Diploma Thesis

Diabetic alert dogs
Medical and social assistance for patients with DM1
A questionnaire based survey

Submitted by

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Graz, September 19th 2016

Declaration in Lieu of an Oath

I hereby declare that the content of this thesis corresponds to my work, which has not been submitted for a degree at this University or any other institution, and that other sources of information used in the text have been clearly acknowledged.

Graz, September 19th 2016 *Sarah Sutter eh*

"Dogs are miracles with paws"

Attributed to Susan Ariel Rainbow Kennedy

Abstract

Diabetic alert dogs (DAD) are known to detect hypo- and hyperglycemia. But these dogs do not simply serve as medical assistance; they are also an important partner and supporter for patients with type 1 diabetes. By applying this questionnaire we evaluated the quality of life and glycemic control for patients with type1 diabetes and the change since getting the DAD. The average decrease of the HbA1c (n=14) under assistance of a DAD trained by the Animal Training Center was -0,3 and ranged from +1,2 to -1,3. We assumed the limit of hyperglycemia ≥ 200mg/dl and hypoglycemia ≥80mg/dl. Individual variations may appear between different patients. The fear and concern for hyperglycemia improved since ownership of a DAD <1year by 63% (33% much better, 30% better) and >1year by 78% (50% much better, 28% better), for hypoglycemia <1year by 77% (33% much better, 44% better) and >1year by 94% (72% much better, 22% better). The increased frequency of testing blood glucose and the related pain causes an inconvenience for 40% of the patients. The families owning a DAD feel their emotional and psychological burden eased by 65% (38% much better, 27% better) by ownership <1year and 76% (53% much better, 23% better) by >1year. The sleeping behavior of the ones in responsibility improved for overall 57% (43% much better, 14% better).

We evaluated notification protocols of six real life existing patient-with-DAD-teams, covering several months each. The overall best dog showed 87% correct alerts (the worst dog 50%), 12% wrong alerts (the worst dog 36%) and 1% missed alerts (the worst dog 12%). 55% of the owners described the alerting behavior of their dog as good, 15% as satisfactory and 30% as excellent.

Zusammenfassung

Diabetikerwarnhunde sind dafür bekannt, Über- und Unterzuckerungen anzeigen zu können. Diese Hunde stellen jedoch nicht nur medizinische, sondern auch eine psychologische und emotionale Unterstützung für Typ 1 Diabetiker dar. Wir evaluierten die Lebensqualität und die glykämische Kontrolle der Diabetiker mittels eines Fragebogens und die eingetretene Veränderung seit dem Besitz des Diabetikerwarnhundes. Durch den vom ATC trainierten Hund kam es zu einer durchschnittlichen Senkung von -0,3 des HbA1c (+1,2 to -1,3; n=14). Angst und Sorge vor Hyperglykämie besserte sich bei DAD- Besitz <1Jahr um 63% (33% viel besser, 30% besser) und bei Besitz >1Jahr auf 77% (33% viel besser, 44% besser) und bei über einem Jahr um 94% (72% viel besser, 22% besser). Durch die erhöhte Stichfrequenz zur Blutzuckermessung berichten 40% der Diabetiker erhöhte Schmerzen als Unannehmlichkeit. Die psychologische und emotionale Belastung verbessert sich bei Besitzern unter einem Jahr um 65% (38% viel besser, 27% besser), bei über einem Jahr um 76% (53% viel besser, 23% besser). Das Schlafverhalten der Verantwortung Tragenden besserte sich zusammen um 57% (43% viel besser, 14% besser).

Wir evaluierten Anzeigeprotokolle von 6 bestehenden Mensch-Hund-Teams, zusammengefasst auf jeweils ein paar Monate. Der beste Anzeige-Hund brillierte mit 87% korrekten Anzeigen (der schlechteste als Vergleich 50%), nur 12% Falschanzeigen (schlechteste 36%) und nur 1% verpasste Anzeigewerte (der beste Hund auf diesem Gebiet verpasste keine einzige gemessene Abweichung vom „Normalwert"; schlechteste 12%). 55% der Besitzer eines DWHs beschrieben das Anzeigeverhalten ihrer Hunde als „gut", 15% als „befriedigend" und 30% als „exzellent".

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Abbreviations

ATC	Animal Training Center
BMI	Body Mass Index
BU	Bread Unit
CGM	Continuous Glucose Measurement
CMV	Cytomegalia Virus
DAD	Diabetic Alert Dog
DCCT	Diabetes Control and Complications Trial
DKA	Diabetic Ketoacidosis
dl	Deciliter
DN	Diabetic Nephropathy
DPP-4	Dipeptidyl- peptidase- 4
DR	Diabetic Retinopathy
EATM	Exotic Animal Training and Management Program
FFA	Free Fatty Acids
g	Gram
GFR	Glomerular Filtration Rate
GIP	Gastric- inhibitory peptide
GLP-1	Glucagon-like peptide 1
h	Hours
HbA1c	Glycosylated Hemoglobin
HHS	Hyperglycemic Hyperosmolar State
HLA	Human Leukocyte Antigen
IDF	International Diabetes Federation
IFCC	International Federation of Clinical Chemistry
kg	Kilogram
MDI	Multiple Daily Injection
mg	Milligram
mmol	Millimol
MODY	Maturity Onset Diabetes of the Young
mOsmol	Milliosmolarity
n	Number
NGSP	National Glycohemoglobin Standardization Program
NPDR	Non Proliferative Diabetic Retinopathy
NPH	Neutral Protamin Hagedorn
o1a	Over 1 year
PAOD	Peripher Arterial Occlusive Disease
PDR	Proliferative Diabetic Retinopathy
SAP	Sensor Augmented Pump
T1D	Type 1 Diabetes
T2D	Type 2 Diabetes
u1a	Under 1 year

VEGF	Vascular Endothelial Growth Factor

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1 Introduction

1.1 History

One of the earliest known documents of diabetes was recorded by Hindu scholars around 1500 BC. The symptoms they described in patients included excessive thirst and frequent urination stuck with ants and flies. Apollonius used the term „diabetes“ most likely for the first time around 250 BC in Memphis, Egypt. It meant *to go through,* showing that the patients lost more fluid than they were able to consume (10). 1675 the Briton Thomas Willis (11) added the Latin word *mellitus*, describing the honey sweet scent and flavor of the urine (10).

Until recently, the health-consequences for patients with diabetes mellitus type 1 had been serious. The pancreas is not able to produce the needed amount of insulin and in earlier times it was impossible to provide insulin externally. The affected people grew weaker and after a few weeks they fell into a coma, from which they never awakened.

In the beginning of the 20th century, scientists were able to prepare extracts of the pancreas, lowering the blood sugar and glycosuria in test animals. However, they were incapable to remove impurities. Toxic reactions had been found with the animals and therefore the use in humans was prohibited.

In 1920, *Frederick Banting* read an article written by *Moses Barron* about the relation of islets of Langerhans and pancreatic lithiasis. The author described a completely obstructed main pancreatic duct. The acinar cells had disappeared through atrophy, but most of the islet cells had survived. Banting found out by literature research that this procedure could be repeated by ligating the main pancreatic ducts in animals. As long as the islet cells stayed intact the animals showed no signs of glycosuria. Therefore the experimental and

Fig. 1: Banting and Best (1)

pathological evidence intensified the belief that the islets of Langerhans were the key to figure out diabetes (12).

In 1920, Banting approached *JR Macleod*, a professor at the University of Toronto, and convinced him to provide him with a laboratory in order to experiment with the isolation of insulin from the pancreas of dogs. Banting got help from one of Macleod's research assistants, *Charles H Best.* Together they successfully isolated insulin and reduced the blood glucose levels in a diabetic dog, whose pancreas had been surgically removed (12, 13).

However, the main problem still was the impurity of the isolated insulin. It still caused pain (due to the saline solvent) and caused local reactions, such as abscesses.

With the help of *James B Collip* the team was able to purify the insulin. In 1922, a 14-year-old was successfully treated for the first time.

When Banting and Macleod were awarded with the Nobel Prize in 1923, Banting chose to give the half of his prize money to Best, followed by Macleod giving half of his own to Collip. Banting publicly acknowledged Best's participation in the discovery of insulin (12).

1.2 Anatomy of the pancreas

The pancreas is a retroperitoneal gland organ, situated in between duodenum and spleen. The weight of a human pancreas ranges between 40 and 150g.

Functionally, the gland organ is divided into two parts: the exocrine- and endocrine pancreas (9, p69).

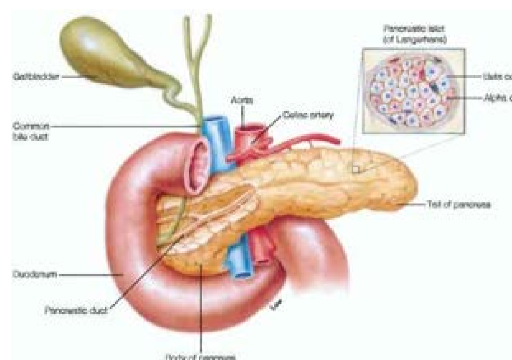

Fig. 2: Anatomy of the pancreas (2)

1.2.1 Exocrine pancreas

The major amount of pancreatic cells belongs to the exocrine pancreas. They are composed of lobules, which consist of acini. Acini produce and secrete pancreatic juice containing digestive enzymes including amylase and trypsin. These acini are connected to a wide network of ducts, into which they secrete their enzymes. The ducts lead to the intestine, where the enzymes are released into the duodenum (9, p69).

1.2.2 Endocrine pancreas

The endocrine pancreas comprises hormone producing cells, part of the islets of Langerhans. Although the endocrine pancreas is just a minor part of the pancreas, there are four main cell types in the islets, which are essential for the metabolism of the body, especially for the glucose regulatory system. The islets are scattered throughout the exocrine pancreas. There are approximately 1 to 2 million islets, which corresponds to about 2% of the pancreatic mass (9, p. 69).

1.3 Glucose metabolism and regulation

1.3.1 Insulin

Insulin is a hormone produced by the beta cells of the Langerhans islets in the pancreas. Until needed it is kept in vesicles (4, p9).

Highest rates of basal insulin can be measured in the early morning according to the peak of cortisol and growth hormones in the bloodstream. The increased blood glucose in the morning, caused by hormones, is called *dawn phenomenon* (14, p68).

The biggest stimulation is an increased postprandial amount of glucose in the blood circulation. The insulin secretion comes in two consecutive waves. The first wave takes place about five minutes after glucose intake; the amount of secreted insulin rises fast and falls fast again.

The second wave is stimulated by a longer lasting increased amount of glucose in the blood circulation. After 6-7 minutes the falling amount of insulin is restored.

After 60 minutes a plateau is reached. This plateau is kept until it is not longer required.

On the cell surface, insulin is needed to increase the number of glucose transporters and allow glucose to diffuse into the cell.

Insulin stimulates the synthesis of glycogen, the lipogenesis and synthesis of proteins in specific organs and tissues. Liver, heart- and skeletal muscle, fat tissue and the brain play a major role in the metabolization process (4, pp9, 25-27).

1.3.2 Glucagon

Glucagon inhibits the glycolysis and stimulates the gluconeogenesis. This hormone is therefore the most important counterpart of insulin. It is produced by the alpha cells of the pancreatic Langerhans islet cells. Glucagon is counteracting the life threatening possibility of hypoglycemia by stimulating hepatic glucose production.

Glucagon is not only found in the liver, but also in fat tissue and adrenal cortex. In fat tissue it stimulates the lipolysis and in the adrenal cortex the glucocorticoid production. It comes to a synergistically amplification of gluconeogenesis (4, p30).

1.3.3 Catecholamine

Catecholamines are released in stressful situations for rapid resource mobilization. They lead to increased contractility of the heart, blood pressure and broncho dilatation. Catecholamine-stimulated beta 2 receptors increase gluconeogenesis and lipolysis in liver, fat tissue and muscles. They help to steady the metabolic cycle (4, pp30-31).

