood sampling	Cleaning hands	F1
	Drying hands	F1
	Inserting/changing lancets	F3
	Adjusting the prick depth	F3
	Stimulating circulation (if needed)	F3
	Pricking of finger pad	F3
	Squeezing out the blood	F1
Strips	Storage of strips	F1
	Expiration date of strips	F1
	Use of the correct strips	F1
Glucometer	Cleanliness of device and measuring cell	F2
	Settings (date, time)	F5
	Choice of unit (mmol/L, mg/dL)	F2
	Coding the device when changing to a new lot of strips (newer systems often do not require manual coding)	F1
Measurement	Inserting the test strip/the disk	F4
	Applying the sample	F2
	Quantity of applied blood	F2
	Changing between different devices	
Other	Saving/documenting the results	F5
	Check with glucose control material	F1

Specificity of test strip enzymes

High specificity in enzyme activity, i.e. that the enzyme prefers glucose as a substrate and is not affected by the presence of other molecules, is a good prerequisite for its use in test strips. However none of the enzymes used are completely specific for glucose, and high concentrations of enzyme in the formula can make low side effects a real interference.[59] As an example, the different forms of GDH are affected by maltose, mannose, galactose, lactose, or xylose in varying degrees. Most people do not have these sugars in their blood, however some drugs and rare diseases can lead to maltose, galactose or xylose being present, and if these patients use a GDH system they risk falsely high readings. A tragic example of this is reported by Kroll and Maher.[87] Their case report describes a patient with insulin dependant type 2 diabetes, who is admitted to the hospital for a thyroidectomy and who dies from hypoglycaemia due to falsely high glucose readings by a SMBG device used at the hospital. The patient was in treatment for end stage renal disease by continuous ambulatory peritoneal dialysis, and the dialysate used for this, isodextrin, is hydrolysed to maltose, thus leading to the high measurements and the wrongful administration of insulin to an already hypoglycaemic patient.[87] Researchers in an American hospital found substances that interfere with GDH based glucometers in 1.2% of patients admitted over a 12 month period. Thirty six percent of those patients had an active order for an insulin product during the interference time interval, which means that they were dependant on SMBG measurements.[88] To use a method based on GOD might seem the better choice, because while it is affected by mannose as well as 2- and 6-deoxyglucoses, neither of these are present in today's medications. However, GOD's natural second substrate is oxygen, which it reduces to hydrogen peroxide, and thus oxygen content of the sample may affect the result both in systems using oxygen as a mediator and those where another mediator is used.[59] As it influences oxygen content, altitude can affect results.[89] Other reducing substances may also interfere with the measurement such

as bilirubin, uric acid, ascorbic acid, paracetamol or dopamine.[59;90] With the exception of paracetamol, these interferences are found when the plasma concentrations are well above the therapeutic level,[90] however many diabetes patients develop renal impairment and failure, leading to unusually high plasma levels of drugs. Using mediators with low redox potentials reduces cross reactivity with other molecules and allows the measurement electrode to operate at a lower applied voltage which will reduce the interference and inaccuracy of electrochemical sensors.[59]

Enzyme activity is sensitive to temperature, as is the diffusion process and therefore most meters contain a temperature sensor and adjust the results accordingly. Still many meters are sensitive to differences in temperature between meter and strips.[59;85]

Hematocrit

Earlier it was common that glucometers were calibrated to convert results to whole blood content, but as most clinical laboratory methods measure in plasma, this led to a great deal of confusion. Following a 2001 recommendation published by the International Federation of Clinical Chemistry that recommended all results being reported as plasma values,[91] today, at least in Europe, most instruments show plasma values.[72] The difference between plasma and whole blood glucose results[85] is the result of plasma containing a higher percentage of water than erythrocytes do (approximately 93 % and 71 %, respectively), and because glucose is soluble in the water phase, there is a higher concentration of glucose in plasma then in whole blood. While SMBG is performed on whole blood, the meters measure the glucose content of the plasma fraction. A membrane in the strip does not allow red blood cells to enter the reagent layer where the enzymes are found (Figure 1). This should have eliminated the hematocrit-error from the results, but this is not always the case.[85;92] While one is not sure of the reason for this, it has been suggested that it is because the blood cells block the pores in

the membrane, or because a high amount of blood cells limits the volume of plasma available. Another reason may be that a high hematocrit may alter blood viscosity and thereby decrease fluid permeability into the reagent layer.[92]

HemoCue Glucose instruments measure the glucose content in whole blood, as a saponin in the cuvettes is used to hemolyze red blood cells so total glucose is determined.[93] This would have reduced the error caused by hematocrit, but HemoCue instruments convert the measured value into corresponding plasma values by means of a fixed factor (1.11 [91]), thereby introducing the hematocrit error in the reported glucose result.

Lot-to-lot variation

Several studies have found that there may be significant lot to lot variation in glucometer test strips.[73;76;85;94] Results varied with as much as 0.8 mmol/L between different lots of the same test strips when measuring capillary blood, and with as much as 1.3 mmol/L when measuring control material, differences that are clinically important at critical decision limits for glucose.[76] Also, between-lot differences present in capillary blood can not necessarily be detected by the use of other control materials, as instruments that show little between-lot variation when using control material may still experience a significant between-lot variation when using capillary blood.[76] It is therefore recommended that "manufacturers should be urged to produce more consistent glucose strips, and commutability studies should be carried out to ensure that control materials give valid results."[76]

Cost of SMBG

Substantial resources are spent on SMBG. It is difficult to find accurate and current worldwide figures, however an estimate from 2004 suggested that the cost was over 5 billion US dollars worldwide, with a yearly growth rate of 11.5 %.[95] The American Diabetes