1.3.4 Glucocorticoids

Glucocorticoids, especially cortisol, influence the gene expression and represent a powerful counterpart of insulin. The have a stimulating effect of the gluconeogenesis by expressing key enzymes (4, p32)

1.3.5 Incretin hormones

There are two known important kinds of incretin hormones related to diabetes. The glucagon-like peptide 1 (GLP-1) and gastric-inhibitory peptide (GIP) are emitted by the oral intake of food and stimulate the secretion of insulin and somatostatin. They inhibit glucagon and slow the gastric emptying. GLP-1 and GIP are degraded by the dipeptidyl-peptidase- 4 (DPP-4).

DPP-4 inhibitors and GLP-1 analogues are used in the treatment of diabetes (15, p115).

1.3.6 Counter regulation

The counter regulation system normally corrects inappropriate blood sugar levels immediately and prevents hyper- and hypoglycemia. During a period of low blood sugar level the amount of insulin decreases followed by an increase of glucagon (or epinephrine) to counteract the decrease of the blood glucose level (16). Hypoglycemia elevates the sympathetic nerve activity of the muscle and therefore an increase of alpha and beta adrenergic activity can be noted. Beta activity means a release of free fatty acids for increased glucose production. Alpha activity counteracts beta adrenergic vasodilatation. It may also diminish neuroglycopenic symptoms (17).

1.4 Types of diabetes

1.4.1 Type 1 diabetes mellitus

Type 1 diabetes mellitus (T1D) is an autoimmune disease. The insulin producing cells, the beta cells of the pancreatic islet, are destroyed, leading to an absolute deficiency of insulin and hyperglycemia. The destruction is led by CD4+ and CD8+ T-cells as well as macrophages, resulting in insulitis. It is classified in mainly two different types: immune mediated type (about 90%) and idiopathic type (up to 10%, lack of HLA association). The prevalence is low compared to T2D.

T1D can be associated with other autoimmune diseases such as thyroiditis (up to 30%), celiac disease (up to 9%), pernicious anemia and Addison disease (0,5%) (19).

Many studies have shown an increasing incidence of type 1 diabetes worldwide, varying between countries and within different geographic regions. The highest increase occurs in boys and girls alike at the age group of under five year old (20, 21) although the clinical onset of T1D may occur at all ages. The age adapted incidence of T1D differs from 0,1 per 100.000/year in Venezuela and China and 40,9 per 100.000/year in Finland among 114 populations. The overall median increase of incidence was 2,8% per year (22).

There are four different major phases of T1D: pre-clinical diabetes (sub-clinical signs), overt diabetes, partial remission (honeymoon) and chronic phase (lifelong dependency to external insulin supply). The clinical onset happens at about 80-90% loss of function of beta cells, when the body is no longer able to compensate (19).

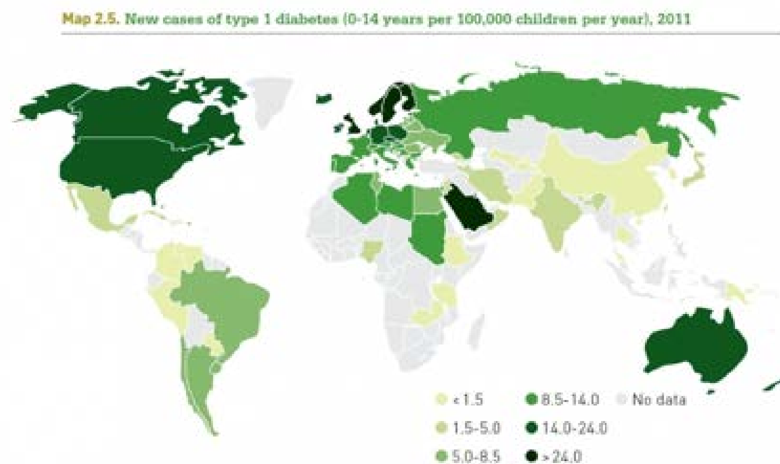

Fig. 3: New cases of T1D according to IDF (3)

Symptoms: Since the rising awareness of diabetic diseases, less children and adults present a diabetic ketoacidosis (DKA) at the onset of T1D, but it is still commonly seen at the age group of under four years old. Diabetic ketoacidosis is a life-threatening acute complication of diabetes. It is not specific to T1D, it can also occur with T2D.

With current methods it is possible to detect individuals with increased risk for T1D based on high risk HLA and islet antibody positivity. Through observation it was possible to develop a better understanding of the pre-clinical phase. Studies have revealed that auto-antibodies and a decreased ability to answer a higher level of blood glucose may develop years before the first clinical symptoms. So far it has not become part of the clinical routine.

At onset, the key-symptoms are polydipsia, unexplained loss of weight and polyuria. DKA is characterized by acetone odor, hyperventilation with air hunger (Kussmaul respiration), abdominal pain with nausea and vomiting, polydipsia and polyuria. Without the right treatment, the patient dehydrates through the loss of electrolytes and fluids. The consciousness fades due to the cerebral edema which can lead to a coma and subsequently death (19, pp672-682).

Environmental factors: The long pre-clinical (latent) period indicates that the autoimmunity is triggered long before the occurrence of the first clinical symptoms. Though the disease has its genetic component, the multi-factorial environment can also contribute the onset of DM1.

Additionally, a discussion topic are infections with viruses such as Coxsackie, Rubella, Mumps, CMV, Rotavirus and Echovirus, early introduction (before 4 months of age) to cow's milk and gluten, vitamin D deficiency (23) and toxins. Also the excess stress to beta cells by growth, body size, weight gain and psychological stress, as well as the hygiene theory (inadequate maturation of the immune system by improvement of environment; through loss of early exposure to pathogens the immune system is no longer able to suppress the autoimmune activity leading to the loss of pancreas function) are well known theories (19, pp672-682).

1.4.2 Type 2 diabetes mellitus

Over the last decades, the number of cases with type 2 diabetes mellitus (T2D) has doubled (19). The increase of incidence of T2D is direct proportional to rising numbers of people with obesity. In recent years, people developing T2D have been younger than before (24). Today, T2D and obesity are major health problems of the health-system worldwide. Unlike T1D, there is a combination of defects of

the pancreatic beta cell function (relative insulin insufficiency) combined with decreased sensibility of the glucose up-taking cells to insulin.

Although T2D has been considered a disease with an age of onset after 40 years, it is now steadily increasing amongst the youth population. Individuals with T2D have a higher prevalence of metabolic problems such as obesity, dyslipidemia and hypertension and therefore a high risk for atherosclerotic disease (19, pp672-682).

Tab. 1: Diagnostic criteria between T1D and T2D (4, p88)

Criteria	Type 1 Diabetes	Type 2 Diabetes
Incidence	rare	frequent
Age of onset	mostly children and adolescents	middle to old age
Onset	acute/ subacute	slow process
Symptoms	polyuria, polydipsia, weight loss, weight loss	mostly none
Body weight	mostly normal	mostly overweight
Insulin secretion	decreased to none	normal to high
Insulin resistance	little or none	strong
Ketoacidosis	tendency high	tendency low to none
Familial incidence	low	typical
Islet cell antibodies	85-95%	none
Plasma C peptide	none	high
HLA association	yes	no
Metabolism	unstable	stable
Insulin treatment	needed	only in an advanced stage

1.4.3 Other types of diabetes

There are many more different types of diabetes. Beside diabetes being a primary disease, there are kinds of diabetes caused by other factors. You can find a short overview of some important types below (19, pp665-668).

1.4.3.1 MODY

MODY means *maturity-onset diabetes of the young* and was described with hyperglycemia at early age. It is inherited autosomal dominant. MODY is a genetic defect of the beta cells, the mutated genes are partly responsible for regulating insulin.

Until now, six major forms have been described. Every form is associated with a defective insulin secretion without a considerable degree of insulin resistance. The different forms describe different levels of severity (19, pp665-668).

1.4.3.2 Pancreatic disease

Hyperglycemia during an acute infection of the pancreas is associated with a poor prognosis, but not every episode leads to diabetes, as well as not every removal of the pancreas (up to 90%), e.g. due to pancreatic cancer, causes diabetes. The pancreas is able to keep its original function, as long as there are enough insulin producing cells left.

A significant problem-group are individuals with cystic fibrosis who develop diabetes (5-15%), since the insulin replacement is challenging, as the patients react sensitively to external insulin supply and are vulnerable to hypoglycemia (19, pp665-668).

1.4.3.3 Drug-induced and endocrinopathy

Some hormones, such as cortisol, growth hormone, glucagon, epinephrine and norepinephrine, can antagonize insulin action. Through external or internal excesses (drug induced or tumors) hyperglycemia and overt diabetes can develop (19, pp665-668).

1.4.3.4 Gestational diabetes

Gestational diabetes is commonly known as hyperglycemia first recognized during pregnancy. The prevalence is increasing parallel to the prevalence of T2D.

Medical complications are a concern for mother and child and include more often a caesarian section as a way to give birth.

Children are large for gestational age. They suffer from macrosomia and postnatal hypoglycemia. Women have a higher risk of postpartum resistance of hyperglycemia.

Risk factors of getting gestational diabetes are advanced age of the mother, high body mass index, multiple pregnancy and family history of diabetes (19, pp665-668).

1.5 Risk factors and prevention

As already mentioned, multi-factorial contribution of environment, genes and other factors can trigger the development of T1D. Trends of statistically significant increase have been shown in Asia (4,0%), Europe (3,2%) and North America (5,3%). A decrease was described in Central America and West Indies (3,6%). T1D is a global disease of rising incidence. Continuous monitoring of incidence is recommended in order to evaluate prevention work (22).

1.6 Therapy

The modern therapy for T1D is composed of periodical blood glucose measurement and multiple day substitution of insulin to imitate a physiological insulin secretion. The dosage of insulin is adjusted to diet and exercise (14, p68).

1.6.1 Insulin

Since the 1980’s, the bovine and porcine insulin, the only available insulin until then, has been replaced by human sequence insulin step by step.

Fig. 4: Insulin pen

Nowadays, insulin can be divided into short, intermediate and long acting types. Insulin is injected sub-cutaneously in everyday use. The intermediate and long acting insulin is used to cover up the basal metabolic rate. The short acting insulin is injected to buffer food intake and to balance blood glucose fluctuations.

The combination of short and long acting therapy is *basal-bolus* regimen or *MDI (multiple daily injection)* (14, pp68-69).

1.6.1.1 Short acting insulin

By injecting insulin subcutaneously, the uptake takes place in the peripheral, not the portal bloodstream. Bovine and porcine insulin needs a long time to be absorbed. It has therefore to be injected 30 minutes before the meal. Human insulin is absorbed much quicker and can be injected much closer to the food intake. The delay of absorption is a result to the chemical structure. It needs to be dissociated before being able to be taken into the bloodstream.

The step taken to resolve this problem was to modify the chemical structure and therefore speed up the absorption. The short acting insulin analogues (Aspart, Glulisine, Lispro (5, p295)) have their peak of action after 1-2 hours (compared to 2-4 hours for a conventional, and slightly less for human insulin). This is the reason for insulin analogues being injected right before eating or even during meals. Using insulin analogues is more comfortable for patients.

Systemic reviews have shown that there is a benefit in using analogues for reduced nocturnal hypoglycemia, post-prandial hypoglycemia and higher pre-prandial blood glucose levels. There was no consistent advantage in glycemic control (14, pp69-70).