Association reported that the 2007 cost of diabetic supplies in USA was nearly 2 billion dollars.[96] In 2008 Norwegian pharmacies sold test strips for more than 43 million Euros.[97] In addition there are costs of lancets and of the glucometers themselves. Most glucometers are sold at low cost or given to patients free of charge by the manufacturers. Patients pay approximately 10 % of the total costs of blood glucose strips through a co-payment for each prescription, the remaining 90 % is covered by The Norwegian Social Insurance Scheme.[98;99]

Research on cost-effectiveness[100-107] faces the same problems as all effectiveness studies of SMBG do; namely that the clinical effect of SMBG relies on the patients using their SMBG results to modify treatment approaches or lifestyle.[108] The limited amount of research done in this field mostly indicates that SMBG is cost effective.[100;103-106;109-111] However, as this cost efficiency is based on assumptions of accurate measurements and compliant patients and as research shows this is not the case for many patients, perhaps a percentage of the total costs of SMBG should be directed towards SMBG education and follow-up of patients.[72]

The role of the pharmacist in the care of patients with diabetes

Around the world community and hospital pharmacies are extending their focus from drug production and dispensing to a range of health care services.[112] These include drug based services (e.g. medication reviews, dose adjustment);[113-118] point of care testing (blood pressure, lipids, blood glucose, bone density),[116;119-123] patient education and information services,[114;119] and lifestyle adjustment services (smoking cessation classes, dieting classes)[120;124;125]. Several prescription-only drugs have been reclassified as OTC, such as the morning after pill, allergy medications and anti-obesity drugs, rendering the pharmacy employees with more responsibility for patient information. During the fall of 2009 Norwegian pharmacists were given the right to prescribe influenza A medications following a severe increase of influenza A infections.[126]

The concept of *pharmaceutical care*, introduced by Hepler and Strand in 1990 as a way of addressing the problem of medication related morbidity, is defined as "a patient-centred practice in which the practitioner assumes responsibility for the patient's drug-related needs and is held responsible for this commitment".[127] Today, this model and others like it are being used by thousands of pharmacists across the world.[128] Patients with diabetes are good candidates to receive such care, as diabetes is a disease that requires complex treatment regimes and follow-up, as well as a high degree of commitment from the patient.[25] Studies on drug related problems (DRPs) in patients with type-2 diabetes have found an average number of DRPs from 1.2 (Norway)[129] to 4.1 (Denmark)[130] and 4.6 (Australia)[131] per patient. These included adverse reactions, dosing problems, interactions and non-adherence.[129-131] Diagnosed patients receiving drug treatment will visit the community pharmacy regularly, providing the pharmacists a unique opportunity to follow-up and discuss treatment and compliance.[132] Therefore diabetes patients could benefit from the inclusion of a pharmacist in the team of health care workers committed to helping with disease management.[29;133-135]

The Norwegian pharmacy system

The Norwegian pharmacy market is dominated by three pharmacy chains, Apotek 1 AS, Vitusapotek and Alliance apotek/Boots apotek, which by 1st of January 2010 fully owned 538 of 629 privately owned pharmacies in Norway. In addition Norway has 33 hospital pharmacies owned by the Regional Health Authorities.[136;137] The Norwegian pharmacy system went trough a radical change in 2001. New legislation allowed anyone (except pharmaceutical companies and prescribing physicians, veterinarians and dentists) to own pharmacies, provided that they employ a pharmacist holding a masters degree to run the pharmacy. Before 2001 Norwegian pharmacies were independently owned by certified pharmacists, and the number of pharmacies was strictly regulated.[137;138] In January 2001 there were 397 pharmacies in Norway; in January 2010 the number was 662, an increase of 67%. While only 5 new pharmacies were established in the year 2000, approximately 30 new pharmacies have opened every year since.[139] In 2009 Norwegian pharmacies dispensed over 30 million prescriptions to 3.4 million different patients, i.e. 70 % of the Norwegian population. Including over the counter sales the pharmacies had 45.6 million customer visits in 2009.[7;136;140] Most Norwegian patients with diabetes visit a pharmacy at least once every three months to collect prescription medication, as a three months supply is the set maximum amount the Norwegian social insurance scheme (NAV) will refund.

Research on pharmacy services for patients with diabetes

Many researchers have investigated the effects of diabetes care services in the pharmacy. Often the interventions are not a single defined service, but rather multifaceted comprehensive programs.[121;134;141-152] The programs vary in content, but include services such as patient education, monitoring of blood glucose, blood pressure and lipids, medication reviews and/or adherence support. These report of significant improvements in HbA1c,[121;141-144;146;148;149

percentage of patients with HbA1c less than 7%,[121;142;143;147;149] mean blood glucose[141;150], blood pressure,[121;134;143;144] percentage of patients who achieved target blood pressure (130/80 mmHg),[141;143] lipid levels,[121;143;149] self-reported non-adherence[145], drug-related problems,[121] as well as reductions in health care costs[143;149], days of sick-time[149] and estimated 10-year risk of coronary heart disease.[144]

Studies have also been performed were the intervention was limited to a single service. Examples of interventions include group counselling,[153] control of SMBG performance,[86] and screening.[154-157] Counselling showed a significant reduction in HbA1c that remained after 24 months,[153] while the SMBG controls halved the number of patients who made user errors.[86] Methods of screening varied, from simple risk assessment using a tick-test (questionnaire), referring patients with one or more risk factors to their GP for diagnosis,[156] to sequential methods starting with risk assessment, followed by measurement of plasma glucose for the at-risk group before referral to GP for diagnosis.[155;157] Krass et al compared the two methods and found significantly better costs efficiency and increased uptake of referrals to GPs in the group that received sequential screening.[154]