Tab. 2: Properties of insulin-preparations (5, p295)

Preparation	Onset (h)	Peak (h)	Effective duration (h)
Short acting			
Aspart	<0.25	0.25-1.5	3-4
Glulisine	<0.25	0.25-1.5	3-4
Lispro	<0.25	0.25-1.5	3-4
Regular	0.5-1.0	2-3	4-6
Long acting			
Detemir	1-4	minimal peak activity	up to 24
Glargine	1-4	minimal peak activity	up to 24

1.6.1.2 Intermediate and long acting insulin

Neutral Protamine Hagedorn (NPH) insulins are the most frequently used insulins worldwide. The insulin analogues (e.g. Detemir, Glargine) are designed to have a relatively steady level of activity by replacing certain kind of amino acids. Long acting insulin analogues are mainly given once daily (14, p73). In Layman's terms it means that glucose levels between meals are lower and the risk of hypoglycemia during night-time sleep is reduced. (5, p295). The morning cortisol and high blood glucose level can be intercepted by late injection (14, p73).

1.6.2 Conversion food to bread units

The required amount of carbohydrates differs in each person and depends on the level of activity and personal food preferences. Patients with diabetes have to match the given dosage of insulin according to the ingested amount of carbohydrates to keep up with their glycemic control. Carbohydrates influence the blood glucose level by time and manner given (25).

Tab. 3: Simply counting carbohydrates (6, 7)

Food	**Size**	**Carbohydrate exchange (bread unit BU)**
Krapfen	1 piece	2 BU
rice, pasta, couscous	1/3 cup	1 BU
apple, orange	1 small, 1/2 big	1 BU
kohlrabi, eggplant, broccoli	5g per 1/2 cup cooked, 1cup raw	1 BU
Popcorn	3 cups	1 BU
cows milk	1 cup	1 BU

Comment: 1 cup matches 8 fluid ounces

1.6.3 Objectives

1.6.3.1 HbA1c

Physiologically, glucose has the ability to bind to proteins by glycation. Different extracellular proteins, not just hemoglobin, can be glycated. The level of glycation increases with the amount of glucose. Furthermore, it is an irreversible effect. Once glucose has bound to the protein it is stuck until degradation (4, p44). Erythrocytes have a life span of 120 days. As long as the erythrocytes live, the hemoglobin stays glycated. That makes the HbA1c, the glycated hemoglobin, a good long term parameter of metabolic control (3 to 4 months control) the most widely used clinical test in diabetes.

There is a relationship between glycemic control, manifested as HbA1c, and the development of micro-angiopathy, especially retinopathy. There is a smaller association between higher HbA1c and macro-angiopathy.

The results of the blood test can either be reported according to International Federation of Clinical Chemistry (IFCC) in mmol/mol and/or according to National Glycohemoglobin Standardization Program (NGSP) in % (4, pp107-111).

1.6.3.2 Exercise and T1D

Healthy people are able to adjust automatically to all kinds of blood glucose conditions and situations, as mentioned in the chapter „Glucose metabolism and regulation“. Individuals with T1D are not able to adapt properly, they are depending on their subcutaneous injection of insulin and the given amount of glucose.

During exercise the normal plasma insulin level is low in healthy people. Patients with diabetes, who injected the same dose they normally use on non-exercise days, have a normal or increased insulin level. High plasma insulin levels inhibit the normal hepatic gluconeogenesis for exercise and impel the glucose uptake into the muscle. Therefore, the occurrence of hypoglycemia, especially during and after exercise, increases.

If the insulin dosage is too low, the liver produces more glucose than needed, together with the release of free fatty acids from adipose tissue and inhibition of

glucose uptake of the muscle. The production of ketone bodies and muscular fat oxidation increases as a result.

For persons with T1D, exercising means keeping the balance between hypo- and hyperglycemia (26, pp592-607).

Glycemic control is a challenge not only during exercise. Large deviations commonly occur many hours after training and the risk of severe hypoglycemia increases. The fear of hypoglycemia is a major reason for T1D patients to refrain from participating in daily exercise sessions.

However, evidence shows that regular exercise does not merely improve the overall glycemic control, it also benefits to cardiovascular health, lipid profiles and psycho-social wellbeing.

Recent improvements, like continuous glucose monitoring and insulin delivering systems, e.g. insulin pump, lead to improved care for patients with diabetes mellitus type 1. They allow a better control and safer participation in exercise (27).

1.6.3.3 Metabolic control

Metabolic control represents how far the diabetic metabolism differs from a healthy one. It is mostly assessed by blood samples focusing on the blood glucose level. A patient with diabetes has a good metabolic control if he or she is able to maintain a near-normal blood glucose concentration throughout the day (14, p61).

The Diabetes Control and Complications Trial (DCCT) constituted that a good metabolic control has beneficial effects on long term consequences in young and mature patients with diabetes mellitus type 1. It is recommended to optimize the metabolic control as early as possible to a nearly normal glycemic metabolism in order to prevent and reduce the risk for micro-vascular alterations.

Diabetes treatment and the amount of insulin injections have been intensified during the last 15 years. The therapy has changed from twice-a-day to multiple injections to continuous subcutaneous insulin application. Since the year 2000, the insulin injection by means of a pump has increased considerably. The self-monitoring of the blood glucose concentration increased parallel to the increase of the use of an insulin pump, since the knowledge of the measured blood glucose defines the applied amount of insulin.

In order to clarify the importance of metabolic control, patients with T1D should be given the knowledge and skills needed to carry out important behavioral tasks (e.g. blood glucose monitoring frequency, insulin administration, dietary and physical activity). The combination of behavioral teaching and involvement of emotional, social and family processes, as well as improvement of individual's coping skills together is more potent for a good management of the disease (multi-component intervention) (28).

The patients have to keep the balance of glycemic control while minimizing the risk of hypoglycemia. Important tasks involve addressing the issue, considering the risk factors for iatrogenic hypoglycemia and developing an individualized therapy. Iatrogenic hypoglycemia can be triggered by the drug dose, timing of drug administration, food ingestion, exercise and interplay with alcohol and other drugs (18).

Significant predictors of metabolic control are (specifications indicated in brackets stand for statistical factors for worse metabolic control): Age (older), sex (female), diabetes duration (longer duration), BMI (upper BMI tercile), insulin dose (higher insulin dose) and migration background (28). Young adults between 14 and 18 years had a worse glycemic control with an, on average, 0,56 higher HbA1c than children from 2 to 8 years. Children under regular supervision in the hospital (three to four times a year) had a lower HbA1c (on average 0,46 lower) than children who visited less often. The glycemic control was better in children of married parents than separated, single or divorced (on average 0,47%). This effect may be caused by the median number of glucose checks per day (29).

Furthermore, in children and adolescents with lower glycemic control (higher HbA1c concentrations), caries, gingivitis and a decreased salivary flow occur more often (30).

Good glycemic control, intensified therapy with insulin and younger age are also related to a good health-related quality of life (31).

1.6.4 Technical additives

Technical additives and methods for monitoring glucose levels play a crucial role in the life management for patients with diabetes. One of the most important tasks

beside the external supply of insulin is alerting in case of occurring hypoglycemia. For optimal treatment of diabetes, the blood glucose levels has to be kept in range, so that neither long term complications from hyperglycemia nor acute complications such as hypoglycemia occur (32).

1.6.4.1 Capillary blood glucose monitoring

Fig. 5: Capillary blood glucose meter

The control of blood glucose is a very important component of the therapy for diabetes mellitus. Therefore, patients with T1D or insulin dependent T2D have to measure the capillary blood glucose periodically every single day due to unpredictably occurring variations in the blood glucose levels.

In order to test their blood glucose level, patients need to use a needle for puncturing their skin to get blood, special enzyme-impregnated reagent strips and an appropriate meter. The main reason for poor patient compliance is the discomfort while using the lancet. Most needles nowadays are spring loaded and have a depth adjustment.

Depending on the production companies, the meters are equipped with different features, like the ability to generate blood glucose profiles when connected to a computer and advice on insulin dosage prior a meal according to an installed algorithm.

All meters are prone to be less precise at lower blood glucose and have an upper limit of recognition (14, pp61-62).

1.6.4.2 Insulin pen

At the rear end insulin pens contain a barrel for a 3ml cartridge. The injected dosage is adjustable and the insulin is delivered through a fine needle. The needle is removable and located on the opposite end of the barrel.

The advantage over conventional syringes is that the needle is thinner and stays sharp for a longer time due to the needlessness of piercing through rubber to mount insulin from a vial.

1.6.4.3 Insulin pump

The use of insulin pumps in children and adolescents increased over the last 15 years and led to further development in pump technology (33).

A portable electromechanical pump is used to imitate a non-diabetic insulin delivery. Most common pumps have the size of a pager. They contain a reservoir of insulin, a small control mechanism linked to a computer, a small battery-operated motor and a cannula with a tubing system used as subcutaneous infusion set (34).

Insulin is given continuously in pre-determined basal rates over the whole day. In order to compensate for the additional need of insulin due to food-intake or hyperglycemia, patients can give boluses when needed. These standard pumps are not equipped with an alerting system (35).

Pediatric investigations have shown that pump therapy is associated with a decrease of the HbA1c level and reduced numbers of hypoglycemia. Simultaneously, overweight has not risen (33).

1.6.4.4 Continuous glucose measurement

Other than single signal information, continuous glucose monitoring (CGM) seeks to monitor indications related to current glucose levels. These signals potentially allow the estimation of blood glucose levels over a broad range and the ability to provide further information. The sensors are placed subcutaneously (32).

The main objective of CGM is to identify glucose trends and reduce the risk of hypoglycemia in frequency and severity (34).

1.6.4.5 Sensor-augmented pump

A new development in technology production is the combination of an insulin pump merged with a continuous glucose monitor. It allows the user to measure the glucose levels subcutaneously with a high frequency. The combination is called

sensor-augmented pump therapy (SAP). Compared to multiple daily injections, controlled studies have shown that SAP therapy helps to decrease HbA1c levels and glycemic fluctuations in children and adults (36). The SAP therapy allows patients and physicians to record the treatment and the patients' reaction to it through Internet-based software (37).

A study presented in the year 2010 compared two groups of patients with diabetes within the age range of 7 to 70 years. One group was treated with multiple daily injection therapy (MDI), the second with SAP. All patients received intensified training on how to use the provided device. The SAP study group got introduced to only one advice at a time over a period of five weeks. The patients were seen 3, 6, 9 and 12 months after randomization for a follow up.

After one year, the mean HbA1c levels (initially 8,3% in both study groups) had reduced to 7,5% in the SAP group (0,8±0,8%), compared to 8,1% in the MDI group (0,2±0,9%). The difference of the groups was 0,6%. HbA1c levels also differed between adults and children (7 to 18 years). The absolute reduction among adults in the mean HbA1c level was 1,0±0,7% in the SAP group and 0,4±0,8% in the MDI group. Among children, the decrease of the HbA1c level in the SAP group was 0,4±0,9% compared to the MDI group with an increase of 0,2±1,0%.

The most considerable decrease of HbA1c occurred in both children and adults of the SAP group within the first three months of the trial. The decreased level of the glycated hemoglobin remained lower than levels of the MDI group for the rest of the study. It was shown that an increased use of the SAP sensors is associated with a higher reduction of HbA1c levels within one year.

Overall 27% (34% adults, 13% children) of the SAP group and 10% (12% adults, 5% children) of the MDI group were able to reach the goal of HbA1c levels below 7%.

On average, the weight of the included adults increase by about 2,4 kg in the SAP group and 1,8 kg in the MDI group.

In both study groups and over all ages the rates of severe hypoglycemia and ketoacidosis were alike.

In summary, an advanced metabolic control for patients with suboptimal glycemic control has been exhibited, much greater than expected compared to using insulin-pump therapy (37).

It has been demonstrated that the time spent in a hypoglycemic state was decreased while using SAP therapy compared to pump therapy alone. Nevertheless, episodes of hypoglycemia could not be averted (38).

1.6.4.6 Artificial pancreas

An arising method is the artificial pancreas, also known as closed-loop insulin delivery. It is a new therapeutic approach composed of a linked CGM and an insulin pump. The wireless automated data-transfer enables the communication between CGM and the pump without human interference.

A close loop system works according to pre-dominated algorithms in intervals from 1 to 15 minutes. Intestinal measured glucose levels prescribe the following action of the pump.