In spite of promising results when the studies are read individually, review studies point out methodological limitations. Blenkinsopp et al published a review of the effectiveness and acceptability of community pharmacy based services for patients with type 2 diabetes, but found too few studies in community pharmacy settings to make any general conclusions about effectiveness.[119] In 2007 Machado et al[158] published a systematic review/meta-analysis focusing on the sensitivity of patient outcomes to pharmacist interventions in diabetes management. They found that HbA1c is sensitive to pharmacist interventions, while fasting plasma glucose and systolic blood pressure were considered possibly sensitive. Lipid levels, adherence, knowledge and quality of life were considered probably not sensitive to pharmacists interventions. However the authors also point out that the quality of the literature

they have assessed can only be considered fair, mostly due to lack of blinding of patients and caregivers, and due to lack of reports of adverse drug events and adherence to interventions, and they argue that more research is needed to establish the association between intermediate and final health outcomes.[158] This concurs with the results of a review of the effectiveness of pharmaceutical care looking at all patient groups, not only diabetes.[159] It concludes that pharmaceutical care was effective in improving symptom management, medication use and surrogate endpoints such as blood pressure, HbA1c and cholesterol levels, but does not provide evidence supporting improved health related quality of life. The authors point out that greater consideration should be given to the outcome levels employed in the studies being done.[159] A Cochrane study of the effects of extended pharmacy roles in general found that the research done supported the expanded roles of pharmacists in patient counselling but also points out flaws in study designs, and states that more rigorous research is needed to document the effects of outpatient pharmacist interventions.[160]

Point of care tests (POCT) at the community pharmacy

Point of care testing (POCT) is defined as "laboratory diagnostic testing performed close to the site of patient care, typically by clinical personnel whose primary training is not in the clinical laboratory sciences or by patients."[161] Point of care tests for glucose, HbA1c, lipids and blood pressure are part of the services being offered in several of the programs for diabetes care at community pharmacies around the world.[116;120;148;162-164] The pharmacist as a provider of laboratory test results has been subject to much discussion,[123;155;164-166] the main objections being that pharmacy employees are not trained to perform POCTs, and that over-utilization and inappropriate test utilization can lead to significant increases in cost of care.[161] It has been pointed out that while performing POCT may seem simple, it can be difficult to comprehend the complexity of the testing process and the many variables that can affect the test results.[167] Those who are positive to pharmacies providing POCTs argue that pharmacists

"may represent an additional point of choice and access to health care, potentially reducing the number of journeys (patients) have to undertake".[164]

The following should be considered before introducing POCT to the pharmacy setting:

- Why should the tests be performed in the pharmacy?
- How are the results going to be used?
- How to educate the pharmacy staff in laboratory testing
- How to educate the pharmacy staff in counselling patients on the results of the tests
- How to ensure best possible quality of the instruments and measurements
- How to convey the result to the patients' general practitioner (GP)

Performing high quality POCT tests requires staff training and competency, method validation, and ongoing comparison with core laboratory results. An appropriate record trail should be maintained (linking operator and his/her training/competency with device validation/maintenance/quality control). Dedicated resources and multidisciplinary commitment and cooperation are necessary to ensure the highest quality services.[161;168]

The choice of POCT instrument used in the pharmacy should rely on the purpose of the tests. For example, though glucometers for SMBG may obtain measurements of sufficient quality to monitor the progression of a single patient's disease, the maximum allowed total error of 20 % means that these devices are not suited to diagnose diabetes. Also, though instruments may be easy to use, they still require a quality assurance regime and the person performing the test must be trained in the instrument's use and quality assurance. The intended use of the results will also dictate the procedures for information provided to the patient and potentially to his or her GP. If the tests are intended as an ongoing monitoring of the disease and effects of medication, it is essential that this is agreed upon beforehand with the patient's GP and that the GP receives a copy of the results to avoid unnecessary double tests and costs, and also to

avoid confusion if the patient receives deviating results from his GP and his pharmacist. If the test is intended to identify people at risk of having diabetes, the pharmacy should use equipment suited for this purpose, have strict guidelines for what value constitutes risk and how to follow-up patients at risk to ensure that they visit their GP for diagnosis and potentially treatment. Careful consideration must be given on how to relay information about risk to patients to facilitate that these contact their GP, but at the same time avoid unnecessary anxiety.

A few years ago it became possible to buy self-tests for a long list of ailments from community pharmacies, from Chlamydia and urinary tract infections to allergies and celiac disease. However, especially the Chlamydia test was widely criticised for being of poor quality and today many of these products have been withdrawn from the pharmacies.[169]

While it may be temping for health personnel and patients both to perform tests "because we can" it is important from both a health cost view and a public health view that only tests with a clear purpose are performed, and that the pharmacies can document the quality of tests they provide and of the self-tests they sell. The new pharmacy contract in England lets the patient's GP delegate tasks to the pharmacy, and this ensures that the GP gets to keep the coordinator role and overview over the patients' treatment and follow-up. However, there is no regulation of POCT, and this, it has been stated, "underlines the central role for established NHS professionals in developing suitable frameworks on behalf of primary care".[164] In Norway, the Norwegian Quality Improvement of Primary Care Laboratories (NOKLUS) has begun this work by ensuring support and influencing guidelines for laboratory tests performed in primary care, mainly aimed at GPs' offices, but also in nursing homes. If the pharmacies are to perform POCTs they should also be enrolled in NOKLUS' systems for quality assurance. Before we begun the studies that this thesis is comprised of, little was known of the extent of

pharmacy services offered to diabetes patients in Norway, the extent of POCT tests being performed, and the quality of tests performed at the pharmacy.