Until now, two different algorithms are tested: Fully closed loop, in which the pump is authorized to work on its own, and closed loop with meal announcement. In case of over-insulinization an integrated glucagon cooperation system is supposed to be integrated (39).

Until now the artificial pancreas has only been tested in a controlled laboratory environment. The next step is to assess this system in a patient's home. The future use will depend on the medical and technical supportive infrastructure (34).

1.6.4.7 Diabetic alert dog

Dogs are a unique medical aid in alerting hypoglycemia. One report points out, that more than one third of untrained dogs living with patients with diabetes change their behavior during episodes of hypoglycemia over time (40).

Fig. 6: DAD - Special alerting behavior I

Despite the high acquisition cost, an increasing number of patients with

diabetes type 1 rely on diabetic alert dogs for detecting and alerting hypo- and hyperglycemia. Owners of diabetic alert dogs and trainers have reported that the precision of the alerting behavior equals blood glucose monitoring technology. They also described improved glycemic control and a better quality of life (41).

1.7 Complications

The brain’s function depends on constant supply of glucose from the blood circulation (42). It is not able to synthesize or store glucose (for more than a few minutes). During normal or elevated arterial glucose concentration, the brain’s metabolism needs less glucose than provided by the blood circulation. As soon as the arterial blood glucose concentration falls below the physiological range, the provided glucose is the limiting factor for the brain’s metabolism. The constant supply with glucose is ultimately important for survival.

If it was not for the devastating effects of hypoglycemia to the brain, the treatment of the glycemic management of diabetes (T1D and T2D) would be rather uncomplicated and it would be easy to prevent hyperglycemic complications (such as ketoacidosis, hyper-osmolar syndrome and long term microvascular and macrovascular risks) (18).

1.7.1 Hypoglycemia

Dealing with Hypoglycemia is part of daily life for patients with diabetes. The frequency of occurrence for people with T2D is lower than in T1D. Severe periods of hypoglycemia occur in T2D about 10% compared to T1D, even while receiving an aggressive therapy with insulin.

Patients with diabetes, who try to improve or maintain their glycemic control, show countless numbers of asymptomatic hypoglycemias in a lifetime. In approximately 10% of the time their plasma glucose level is lower than 50-60 mg/dl. They experience an average number of two episodes of symptomatic hypoglycemias per week and at least one episode of severe, minimally temporarily disabling hypoglycemias per year. About 2-4% of T1D patients are lethally attributed with hypoglycemia (18).

Clinical studies have shown that dysglycemia in T1D can impair neural cells in activity, survival and function. Young age, a diabetic ketoacidosis at onset and severe hypoglycemia under the age of six followed by chronic hyperglycemia seem to be the most prevalent neurotoxic conditions for the development of impairments in brain morphology (42).

A major problem for patients with diabetes is the unawareness of hypoglycemia. Especially for experienced individuals with diabetes, the neuroglycopenic symptoms are common and therefore non-specific and imperceptible. Many episodes of hypoglycemia are not recognized and therefore dangerous (16). 25% of T1D patients mention unawareness of hypoglycemia. This heightens their risk for grave episodes of hypoglycemia six- to seven-fold (43).

Symptoms range from anxiety, palpitations, hunger, sweating, tremor, behavioral changes, cognitive dysfunction to seizures (18), tachycardia, coma and ultimately death (32). Whilst short periods of hypoglycemia only cause temporary issues, severe and long-lasting episodes of hypoglycemia can cause permanent damage to the brain.

Nocturnal Hypoglycemia: Most severe events of hypoglycemia occur in the night during sleep. It was observed that the nocturnal frequency of hypoglycemia is increased following afternoon exercise (38).

In this connection, the problem is not only the occurrence of the hypoglycemia itself, but also the psychological effect and the fear of it. Patients have been reported to feel high levels of anxiety, ostracized from sociality and lower levels of overall happiness. The fear of the above mentioned points can be a barrier of good glycemic control (18, 35).

A questionnaire of adolescents under the age of 19 has shown that they had an overall feeling of high quality of life, though it was lower in patients who had experienced severe hypoglycemia over the last year. The risk of severe hypoglycemia caused more disturbance than mild forms of hypoglycemia, insulin injections and blood sugar monitoring. The perceived concern increased in extreme situations like exercise, parties and travel.

The major concern within this group of questioned adolescents was the fear of unconscious severe hypoglycemia followed by late complications and severe,

conscious hypoglycemia while they are in need of assistance. Mild hypoglycemia and ketoacidosis were the least concerns (44).

1.7.2 Diabetic ketoacidosis

Diabetic ketoacidosis (DKA) develops from uncontrolled diabetes and insulin deficiency. It is a severe syndrome characterized by metabolic acidosis, hyperglycemia and hyperketonemia (14, p87). DKA is one of most serious acute metabolic emergency cases for patients with T1D and T2D (26, p799). Due to increasing numbers of T1D the cases of DKA are on the rise. In the USA, about 50% of deaths of T1D patients in the age under 24 can be imputed with the syndrome. The forms of manifestation can be divided into mild, moderate and severe, according to biochemical and clinical features.

Triggering events or influencing factors can be infection (up to 56%), insulin errors or even insulin omission (up to 41%) and onset of T1D with DKA (up to 22%). Less frequently, heart attack, stroke, pulmonary embolism, alcohol excess and steroid usage can lead to DKA (14, pp. 87-89, 26, pp800-801).

Pathogenesis: DKA results from relative or absolute insulin deficiency and the overwhelming stimulation of counter regulatory mechanisms of stress hormones (glucagon, cortisol, adrenalin and growth factors).

Hyperglycemia mainly derives from gluconeogenesis of the liver combined with higher glycogenolysis and the inhibition of glycogen synthesis. The increased lipolysis leads to higher concentrations of free fatty acids (FFA). FFAs are basic products for ketogenesis. The end products of ketogenesis lead to metabolic acidosis and the typical foetor ex ore.

The kidneys work to reduce the excess of glucose by osmotic diuresis. In order to achieve this goal, the patients face a massive loss of fluids (up to 15% of bodyweight) and electrolytes, especially sodium and potassium (4, pp332-333).

Clinical symptoms: The first clinical signs are thirst, polyuria and weight loss. Some patients complain of nausea and vomiting, sometimes diarrhea. Although in 30% of cases an infection is a triggering event to DKA, most patients are normo- or even hypotherm. The hypothermia results from peripheral vasodilatation caused by the metabolic acidosis.

The patients are hypotonic and show a *Kussmaul breathing,* hyperventilation with irregular and deep breathing as attempt of the body to compensate for the metabolic acidosis. The neurologic symptoms vary from untroubled vigilance to coma. At the time of hospitalization about 70% of the patients are at least somnolent (4, pp331-340).

Tab. 4: Therapy of DKA (4, p336)

Liquid substitution	liquid deficiency 5-8l - 50% substitution of liquids in 8hours 1st hour: 1-2l NaCl 0,9% 2nd-4th hour: 0,5l/h NaCl 0,9% 5th- 24th hour: 0,25- 0,5l/h NaCl 0,9% - if blood glucose level is 250mg/dl: glucose 5% and NaCl 0,9% in even parts
Insulin therapy	bolus therapy 0,15IE/kg regular insulin iv, when potassium >3,3mmol/l if potassium is lower, first potassium substitution - continuous regular insulin infusion 0,1IE/ kg/ h to decrease blood glucose from 50-70mg/dl per hour - if reduction <50mg/dl, double insulin - if reduction >70mg/dl, halve insulin, if necessary glucose 5% infusion
Potassium substitution	- serum potassium <3,3mmol/l: 40-60mmol/h iv substitution, until potassium reaches level >3,3mmol/l - serum potassium 3,5-5,5mmol/l: 20-30mmol/h iv substitution - serum potassium >5,5mmol/l: close monitoring, no substitution

1.7.3 Hyperglycemic Hyperosmolar State (HHS)

HHS is a special form of DKA and a hyperglycemic emergency crisis. Mostly affected are dehydrated T2D patients with extremely high blood glucose levels (above 600mg/dl).

Due to the small amounts of insulin secreted by the pancreas the lipolysis is still inhibited and there are no or only minimal amounts of ketone bodies.

Triggering events resemble those of DKA. Acute infections (pneumonia and urinary infections), non compliance or application errors and severe underlying diseases cover most of it. Mortality is higher due to triggering diseases and is estimated at about 15%.

Clinical symptoms: The clinical symptoms develop during several days to weeks and are not specific at the beginning. Fatigue and exhaustion are commonly

reported. Furthermore, the patients may feel symptoms like blurred vision, polyuria, polydipsia, weight loss and cramps in the calves.

The patients show signs of dehydration like dry mucosa and skin as well as hypotonia.

Neurological symptoms such as depression of vigilance, aphasia, hemi-paresis as well as focal and general cramps can occur. Under adequate therapy the neurological symptoms are potentially reversible.

Adequate therapy includes rehydration as well as infusion of low-dosed insulin and potassium (4, pp343-347).

Tab. 5: Differences between DKA and HHS (8)

	Diabetic ketoacidosis	**Hyperglycemic Hyperosmolar State**
Blood glucose levels	mostly >300mg/dl (not necessarily this high)	mostly >600mg/dl
Ketonuria	++ , +++	+/- , +
pH level	<7,3	>7,3
Bicarbonate	< 15mmol/l	>15mmol/l
Osmolality	variably	mostly >320mOsmol/kg

1.7.4 Hyperglycemia and long term consequences

Angiopathies are the most common cause of death in patients with diabetes (over 75%). Long term consequences depend on the localization (retina, kidneys, coronary arteries, cerebral arteries, peripheral vessels) and the expansion of affected areas.

A distinction is drawn between micro- and macroangiopathy. Both types of angiopathy are influenced by age of manifestation, quality of metabolic control and certain risk factors (4, p354).

1.7.4.1 Microvascular consequences

Hyperglycemia is assumed to be the main pathophysiological cause for the development of microvascular issues. Although there are already several

pathways known, the molecular mechanisms is not investigated to the full extent. High blood glucose levels lead to an increase in the formation of advanced glycation end-products. Furthermore, protein kinase C is enabled, the production of reactive oxygen species and eventually the oxydative stress is stimulated. Hyperglycemia triggers the activation of several pro-inflammatory pathways.

Randomized trials, organized by the DCCT, have shown that tight glucose control and therefore good glycemic control over a longer period of time significantly reduce the risk of microvascular diabetic complications (diabetic retinopathy, nephropathy and neuropathy) (19, pp898-901).

1.7.4.1.1 Diabetic eye disease

Nearly all patients with diabetes mellitus develop a form of eye disease over the years. Although the risk of cataract and retinal vascular occlusion is increased too, the most common diabetic eye disease is the diabetic retinopathy (DR). DR is accountable for visual impairment in about 10% of adults with diabetes in the developed world.

Tab. 6: Risk factors for diabetic retinopathy (9, p892)

Modifiable risk factors	**Non-modifiable risk factors**
Hyperglycemia	Age
Hypertension	Diabetes duration
Dyslipidemia	Ethnicity (Hispanic, South Asian)
Cataract surgery	Genetic predisposition
Obesity *	Puberty
Smoking *	Pregnancy
Alcohol consumption *	Nephropathy

The progressive nature of this disease (lesions including hemorrhages, micro aneurysms and vasodilatation) can lead to underserved (or even not perfused) areas. Retinal edema and exudates are caused by increased vasopermeability. Hyperglycemia stirs pathological vessel growth in the eye, resulting in hemorrhage, neovascular glaucoma or tractional detachment. All of these complications can lead to visual impairment or even blindness.

Main purpose of the medical assessment is to detect already acquired damage and prevent its further development. In case of absence of manifested impairment, the existing risk factors have to be revealed and, if possible, removed.

Even severe DR may have no symptomatic visual impairment. Merely asking about the patient's subjective feelings can be misleading.

Several stages of DR can be classified. Non proliferative diabetic retinopathy (NPDR) is the first pathological stage and can be divided in mild, moderate and severe followed by proliferative diabetic retinopathy (PDR). A diabetic edema can occur together with every stage; if it is clinically significant, medical intervention is needed in order to prevent visual loss.

Systemic optimization is the most effective treatment in preventing DR. Adequate glycemic control, blood pressure control and lipid lowering therapy (multi-factorial intervention) can lower the incidence of DR by 58% in 8 intensified years. If the damage has already occurred, a panretinal photocoagulation or a vitrectomy can be applied to ease the DR. A clinical symptomatic edema can be treated with steroids, vitrectomy, focal laser therapy and intravitreal anti-VEGF agents (26, pp889-903).

1.7.4.2 Diabetic neuropathy

A distinction is made between sensorimotor polyneuropathy and diabetic autonomic neuropathy.

The sensorimotor neuropathy affects mostly sensitive and motor nerves at the lower extremities. It may slowly spread up the legs or arms in a symmetrical fashion. Patients often report a loss of sensibility and complain about paraesthesia (tingling or burning feeling), cramps or sometimes even pain. The sensations of temperature and pain are decreased, whereby the probability for unrecognized injuries increases. Main problem with motor polyneuropathy is the tendency to stumble caused by a weak foot dorsiflexion. The diabetic neuropathy is a main cause for the diabetic foot syndrome which accounts for many hospitalizations and amputations among patients with diabetes mellitus.

The typical neurological screening methods for sensorimotor polyneuropathy are the ankle reflex, Semmes-Weinstein Monofilament test (sensibility), tuning fork test

(vibration feeling) and temperature test. Neuropathic pain significantly reduces the quality of life, especially due to decreased daily efficiency and sleep disturbance.

The autonomic polyneuropathy manifests in autonomic innervated organs. Every organ can be affected, although the most likely organs are heart (silent myocardial infarction, decreased variability of the heart rate), the urogenital system (bladder atonia, urinary retention, erectile dysfunction) and the gastrointestinal tract (reflux, diarrhea, constipation). Furthermore, the neuropathy can be reason for disturbed perception of hypo- and hyperglycemia (4, pp473-494).

1.7.4.3 Diabetic nephropathy

The development of a diabetic nephropathy (DN) indicates an advanced case. The damage is irreversible and progressive. Typical signs are high blood pressure, microalbuminurea, proteinurea and decrease of glomerular filtration rate (GFR). Without therapeutical intervention the patients with diabetes transcend the point of no return and slide into terminal renal failure. T1 and T2 patients with diabetes with poor glycemic control are equally concerned (4, p361).

In western countries, diabetes mellitus is the most common cause for terminal renal failure. Nowadays, the detection of microalbuminurea is the only commonly used early warning system for diabetic nephropathy. It occurs long before the manifested loss of function. The persistent manifestation of microalbuminurea has to be differentiated from the reversible. The reversible form can be caused by sugar imbalances, physical stress, urinary infections, uncontrolled blood pressure, surgical intervention, feverish infections and heart failure. If persistent microalbuminurea is detected, the renal function has to be monitored regularly.

Tight glycemic control in primary and secondary prevention is the most important task to slow down the progress and even give a chance for partial recovery (4, pp439-443).

1.7.4.4 Macrovascular consequences

Numerous clinical and epidemiological studies have shown that patients with diabetes develop arteriosclerotic diseases more often and earlier than people

without diabetes. The progression is faster and severe complications (myocardial infarction, stroke and ischemic gangrene of the foot) happen more frequently.

The diabetic artery calcification does not differ from those without diabetes, merely the quantity of incidence is increased. All typical forms of alteration in blood vessel structure (intima plaques, media sclerosis, diffuse intima fibrosis) are more common in patients with diabetes (4, pp354-358).

Macrovascular events were not decreased significantly by reduction of HbA1c and better glycemic control, although there was a slight decrease in cardiovascular risk factors. Macroangiopathy is caused by many factors (obesity, hypertension, hyperlipidemia, hyperglycemia), and a treatment approach to multiple factors would be more effective (19, pp902-904).

1.7.4.5 Diabetic foot disease

The etiology of the diabetic foot syndrome cannot be classified in micro- or macrovascular consequences. High plantar stress (e.g. tight shoes, deformities) combined with neuropathy and/or angiopathy (Peripheral Arterial Occlusive Disease (PAOD)) together with cellular healing disorders (caused by glycolization) lead to chronic foot lesions.

Up to 15% of patients with diabetes (both T1D and T2D) get one or more amputations of extremities during their lifetime. Most of the parties concerned are over 65 year old and suffer from the impact of their quality of life. With 40-75% of non-traumatic amputations the diabetic foot syndrome is the most common cause for amputation.

The non-sensible foot can be irritated in different ways:

- Constant pressure (tight shoes) for many hours without pain can lead to local-ischemic necrosis.
- High pressure for a short period of time affects the foot directly. Small objects (nail, sharp stone) immediately damage the foot mechanically.
- Repeated moderate pressure results in inflamed tissue autolysis. The inflammation creates advantage for ulceration.

Clinical presentation: The typical ulceration can be found at predilection sites (metatarsal bone I, heel). The optical appearance is round with a hyperkeratotic border as sign for a high pressure load. Even inconspicuous ulcerations can be deep and inflamed.

Tab. 7: Classification by Wagner/Armstrong (4, p501)

	0	**1**	**2**	**3**	**4**	**5**
A	pre- post ulceration (5%)	superficial wound (5,2%)	wound extends to tendons or capsula (6,8%)	wound extends to bone or joint (33%)	necrotic parts of the foot (23,1%)	whole foot is necrotic
B	with infection (0%)	with infection (4,5%)	with infection (11,1%)	with infection (34%)	with infection (43,3%)	with infection (100%)
C	with ischemia (7,7%)	with ischemia (8%)	with ischemia (13,2%)	with ischemia (37%)	with ischemia (56,3%)	with ischemia (100%)
D	with infection and ischemia	with infection and ischemia (13,8%)	with infection and ischemia (18,8%)	with infection and ischemia (41,8%)	with infection and ischemia (59,3%)	with infection and ischemia (90%)

Comment: The numbers in brackets show the relative risk of amputation

The therapy of a diabetic foot syndrome can be divided in conservative and surgical. Absolute pre-condition for healing the foot conservatively is the effective relief of the pressure. Besides this, one of the most important conditions is achievement of good metabolic control in order to support healing and prevent inflammation as well as further progress of the already taken damage.

The ischemic and inflamed areal has to be ablated regularly to induce granulation. An early and sufficient antibiotic therapy is essential for good chances of recovery.

The surgical therapy of the diabetic foot syndrome should respect three principles in the same order: handling the infection, revascularization and amputation. Exception is the emergency case caused by superinfection of the tissue and imminent sepsis (4, pp495-513).

1.8 Diabetic alert dog

Diabetic alert dogs are specially trained assistance dogs that support patients with diabetes to ensure their glycemic control.

Fig. 7: DAD - Special alerting behavior II

Assistance dogs are known to have many benefits for their owner, including the influence on physical and psychological wellbeing and social integration. Diabetic alert dogs rate among medical detection dogs and are kept as companion animals. They are able to detect changes in the glucose system of the diabetic patient prior to the onset of symptoms.

A recent study discovered Isoprene as volatile organic compound. Isoprene is long known as by-product in the synthesis of cholesterol, although not all pathways are known yet. The increased quantity of Isoprene during hypoglycemia can be measured in an exhaled breath test. Dogs may be able to sniff changes of Isoprene thanks to their powerful scenting ability (45).

Besides the medical benefits, the assistance dog helps to manage the daily life, raises self-esteem and increases safety (46). Several surveys have been conducted on diabetic alert dogs so far. Most of the patients with diabetes reported reduced concern about hypoglycemia (61,1%) and hyperglycemia (61,1%), enhanced quality of life (75%) and less worries about doing sports (75%) (41).

A recently presented research trained six dogs from shelter with suitable conditions to detect the hypoglycemic scent. They were trained by a professional trainer with positive reinforcement. The dog was rewarded after successfully detecting a hypoglycemia sample on its own account. The trained dog had to identify the hypoglycemia-sample amongst seven different samples (two normoglycemia and four plain samples). Every canine was tested eight times with four patient samples in two replicated trials. Statistically, all dogs displayed a significantly higher sensitivity in detecting the hypoglycemia sample (50%-87,5%) than the expected coincidental alert (14%). The dogs' specificity ranged from 50%

to 89,6%. Overall, the four best dogs presented a sensitivity of 87,5% and a specificity of 97,7%, the weakest performed at 50% sensitivity and 89,6% specificity (47).

Companionship was the third most described factor for acquisition of an assistance dog. Only a low percentage of patients described unwanted attention since receiving the dog. The reported overall benefit of having the assistance of a diabetic alert dog is the increased independency of the owner (46).

1.9 Animal Training Center

The Animal Training Center (ATC) was established by Anna Oblasser in the year 2006 after returning from her education at the College for Exotic Animal Training and Management Program (EATM) in America. She and her team are specialized in positive behavioral training with animals. Aside from wildlife education and zoo animal management, dog-training plays a major role in the business.

For a couple of years, Anna Oblasser and her team rose to the challenge to train diabetic alert dogs (DAD) which are able to detect hypoglycemia (<75mg/dl) and hyperglycemia (individual limit, approximately above 220mg/dl) (48).

1.9.1 Necessary conditions

1.9.1.1 Selection of the dog

Every dog is able to learn to recognize the scent of hypoglycemia, but not every dog is suited for the work as an assistance dog. The dogs are selected based on their temperament, sociability, adaptability and confidence. Furthermore, the dog's snout has to be long in proportion to the body in order to ensure a sufficient olfactory sensitivity. They have to be in good physical shape and health in order to fulfill their work properly and for as many years as possible (47).

The ATC educates different kinds of dogs. The careful training for ATC-bred puppies starts at the early age of two days. After three months, they come to live with a host family for six to twelve months, according to the dog's maturity. The host families have the mission to train the basic commands under regular

supervision of the ATC, and to expose the dog to as many different locations and situations as possible.

After this basic training, the dogs return to the ATC and receive professional schooling through ATC trainers. Eventually, the DAD has to be able to master every daily challenge and learn to obey every given command. They learn to alert hypo- and hyperglycemia to their owner, as well as specially commanded behaviours, e.g. to retrieve the blood glucose meter, to retrieve carbohydrates and call for help if needed. The dogs are trained to press an emergency button and show alerting behavior consequently until help arrives. A DAD is not just trained as service dog; it is a friend and supporter in an everyday life situation. It is important, that the families are also willing to accept it as a new family member.

A DAD has to act independently in case of hypo-and hyperglycemia. It is his duty to warn the owner or family. The time aside from alerting, the dog is a “normal” family dog and companion.

Besides their self-bred dogs, the ATC trains suited dogs from shelters and dogs already living with patients with diabetes. The procedure, except for the host family, is the same (48).

1.9.1.2 Patient and family

In order to obtain a DAD, the applicant-family has to go through different stages. Before the application, the new family has to have an introductory meeting with the trainers (48). Diabetic alert dogs need constant training and supervision from their owners to maintain the precise work (47, 48). Not all families are aware or compliant of this fact and an introductory meeting helps to clarify the expectations.

After the introductory meeting, the families and patients with diabetes can formally apply for a DAD. To learn the fundamental basics of training with positive reinforcement, including clicker training and animal behavior, the families have to participate in a special training workshop (“Chicken Camp”), especially designed by the ATC to learn the basics of clicker training. This workshop does not only provide the families with an opportunity to learn about the training mechanism, it also provides the ATC-trainers with an opportunity to get to know the families and assess if they can muster the ability to train a dog properly in the future.

After passing these two steps successfully, the trainers look for a good match. Not every dog fits every family or patient with diabetes. Eventually, the trainers at the ATC aim at balanced and harmonic teams.