Aims of the thesis

- To describe Norwegian pharmacies' involvement in diabetes care, explore pharmacists' views on future services and investigate whether the recommendations in the Norwegian diabetes declaration for pharmacies have been implemented (Paper I).
- To implement a method for glucose measurement at community pharmacies, and to evaluate if it is sufficiently accurate and precise to be used as a comparison method for controlling patients' self-monitoring of blood glucose. Also to investigate whether the pharmacies can achieve glucose measurements of comparable analytical quality to those performed at general practitioners offices. (Paper II).
- To evaluate the analytical quality of Norwegian diabetes patients' SMBG measurements as well as the frequency of user errors among the diabetes patients by performing a control of this at the community pharmacy, to investigate whether these pharmacy controls together with a program for quality assurance improve the quality of the measurements and explore the views of the patients on receiving such a service at their community pharmacy (Paper III).
- To use nationwide data from 2008 to determine the prevalence of self-monitoring of blood glucose among all non-institutionalized persons living in Norway, estimate the prevalence of SMBG among diabetes patients, the frequency and cost of SMBG and the use of different types of strips (Paper IV).

Summery of papers

Paper I. Diabetes care in Norwegian pharmacies: a descriptive study.

Kjome, RLS, Sandberg, S and Granas, AG. Pharm World Sci 2008 30:191-198.

Objective: To describe Norwegian pharmacies' involvement in diabetes care, to investigate pharmacists' views on future services and to investigate whether the recommendations in the Norwegian diabetes declaration for pharmacies have been implemented.

Setting: Hospital and community pharmacies in Norway

Method: All 543 pharmacies in Norway, 511 community pharmacies and 32 hospital pharmacies, were sent a link to a web-based questionnaire. One pharmacist from each pharmacy was asked to complete the questionnaire. The questionnaire covered subjects from the diabetes declaration and the pharmacists' views on which services the pharmacy should offer in the future as well as demographic characteristics.

Results: In total 358 (66%) pharmacists completed the questionnaire. The diabetes declaration was read by 37 % of the pharmacists. Nearly all pharmacies followed the declarations' recommendations in regard to glucose monitoring services. Twenty four percent of the pharmacies offered medication reviews, and about 10 % offered screening for undiagnosed diabetes. Counselling on lifestyle issues was the recommendation that was least implemented. Eighty one percent of the pharmacists reported that they wished to expand their services towards people with diabetes. Services in regard to glucose monitoring scored the highest, but the views on offering a variety of future services varied a great deal. Already performing a service increased the chance of the pharmacist being positive towards offering it.

Conclusion: Norwegian pharmacists report that they are involved in a wide range of diabetes services, even though only 37 % have read the diabetes declaration. The pharmacists wish to be active in supporting patients with diabetes, and further research should concentrate on identifying the areas where the effect of their involvement is the greatest.

Paper II. Implementation of a method for glucose measurements in community pharmacies.

Kjome, RLS, Nerhus, K and Sandberg, S. Int J Pharm Pract 2010;18(1):13-19.

Objectives: This study aimed to implement a method for glucose measurements that could be used as a comparison method for controlling patients' self-monitoring of blood glucose. Further we wished to investigate whether the pharmacies could achieve an analytical quality comparable to glucose measurements performed at general practitioner offices.

Setting: Sixteen community pharmacies in Norway.

Method: Sixteen pharmacy employees were trained in glucose measurement, quality control, and blood sampling. The comparison method, HemoCue Glucose 201^{+}, was validated in four steps: 1) estimation of the variation between the HemoCue instruments to be used at the 16 pharmacies, 2) comparison between the results from HemoCue and the results of a laboratory glucose method, 3) monitoring the quality of HemoCue by use of internal quality controls and 4) participation in an external quality assessment scheme. The pharmacies' results of the external quality assessment were compared to those of 359 general practitioners'' offices.

Main outcome measures: Variation among HemoCue instruments, quality of Hemocue instruments compared to a laboratory method, number of pharmacies achieving measurements of acceptable precision and trueness.

Results: An assessment of the imprecision and bias of the HemoCue instruments showed that the coefficient of variation was 6.1% in the low level, 1.7 % in the normal and high levels, and that negligible bias was present in the normal level. The coefficients of variation for internal quality controls were 4.5%, 1.5%, and 1.2% for the low, normal, and high levels, respectively. All pharmacies achieved good precision and acceptable or good trueness in the external quality assessment. The pharmacies exhibited significantly lower variation between sites (2.2% and 1.2%) than general practitioners' offices (3.8% and 2.9%) on both external

quality assessment samples.

Conclusions: Given correct training and the establishment of a system of quality assurance, pharmacies are capable of obtaining glucose measurements that can be used as comparison measurements for controlling patients' meters. The pharmacies had external quality assessment results comparable to general practitioners' offices.

Paper III. Quality assessment of patients' self-monitoring of blood glucose in community pharmacies

Kjome, RLS, Granas, AG, Nerhus, K and Sandberg, S. Pharmacy Practice (internet) 2010; 8(1):62-69.

Objective: Diabetes patients' self-monitoring of blood glucose was evaluated using a community pharmacy-based quality assurance procedure. We investigated whether the procedure improved the quality or the patient performance of self monitoring of blood glucose. The opinions of the patients taking part in the study were examined.

Setting: Sixteen community pharmacies in Norway.

Method: The results of patient measurements were compared to the results obtained with HemoCue Glucose 201+ by pharmacy employees in 16 community pharmacies. Patient performance was monitored using an eight item checklist. Patients whose measurements differed from pharmacy measurements by more than 20% were instructed in the correct use of their glucometer. The patients then re-measured their glucose. If the results were still outside the limits, the control procedure was repeated with a new lot of glucometer strips, and then with a new glucometer. The patients returned to the pharmacy for a follow-up visit after three months.

Main outcome measures: Number of patients whose measurements deviated from pharmacy values by more than 20 % and number of user errors.

Results: During the first visit, 5% of the 338 patients had measurements that deviated from pharmacy values by more than 20% and user errors were observed for 50% of patients. At the second visit, there was no significant change in the analytical quality of patient measurements, but the percentage of patients who made errors had decreased to 29% ($p < 0.001$). Fifty-one percent of the patients reported a greater trust in their measurements after the second visit. Eighty percent of patients wished to have their measurements assessed yearly. Of these

patients, 83% preferred to have the assessment done at the community pharmacy.
Conclusion: A community pharmacy-based quality assurance procedure of patients' self monitoring of blood glucose improved patients' confidence in their measurements and significantly reduced the number of user errors. The analytical quality of the measurements was good and did not improve during the study. The high analytical quality might be explained by a selection bias of patients participating in the study.