While the dog receives its final training at the ATC, the chosen family gets acquainted to the dog gradually during short visits to confirm the match. After the training is finished, the patient with diabetes and/or the family pays a one-week visit to the ATC, during which dog and human get an intensified training together.

Even after finally having received the DAD, the ATC and the families stay in touch regularly to supervise the training, the alerting behavior and the collaboration (48).

1.9.2 Training

The dogs are trained using positive reinforcement methods. The clicker, an item originally used in dolphin training, helps to acknowledge right behavior at the right moment. The precision of this method and the given goodies motivate the dogs to learn at high speed and work enthusiastically (48).

The specialized training for the scent of hypoglycemia takes place with samples of saliva. During hypoglycemia, the patient with diabetes has to chew a cellulose tissue. After freezing the samples, they are sent to the ATC, where the dogs are trained to recognize this specific scent. Since alerting hyperglycemia is not specifically trained with the dog, it develops the ability to sense hyperglycemia automatically after spending a certain amount of time with its patient.

Fig. 8: Samples of saliva

Once the dog is aware of the target-scent, the trainers add specific alerting behaviors, until the dog links the behavior to the scent. Special alerting signs are: barking, giving a paw, retrieving a special cord or blood glucose meter and pressing an emergency button until the patient reacts or help arrives.

A DAD trained by the ATC must learn to recognize this specific scent in every possible situation, with or without stress, even during the night and whilst playing

with other dogs. The training at the ATC is finished when the trainers are satisfied with the dog's performance (Interview Oblasser).

1.10 Hypothesis

Diabetic alert dogs are social, emotional and medical assistance to children and adults with T1D and are able to detect hypo- and hyperglycemia accurately.

2 Methods

The first year of ownership is known as familiarization phase, in which the dog and its new family get used to each other. During the initial phase, the new found pair (patient and DAD) has to manage many new situations together in order to get to know each other. Due to several misunderstandings and testing each other, the alerting behavior can be unreliable in the beginning. We assumed reliable alerting behavior requires good understanding of each other. This process takes some time. For this reason we split the answered questionnaires, according to the experience of the ATC, in owning the dog over one year (o1a) and under one year (u1a).

2.1 Questionnaire

29 questionnaires were sent out to children and adults with diabetes and their families between the ages of 0-50 years, both genders. The only common denominator was a diabetic alert dog trained by the ATC. 15 completed questionnaires were sent back and available for evaluation (n=15). This corresponds to a number of 52% of participation.

The DAD-questionnaire is inspired by an already existing questionnaire about medical devices for patients with diabetes to ensure the possibility of further investigations and easy comparison between DAD and different technical devices.

We added one question on the recent HbA1c, compared to the last HbA1c before getting the dog. These results provide us insight about the metabolic control and a possible positive or negative change since getting the diabetic alert dog. For this thesis, we chose the unit of the HbA1c in NGSP%.

The questions have been combined in their message as you can see below. The answers are plotted and described.

- How big is the psychological and emotional burden of the diagnosis T1D and is the dog able to ease it? (questions 1, 3, 8, 9, 13)

- Do patients with diabetes follow up with their disease? (questions 2, 5, 7, 10, 21)
- Does the dog help in decreasing the concern of friends and family? (questions 12, 18, 20?)
- Do patients with diabetes feel exhibited or restricted because of their dog? (questions 4, 7, 20, 25, 27)
- How big is the concern for high blood glucose levels? Was the dog able to change this concern? (questions 1, 8, 10)
- How big is the concern for low blood glucose levels? Was the dog able to change this concern? (questions 2, 3, 9)
- Are there any disadvantages in having a diabetic alert dog? (question 11)
- Is there a change in sleeping behavior and the rest for the ones bearing the responsibility since getting the DAD? (question 13)
- Do the patients with diabetes do more sports since getting the dog and do they feel comfortable? (questions 16, 25, suitability question 6)
- How is the subjective feeling of managing their disease for the patients with diabetes? (questions 6, 14, 15, 17, 19, 21, 22, 23, 25)

We asked about the subjective satisfaction of the alerting behavior in different situations, about the size of the dog and the support from the ATC. This gives us the possibility to compare different training centers in future studies.

- How high is the satisfaction of the owner of a DAD? (suitability questions 4, 5, 6, 7)
- Receiving and handling the dog (suitability questions 1, 2)
- How do the patients with diabetes and their families evaluate the competence and help of the Animal Training Center in times of need? (suitability questions 8, 9)

2.2 Notification protocol

During the first year (and in times of alerting problems) the families are prompted to keep records of the alerting behavior, the measured blood glucose level at alerting time and the own measured blood glucose levels, even if not alerted.

With these notification protocols we are able to assess a dog’s ability to alert correctly and have the possibility to compare it to technical devices.

3 Results

3.1 Evaluation of the questionnaire

To show the overall outcome and get a feeling for the questionnaire, we decided to put all questions together, shown in the diagrams below.

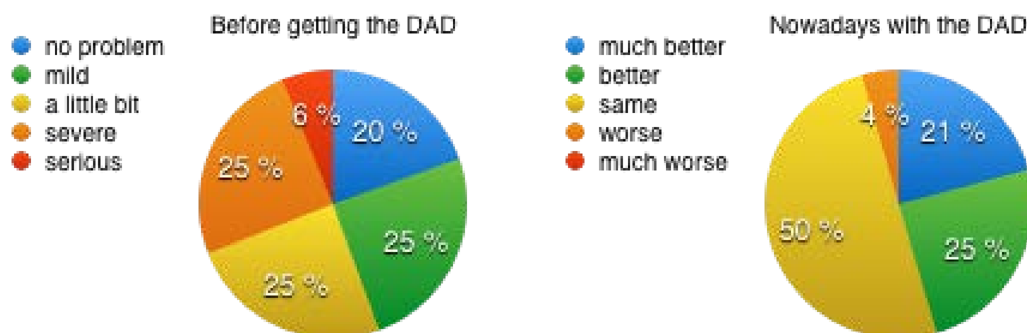

Fig. 9: Evaluation of the full questionnaire, overall handling of T1D, n=15

45% of the participants answered that they had only mild or no problems with their disease, while 31% describe severe or serious issues. The diabetic alert dog was able to improve life for 46% of patients with diabetes. However, the fact that 50% of the interviewees regard their life as the same compared to before getting the dog is due to the fact that many questions determining the life quality of the diabetic are independent from the diabetic alert dog, e.g. in how far insulin and the meals affect the body and how much difference there is between health and sickness.

Major part of the overall 4% "worse" points regarding the DAD relate to the pain involved from the elevated frequency of testing the blood glucose level and the additional effort taking care of a dog.

In all surveys described until to date, no significant reduction of the long term parameter HbA1c was assessed. As part of our questionnaire, the patients with diabetes had to fill in their HbA1c before getting the DAD as well as recent measurement after getting the DAD (n=14).

The reported HbA1c before getting the DAD was on average 7,6 (max. 8,8 and min. 6,5). After getting the dog it decreased to an average of 7,3 (max. 8,5 and

min. 6,3). The average decrease of the HbA1c in patients with diabetes having a diabetic alert dog trained by the ATC was -0,3 and ranged from +1,2 to -1,3.

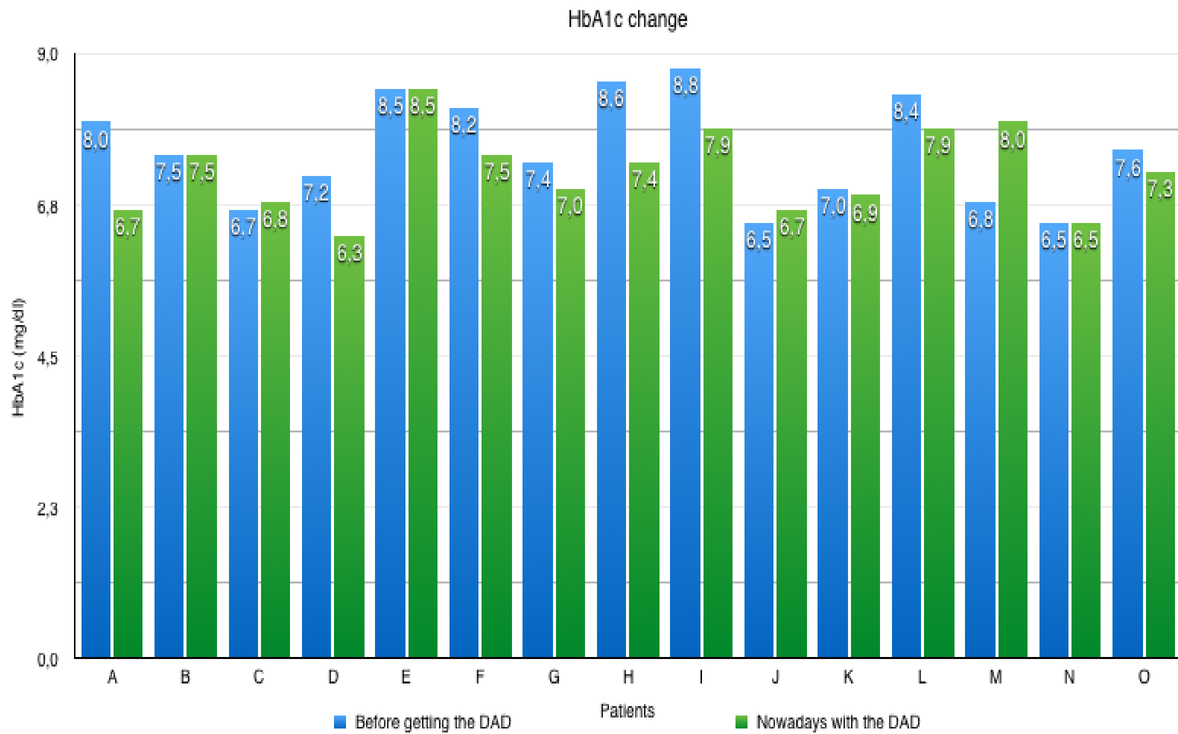

Fig. 10: Change of HbA1c, n=14

In eight patients with diabetes the HbA1c decreased (5 considerable ∆HbA1c ⩾0,7), in three patients it remained the same and in three it elevated, whereby one considerable increase can be registered (+1,2).

3.1.1 Emotional and psychological burden of diagnosis T1D and is the dog able to ease it?

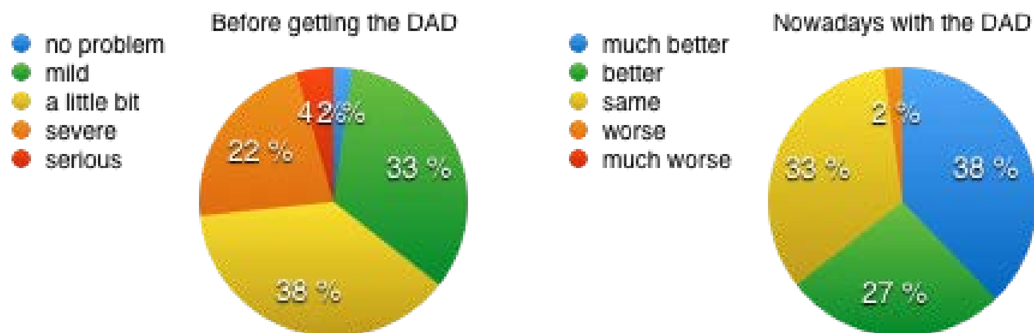

Fig. 11: Emotional and psychological burden
Under 1 year, n=9

The emotional and psychological burden of a chronic disease can be considerable for the patient and his or her family. We summarized the fear of hypoglycemia,

hyperglycemia, the long term consequences and sleeping disorders of the ones bearing responsibility. The results were differentiated between having the dog more resp. less than one year, in order to understand the improvement from a newly growing companionship to a well-functioning team.

As can be seen, even with a rookie team the diabetic alert dog helps to decrease concerns considerably and contributes to the improvement of the quality of life.

The 2% "worse" in u1a can be explained with increased worries for hypoglycemia during sleep.