Paper IV. The prevalence of self-monitoring of blood glucose and costs of glucometer strips in a nationwide cohort

Kjome, RLS, Granas, AG, Nerhus, K, Roraas, TH and Sandberg, S. (2010, submitted).

Objective: To use nationwide data to determine the prevalence of SMBG among all non-institutionalized persons living in Norway, estimate the prevalence of SMBG among diabetes patients, the frequency and cost of SMBG and the use of different glucometers.

Methods: This retrospective, descriptive study is based on data of sales of glucometer strips to non-institutionalized persons in Norway in 2008. The data included: gender, age group, month of purchase, sales-place, type of strips, number of packages dispensed and cost of strips. Additionally, statistics on sales of insulin and oral anti-diabetics were obtained from the Norwegian prescription database.

Results: A total of 96,999 persons purchased strips, a prevalence of 2 %. Approximately 70 % of diabetes patients practice SMBG. Average patients used 1.7 strips per day, and younger patients purchased more strips than older patients. Less than 50% of patients perform glucose measurements daily. One percent of patients used more than 10 strips daily and was accountable for eight percent of total costs. Most patients use only one type of strips, but number of purchased strips increased with number of different strips. The average annual cost of strips was 446 € per person.

Conclusions: Two percent of all non-institutionalized inhabitants and an estimated 70 % of patients using diabetes medication purchases SMBG strips. A small percentage of the patients use a substantial proportion of the costs. This, along with the fact that over half of the patients monitor less than once per day, calls for tighter follow-up of the patients.

Methodological considerations

The empirical data of this thesis was collected using different methodologies described in detail in the separate papers. Table 3 gives an overview over design and data collection used. In the following methodological considerations will be further discussed.

Table 3. Methodological overview over the papers included the thesis

Paper	Design	Data collection	Study population
I	Descriptive study	Electronic questionnaire	One pharmacist from each of 358 Norwegian pharmacies
II	Methodological study	Results of the pharmacies internal and external quality controls, results of GPs' external quality controls	16 employees from 16 community pharmacies, 359 GP offices using HemoCue Glucose 201^{+}
III	Before and after study	Structured patient interviews before the first and after the second pharmacy visit, results of pharmacy and patient glucose measurements at the first and second visit, registered user errors at the first and second visit	338 diabetes patients at the first visit, 308 patients returned for a second visit
IV	Non-experimental database study	Data received from the Norwegian health economics administration on sale of glucometer strips	The 96999 patients who purchased glucometer strips in Norway in 2008

Diabetes care in Norwegian pharmacies (Paper I)

Internal validity

Validity refers to the degree data or results are correct or true.[170] A finding is not simply valid or invalid, but will have some degree of validity for a stated purpose.[171] In this descriptive study we increased the face and content validity of the questionnaire by performing initial interviews with pharmacy employees engaged in diabetes work, and by using a pilot group to ensure that the questions were easy to understand and that the reply categories were relevant and extensive.[172] A validity limitation is that we did not observe the practice of the pharmacists. We can only report what the pharmacists state to do, not what they actually do. The questions inquiring about how often pharmacists provided counselling or referred patients to other health care professionals cannot be used to quantify frequency. While one pharmacist might rate once a week as often, another might rate once a month as often. However the answers can be used as internal ranking of frequency between different types of counselling. The same applies for the items concerning views on future pharmacy services.

External validity

It is always essential to consider whether results also apply to those outside of a study population.[173] In our study, we were in a unique situation as we could include Norwegian pharmacies in the study population. Still, our results might not be valid for all Norwegian pharmacies due to response bias. The one pharmacist most engaged in diabetes activities in each pharmacy filled in the questionnaire and their views may differ from those of the rest of the pharmacists working in the pharmacy. Likewise, due to differences between countries in pharmacy ownership structure, policy, legislation and practice, our results may be transferrable to some, but not all other countries.

Quality assurance of patients' self-monitoring of blood glucose in community pharmacies (Papers II and III)

Internal validity

The validity of the glucose measurements performed at the pharmacy was a main focus of our research, and is described in detail Paper 2. The main conclusion is that the pharmacies achieved glucose measurements of good precision and trueness.

In our study we chose to use the ISO limits of ± 20 % deviation for acceptable performance. In the paper "Quality Assurance of Self-monitoring of Blood Glucose at the General Practitioner's Office", it is suggested that one might adjust these limits based on the method bias as compared to the laboratory reference method.[174] One way of doing this is to correct the pharmacy values using a linear correction formula derived from a linear regression between the pharmacy method (HemoCue Glucose 201^{+}) and the reference method (Architect *ci*8200), and then adding the 20 % limits (see Appendix 4). When applying this to our results from the first patient visits, it did not affect the number of analytically unacceptable measurements (Appendix 4). An alternative way to set quality specifications is to use the Clarke Error Grid Analysis described in the introduction. If we were to use this on the patients' results, only one patient's measurement would have been considered unacceptable (see Appendix 5).

When we were planning the study it was presumed that the checklist items were fairly intuitive (such as "are strips expired?" and "does the patient use a big enough drop of blood?"). Therefore we did not test intra- or inter-tester reliability. In hindsight such tests would have ensured a higher reliability of the registration of patient errors, as some of the items on the checklist might have left room for interpretation. However, the items on the checklist were carefully explained during the training of the pharmacy employees, and careful

instructions were given with regard to the meaning of each item (e.g. “Unsatisfactory sampling” would encompass not changing the lancet, pricking in the middle of the finger pad where there are most nerve endings or squeezing out blood). Also, all the lists were reviewed and compared to the instrument in question’s user manual, to ensure for example that in instruments that did not require coding, lack of coding was not registered as an error. The focus on user error at the course day, the fact that all pharmacy employees received the same training shortly before seeing patients and the thorough review of the completed checklists strengthened the reliability. If one was to repeat this study, it would be beneficial to use a more detailed checklist, similar to the one published by Müller et al[86] to make it easier to interpret the results.

Before the first and after the second visit patients were interviewed about their SMBG habits and their views on participating in the study. We chose to let the employees question the patients to reduce the chance for unanswered questions and to allow for clarification of questions and answers.[175] Since all employees were given the same instructions this should strengthen the reliability of the responses. However there is the issue of recall bias for the questions where the patients were required to remember when they started SMBG and any training they received. Recall bias is also relevant where patients reported HbA1c values. Also patients’ reported service satisfaction may be overstated because the responders answer what they think the interviewer wants to hear[175] and exaggerate how positive they are because the response was not anonymous.

Perhaps the most serious limitation is that our power calculations were based on the assumption that at baseline approximately 15 % of the participating patients would have glucose results that deviated by more than 20 % from the pharmacies’ results, but among our patients only 5 % had analytically unacceptable results. Hence we could not determine whether our interventions had any effect, nor could we establish whether background

variables such as gender, age, HbA1c or instrument could predict poor measurements. The assumption of 15 % poor measurements at the first visit was based on previous studies that found from 9-16 % of patients' results deviated by more than 20 %.[80;82;174] One explanation is that current glucometers are less affected by user error, but we believe that our results reflect a patient selection bias.

External validity

The pharmacies participating in our study all achieved good quality of the measurements they performed. All were from a single pharmacy chain, and therefore we can not with certainty say that the results are applicable to all Norwegian pharmacies. However there are no clear differences between the pharmacy chains that imply that they are not. Still, in the participating pharmacies the project was prioritized by giving the employees responsible time away from regular tasks for training; and necessary resources for this, for enrolment in NOKLUS and for necessary equipment was provided by the pharmacy chain. If these factors are in place other Norwegian pharmacies should be able to achieve the same quality of measurements. The number of employees and size of the pharmacy may be of more significance than chain affiliation, as it may be difficult for the smaller pharmacies with few employees to clear time from the pharmacy's routine tasks to receive training and implement the necessary quality control systems. The quality of measurements performed by GP offices that partake in the NOKLUS EQAS have shown improvement over time[176], and this could perhaps be expected from the pharmacies as well, as they become more experienced with the control procedure and receive feedback from NOKLUS.

Regarding the results of the patients, it is unlikely that these are representative for all Norwegian diabetes patients. All studies where patients volunteer to participate will be affected by some selection bias, and our results lead us to believe that this has been quite

pronounced in our sample, with the most motivated patients accepting the invitation to participate. Patients less interested in SMBG, those who regard it as uncomplicated or those who felt unsure and did not wish to have their performance appraised may have been less inclined to volunteer. The recommended HbA1c value for patients with diabetes is below 7%,[177] and the mean reported value of our patients was 7.1%, which also indicates that these patients are well regulated. Also, while results from paper IV found that only 45 % of persons who purchased SMBG strips bought enough to perform daily measurements, 63 % of the patients in our study replied that they monitored their blood glucose once daily or more (unpublished results, se Appendix 6), and this may imply that the patients participating in our study are more compliant than the average SMBG user. This is problematic because it means that we have not managed to recruit the patients who would have benefitted the most from our intervention. If the study population had been different, for instance diabetes patients chosen by GPs based on high HbA1c levels, we might have seen different results of patients' measurements at baseline.

The prevalence of self-monitoring of blood glucose and costs of glucometer strips in a nationwide cohort (Paper IV)

Internal validity

The validity our nationwide data describing the number of patients who practice SMBG and total prevalence of SMBG is high; as we have data on all sales of strips to non-institutionalized persons in Norway, and it is unlikely that people who purchase strips do not practice SMBG at all. However, while the numbers we find are valid in terms of purchase, patients will not necessarily use all the strips they buy, thus our estimated frequency of SMBG may be too high. The estimated proportion of patients using diabetes medication who practice SMBG is also uncertain, because we only have national data and not person specific data for the patients who use diabetes medication. Thus, theoretically these can be different people than those who purchased strips. Also, some of the medications may have be have been used for other indications than diabetes.

External validity

Our results should be valid for all persons practicing SMBG in Norway. However, SMBG habits may change in the population over time. In 2009, new Norwegian guidelines for the diagnosis and treatment of diabetes were introduced, and though these do not recommend a certain SMBG frequency, they may influence the clinicians' attitudes and thereby also the patients' practice. Our results can most likely not be applied to populations where patients are required to pay in whole for their own strips, but one could assume that the results would be similar in countries such as Sweden, Finland and Denmark, where reimbursement systems are similar. However, this will also depend on national guidelines with regard to SMBG.