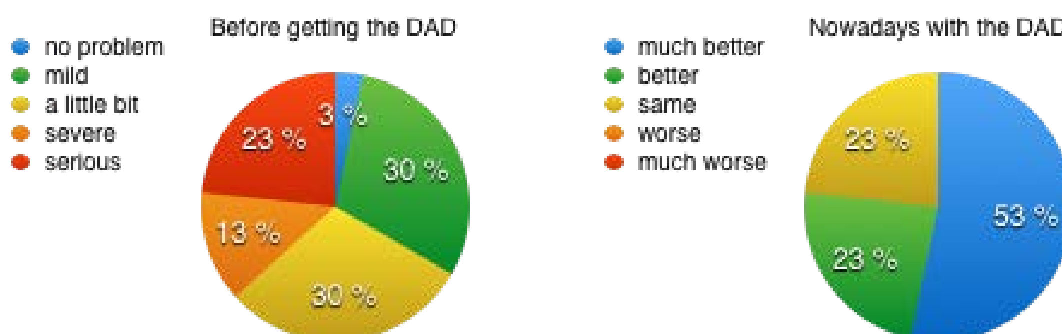

Fig. 12: Emotional and psychological burden
Over 1 year, n=6

36% of the patients with diabetes o1a (26% of the u1a) suffer from serious and severe fears and worries about their state. The increase from 65% to 76% of improvement shows that there is a difference between owning the dog over and under one year. The satisfaction and ease of the disease increases compared to under one year, and the dog plays a more important role.

3.1.2 Do patients with diabetes follow up with their disease?

This question aimed for the efforts made and the time spent due to diabetes. If the possibilities of incidents occupy most of the day, the quality of life is reduced.

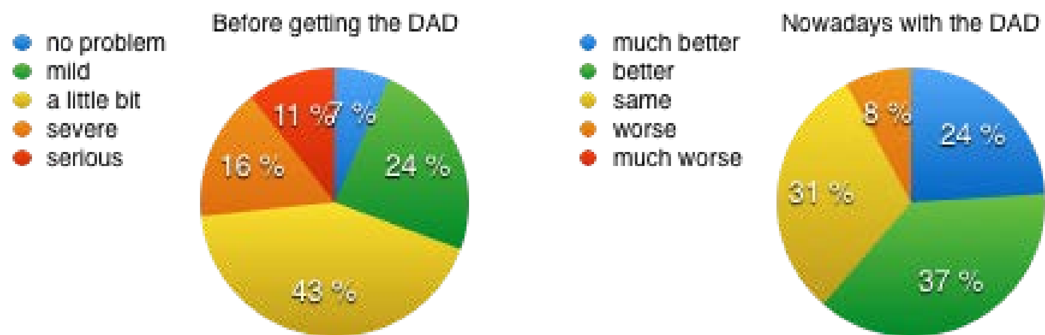

Fig. 13: Follow up of the disease
All together, n=15

The patients with diabetes report their serious worries and efforts about hypo- or hyperglycemia and their level of responsibility. Considerable improvement can be seen with the efforts to not getting into hyper- or hypoglycemia, whereas the level of responsibility stays mostly the same. The time spent with diabetes increases due to the dog's presence and frequent alerting.

With this question we were able to show a difference between u1a and o1a too. The „worse" part decreases from 11% to 2%, the „better" and „much better" part increases from 56% to 76%.

3.1.3 Improvement of the relationship with friends and family

The participants indicate that keeping friendship with non-patients with diabetes is no problem (76% mention no or just mild problems). 77% of the interviewees answered that there is no difference since having the dog.

The worries of family members stayed the same too (60%). 34% mentioned an improvement, 7% a worsening.

3.1.4 Do patients with diabetes feel exhibited or restricted because of their dog?

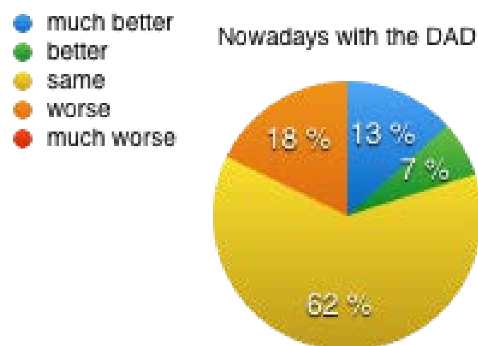

Fig. 14: Restriction and exhibition because of the DAD
n=15

For 62% of the participants the DAD changes nothing. 18% of the patients with diabetes feel more exposed to questions about diabetes and the dog. They have the impression of being more different from others.

3.1.5 Are there any disadvantages?

The biggest disadvantage mentioned is the increased frequency of blood glucose level measurement and the related pain. 40% of patients with diabetes refer to worsening of this situation. The other disadvantages referred to general dog-related problems and are not especially focussed on a diabetic alert dog. Reported disadvantages included increased effort (e.g. walking, training, looking for someone to take care of the dog in case of vacation).

3.1.6 How big is the concern for high blood glucose? Is the dog able to change the concern?

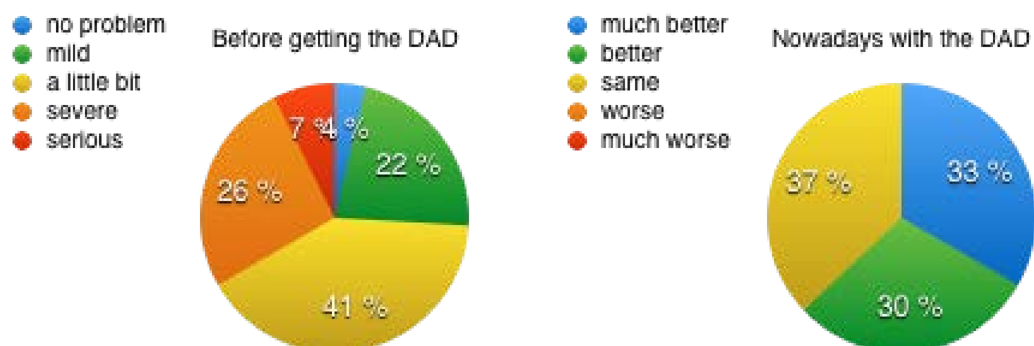

Fig. 15: Concern for high blood glucose level
Under 1 year, n=9

There is a remarkable difference in concern for high blood glucose levels between DAD owner under and over one year. The questions were about the ambition to evade high blood glucose, the concern for long term consequences and the fear of high blood glucose levels. Even at an early stage of the companionship the dog is already able to ease the fear considerably. 66% of the patients with diabetes feel better and much better. Worst observation is that the problems and fears stay the same. No decrease in the quality of life was reported.

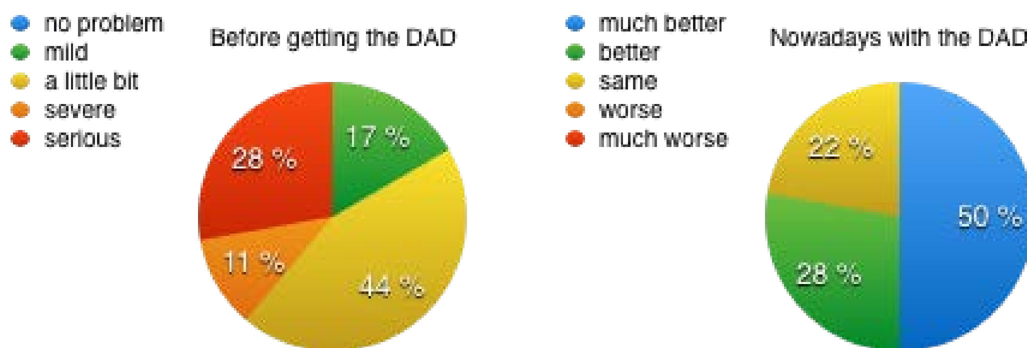

Fig. 16: Concern for high blood glucose level
Over 1 year, n=6

For those cases, in which the dog stayed more than a year with the diabetic, the fear and concern decreases even more. 50% of the questions were answered with „much better", 28% with „better". An overall improvement of 78% was reported.

3.1.7 How big is the concern for low blood glucose? Is the dog able to change the concern?

These questions relate to the concern of getting hypoglycemia during day- and nighttime and the ambition to evade it.

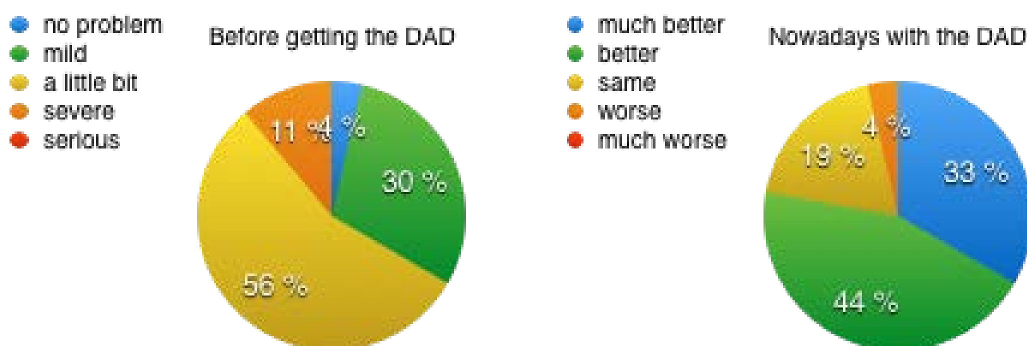

Fig. 17: Concern for low blood glucose level
Under 1 year, n=9

11% of the participants having the dog under one year describe severe concern for getting low blood glucose levels, the greater part has little problems concerning hypoglycemia. Nevertheless 44% report better conditions since getting the dog, 33% even much better conditions.

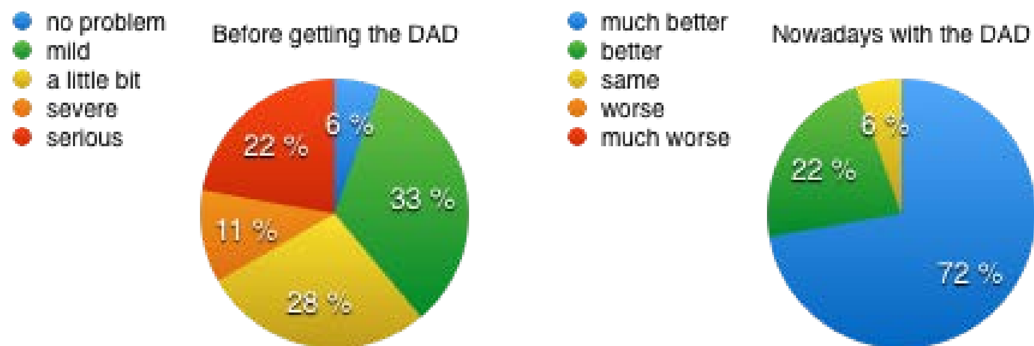

Fig. 18: Concern for low blood glucose level
Over 1 year, n=6

If we compare the DAD-owners under and over one year, we see that the contentment increases from 77% to 94% of getting "better", with the major part getting „much better". The 6% of DAD-owners having reported that their concerns for hypoglycemia stayed the „same", refer to the fear of experiencing hypoglycemia during sleep.