Discussion of results

Self-monitoring of blood glucose is an important aspect of diabetes management for many patients. Nearly one hundred thousand Norwegians purchased glucometer strips in 2008, and more than 43 million Euros was spent on strips.[97] Still, education of patients in the correct way of performing SMBG and follow-up of the measurements performed by patients is not routinely done. In paper III we found that 44 % of the patients had not received any training in SMBG. This concurs with Skeie et al's findings from 2002, where 47 % of the patients interviewed in general practice and 56 % of hospital out-patients stated that they were self-educated.[73] Seventy-eight percent of the 338 patients visiting the pharmacies for an SMBG assessment stated that they never checked if their device showed the correct result (results not published, see Appendix 6), while in Skeie's study 63 % stated the same.[73]

It is the physician who prescribes SMBG who is responsible for ensuring that the patient is taught how to and when to perform SMBG and how to make use of the results. The physician is also responsible for the amounts of strips that are prescribed. The findings from paper IV confirm that there is both over-and underuse of SMBG strips in different sub-groups of patients. In Norway it is common that the prescribing physician writes "Equipment for three months use of SMBG" (or for a year) on the prescription. In practice, this means there are no limits to the amount of strips that the patient can collect during that period. Good guidelines on SMBG frequency are lacking, and with the great variety of equipment on the market today, some prescribers might find it difficult to advise patients on this. Barber's model for good prescribing states that the prescriber should have four aims: to maximize effectiveness, to minimize risks, to minimize costs and to respect the patient's choices (see Figure 4).[178] These aims will often have to be balanced against each other: The patient should monitor often enough to be able to adjust medications, diet and exercise so that he avoids hypo- or hyper

glycemia, but still limit the amount of SMBG, as it is an invasive procedure that involves pain/discomfort. The prescriber should aim to respect the patient's autonomy regarding the necessary frequency of monitoring, while at the same time considering the costs that it involves. The prescriber should come to an agreement with the patient on a maximum yearly use of strips given a sensible testing frequency, depending on the patient's medication regime (insulin or not) and on how well regulated the patient's diabetes is. If the patient for some reason needs more than the agreed amount, he would have to contact the physician, who then can decide whether further follow-up or therapy adjustment is necessary.

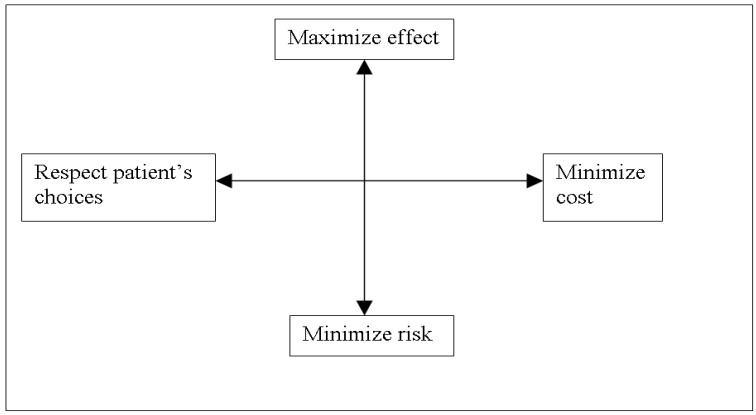

Figure 4. Aims of good prescribing – and their most common conflicts. (Barber[178])

In paper IV we found that there was a small group of patients who bought more than 5000 strips per year, i.e. these patients bought enough strips to be able to perform SMBG more than 13 times per day, every day, throughout the year. One would assume that if the prescriber knew that a patient collected 5000 strips during one year they would find it imperative to discuss the issue with the patient. However, when no maximum amount of strips are indicated on the prescription, it is difficult for the dispensing pharmacist to infer if and when they should contact the prescriber concerning patients who have a high consumption of strips.

Also, a patient may collect strips from several different pharmacies, and a pharmacist will only have a full account of the strips dispensed at his or her pharmacy. Therefore the prescriber has no way of knowing how many strips the patient uses unless he/she chooses to ask the patient. A Norwegian diabetes register, based on consent from diabetes patients and physicians, is under implementation. As a part of this the physicians will be asked to enter patients' SMBG frequency. This may act as a reminder for the physician to address the topic of SMBG frequency, and the feed-back physicians receive from the register comparing results of their patients to national and regional mean frequencies may be helpful in uncovering over- and under utilization of SMBG.

An older patient group, more complex treatment regimes, and focus on treating more patients in primary healthcare has lead to a growing workload for Norwegian GPs.[179] Educating patients in SMBG and following up on their measurements and strips use could be among the tasks GPs delegate to pharmacies. A report commissioned by the Ministry of Health and Care Services and provided by The Directorate of Health, "Medical help in pharmacies" lists "Follow-up of patients with diabetes" as one of the initiatives that have been seen to have an effect in international studies of new pharmacy services, especially patient education, guidance in the correct use of drugs and diabetes equipment and systematic follow-up of diabetes patients with feed-back to the patient's GP. The work group behind the report concludes that Norwegian pharmacies would be suited to provide 1) technical guidance in the use of SMBG equipment, 2) guidance in the use of other medical equipment and 3) identification of persons with unidentified type 2 diabetes or at high risk of developing type 2 diabetes by use of a diabetes risk questionnaire. They point out that while it is common practice in pharmacies to provide advice on use of SMBG equipment, formal agreements defining what information should be given is lacking, and advice that the services should be standardized.

The findings in Paper I confirm that Norwegian pharmacies offer SMBG support in the form of help in choice of glucometer and SMBG training, and also that half the pharmacies offer to assess patients' measurements. However, most pharmacies did not have standardized operating procedures describing what the services should include nor quality control systems in place for these services.[180] To gain maximum benefit from such a service, the role of the pharmacy in patient SMBG education should be agreed upon with the GP, and the content of the service should be standardized so patients receive the same care independently of where they live or which pharmacy they choose to use. In a paper by Johnson investigating the pharmacist's role as a diabetes educator, the author suggested elements in pharmacy-provided SMBG education. He recommended that pharmacists should explain the benefits of SMBG and give instructions on how to use the glucometer (knowledge). Using a new device could then be demonstrated to the patients (vicarious experience), followed by providing time for the patients to use the meter themselves (performance accomplishment). The pharmacist should offer encouragement (verbal persuasion), and lastly, patients should feel they are in a relaxed environment.[181] In addition we would add that pharmacies that offer control measurements to check the patient's glucometer should implement quality control procedures such as those we have described in Paper II, to ensure the trueness and precision of the measurements they provide. There should also be a feed-back system so the patient's GP can be informed if alarming glucose values or other patient needs that require physician follow-up are uncovered.

The results in Paper I show that the pharmacists wish to provide this type of service. The responding pharmacists strongly agreed that pharmacies should offer to assess patients' SMBG measurements. We also asked the 16 pharmacy employees who participated in our second study (paper II and III), to evaluate the service after completing all patient visits. A summary of their replies (not published) can be found in Appendix 7. Overall the satisfaction

with training and execution of the study was high, and they all wished to continue the SMBG service at their pharmacies. In a Dutch study on community pharmacies' involvement in SMBG support for patients with diabetes, they found that the provision of SMBG services varied greatly between pharmacies, but those who were involved in local agreements with other healthcare professionals provided more SMBG services. The authors concluded that even though practice guidelines exist, pharmacists are likely to form their role definition based on self-derived norms, leading to a wide range of professional behaviour. As patient counselling is a relatively new activity compared with technical processes, there is a lower threshold for pharmacists to get involved in SMBG calibration/checking.[182] This could to some degree explain the higher interest of the Norwegian pharmacists in SMBG related activities compared to participating in activities such as dieting courses.[180]

When we offered our SMBG assessment service to pharmacy customers (Paper III) our results lead us to believe that we did not recruit the less motivated patients. It might be advantageous to make both an introductory SMBG education session and follow-up yearly or semi-yearly SMBG assessments mandatory for all patients collecting SMBG equipment, but it is difficult to recommend such an extensive intervention based on our results, as they show the quality of the patients measurements to be good. On the other hand, finding that the quality is satisfactory at one point in time does not mean that later quality control is unnecessary. One could envision implementing mandatory assessments of patients' SMBG as well as their use of strips as a test project over for instance two years. This would be a way to ensure that the money used on SMBG was well spent, and would also give access to some very interesting data about the quality of glucometers in the hands of the patients. A cost-benefit analysis would be an important aspect of such a test project, and one could then investigate different reimbursement alternatives, e.g. including the cost of the service in the cost of the strips, or

reimbursing the pharmacies with a fee for providing the service itself, similar to the way they were reimbursed when pharmacists prescribed influenza medication.[126]

Implications for pharmacy practice and future perspectives

The findings of this thesis indicate that there is a need for better education and follow up of diabetes patients' SMBG, that Norwegian pharmacies are offering SMBG related services to diabetes patients, and that while proper quality control of the services may have been lacking in the past, pharmacies were capable of performing good quality POCTs when enrolled in NOKLUS' EQA scheme.

All pharmacies that offer to perform tests should be required to have the necessary quality control measures in place, and purchasing such services from NOKLUS would most likely lead to a continuing improvement of the quality of tests being performed, similar to what has been seen for laboratory tests performed at GPs offices.[176] Unfortunately, the steering group of NOKLUS, will only allow pharmacies to enrol under the condition that they agree not to perform any type of diabetes screening, a pharmacy service the Norwegian medical association is strongly opposed to. As the pharmacies would not agree to this, they now perform blood glucose measurements, but without access to the best available method for quality assessment of the measurements they perform. This is not favourable for pharmacies or patients. It is important to have an open discussion about where one would achieve the best effect of pharmacies' involvement in diabetes care, with the ultimate goal of ensuring the best possible care for patients with diabetes and also the best possible use of health resources.

Future studies involving diabetes care at the pharmacy should focus on uncovering more information on how patients' use SMBG results, how to help them use their results correctly,[72] as well as finding the ideal frequency of measurements. Identification of patient groups in special need of follow up could ensure a better outcome of interventions. It would be useful to include cost-benefit analysis in all studies of pharmacy services in order to better be able to identify where the time of the pharmacist is best spent.

Conclusions

- As a group Norwegian pharmacies offer a broad range of services for patients with diabetes, however the services offered vary greatly between pharmacies. The Norwegian diabetes declaration has not been successfully distributed and integrated into the pharmacies' routines, but the pharmacies have implemented several of its recommendations. The pharmacists wish to expand their services directed towards diabetes patients, and are especially positive to services regarding SMBG and medication counselling. (Paper I.)

- When given adequate training, follow-up and equipment pharmacy employees can achieve glucose results that are precise and accurate enough to be used as target values for patient SMBG results, comparable to those achieved at GPs' offices. (Paper II.)

- Amongst the patients participating in our study, 95 % achieved SMBG results that deviated from the comparison method by less than 20 %, however 50 % of the patients made one or more user errors. After visiting the pharmacy for a SMBG performance assessment, the number of user errors was significantly reduced and the patients reported more confidence in their results, yet the analytical quality of the measurements was unchanged. Eighty percent of the patients wished to attend such a service yearly and of these 83 % preferred the community pharmacy as the site for such a service. (PaperIII.)

- In 2008 the prevalence of SMBG in the non-institutionalized Norwegian population was 2 %, while approximately 70 % of medically treated diabetes patients purchased strips. One percent of the buyers purchase enough strips to perform 10 or more measurements per day, while 45 % purchase enough to perform daily measurements. Number of purchased strips increased with the number of different types of strips

purchased. Total cost of glucometer strips was 43,250,681 €, an average of 446 € per person. (Paper IV.)

The sum of this work suggests that Norwegian pharmacies can be more actively used in assisting diabetes patients with their SMBG. The employees are motivated, and already involved at a smaller scale. Given correct training and follow-up they are capable of performing services involving point-of-care tests of good analytical quality, and patients are happy to receive this type of service from their community pharmacy. A small number of patients use a disproportionately large amount of the resources spent on SMBG, while a large number of patients rarely perform SMBG, giving room for improvement in the way these resources are being spent.

Challenges that remain are creating multidisciplinary agreements on the provision of SMBG education and follow-up, uncovering how to reach the patients that are in most need of assistance, attaining access for pharmacies to the quality control support from the Norwegian Quality Improvement of Primary Care Laboratories, and ensuring remuneration for the services.

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