3.1.8 Is there a change in the sleeping behavior and the recovery for the ones bearing the responsibility?

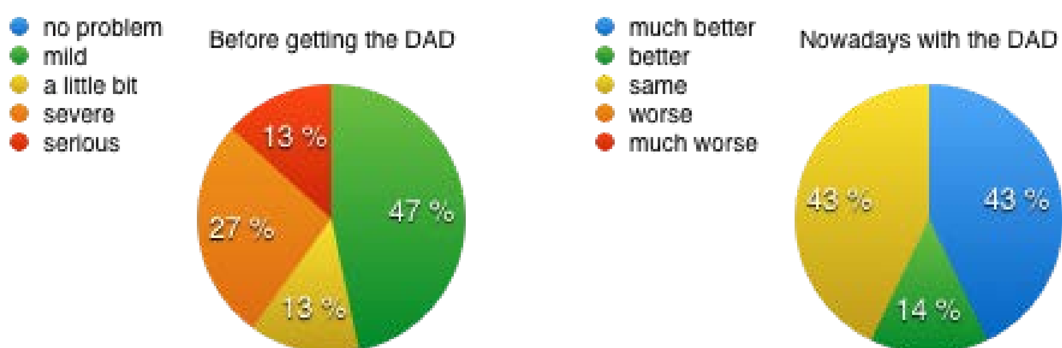

Fig. 19: Changes in sleeping behavior
All together, n=15

43% of the ones bearing responsibility of the patients with diabetes sleep much better since getting the dog, whereby the difference between over and under a year differs between 33% „much better" and 22% „better" under one year and 50% „much better" and 17% „better" over one year.

3.1.9 Do the patients with diabetes attend more sports since getting the dog and do they feel comfortable?

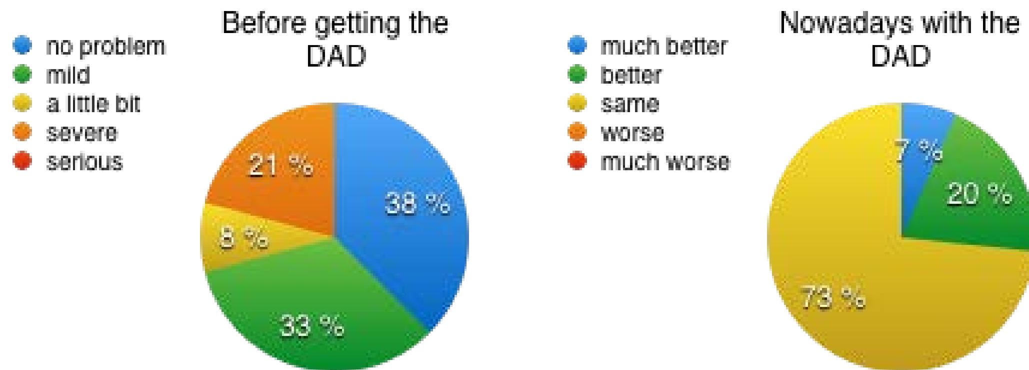

Fig. 20: Differences in attending sports
All together, n=15

The questions relate to the concern of attending sports and the knowledge of how a given amount of insulin affects the body during sports. 71% of the patients with diabetes described mild or no problems with sports and 73% reported the same condition as compared to before getting the dog.

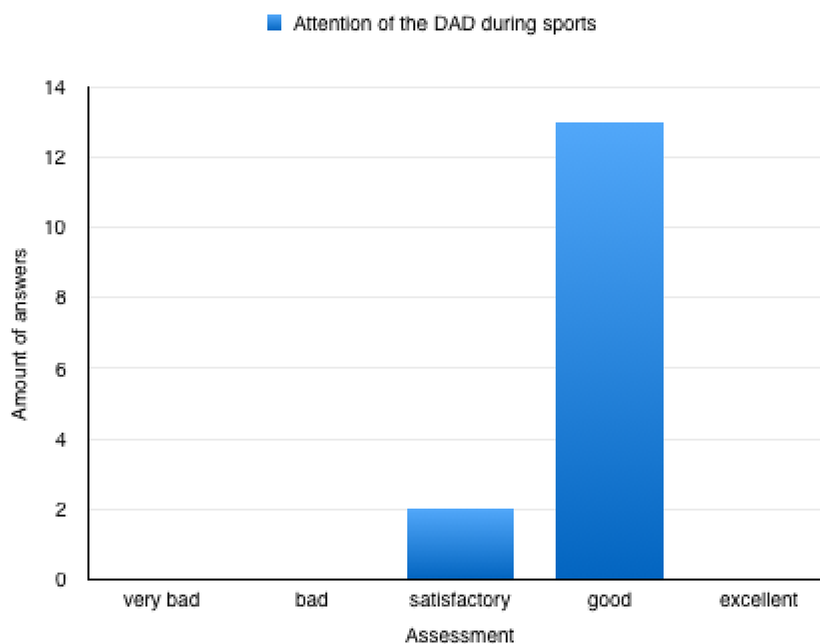

Fig. 21: Attention of the DAD during sports and bathing
All together, n=15

13 out of 15 patients reported the alerting behavior and the DAD's attention to the diabetic during sports as "good", two reported them as "satisfactory".

3.1.10 How is the patients' subjective feeling of managing their disease?

This question summarizes the relation between food and the blood glucose level, managing during work and school, effect of the given amount of insulin in different situations and strictness with the meal plan.

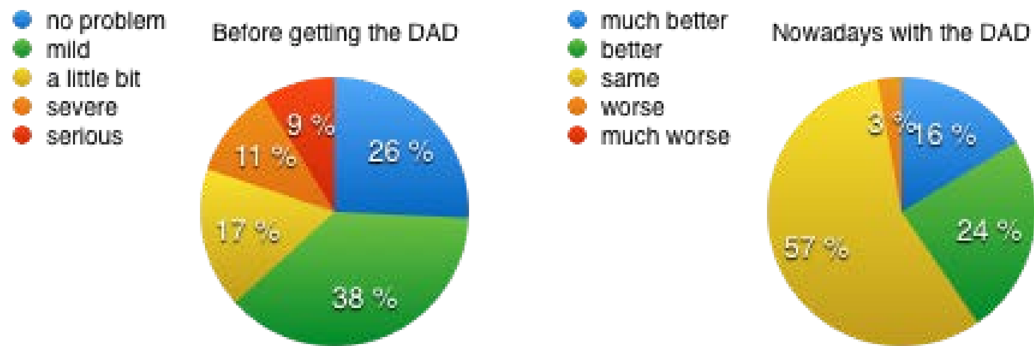

Fig. 22: Managing the disease
All together, n=15

57% see no difference before and after getting the dog. 54% have the feeling to manage their disease without or with only mild problems.

3.1.11 How high is the owners' satisfaction with the DAD?

This diagram summarizes the owners' satisfaction with the DAD's diversity, flexibility, alerting behavior and precision of alerting.

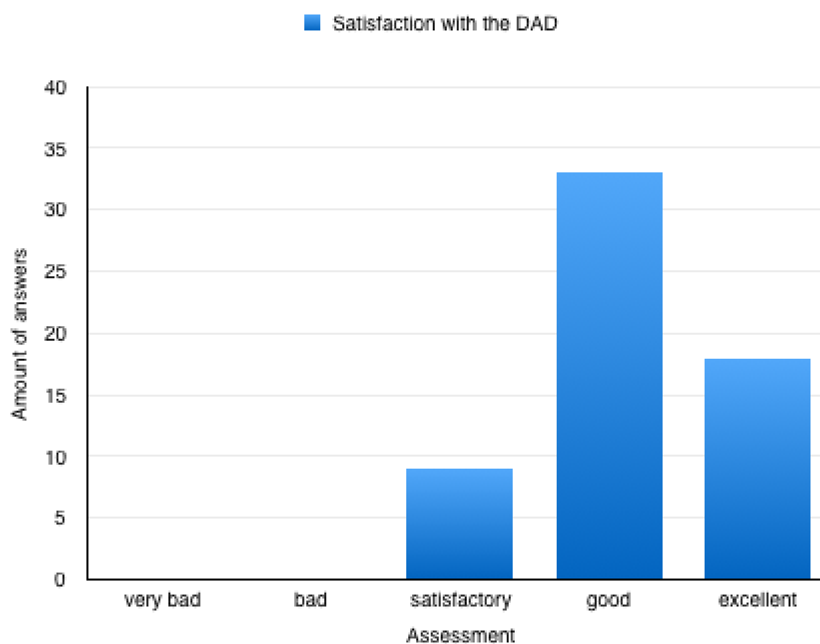

Fig. 23: Satisfaction with the DAD
All together, n=15

3.1.12 Receiving and handling the dog

The following diagram shows the overall high satisfaction of DAD-owners in regard to handling the received dog.

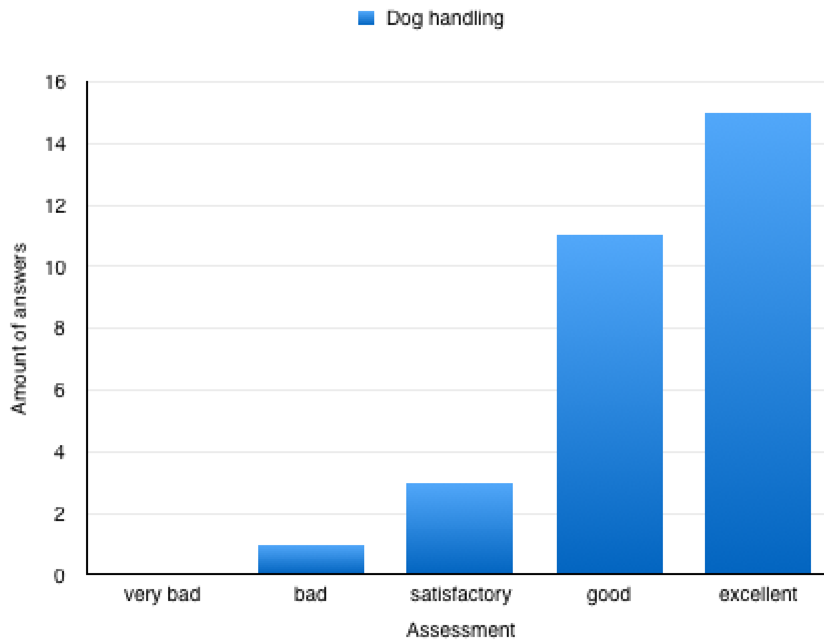

Fig. 24: Convenience of take-over
All together, n=15

3.1.13 How do the patients with diabetes and their families evaluate the competence and help of the Animal Training Center in times of need?

The following diagram shows the overall high satisfaction of DAD-owners with the received help and guidance by the ATC.

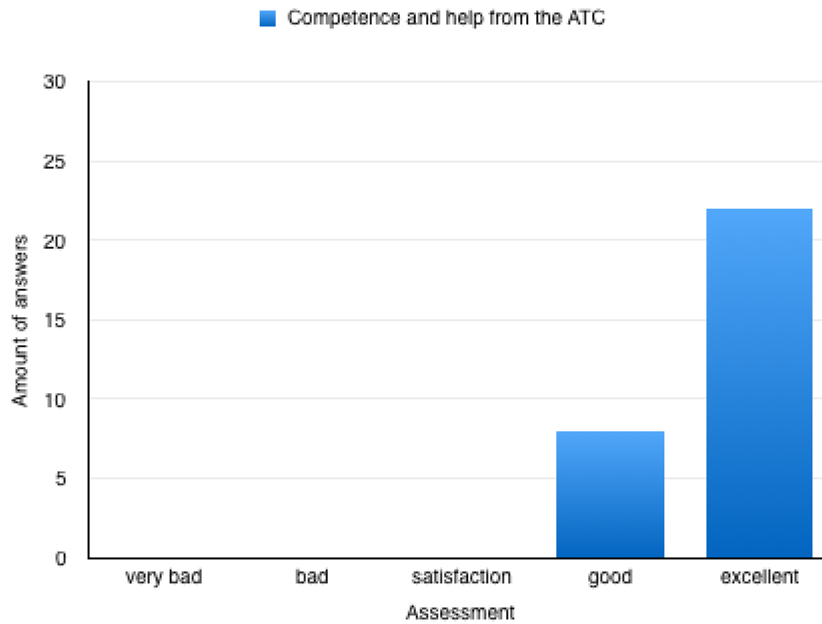

Fig. 25: Help and competence of the ATC
All together, n=15

3.2 Notification protocols

We evaluated the time of alerting, the measured blood glucose levels and if the alerting was correct or wrong or of the dog missed it.

The graphics show the different months with different colors, the alerting time and the measured blood glucose levels.

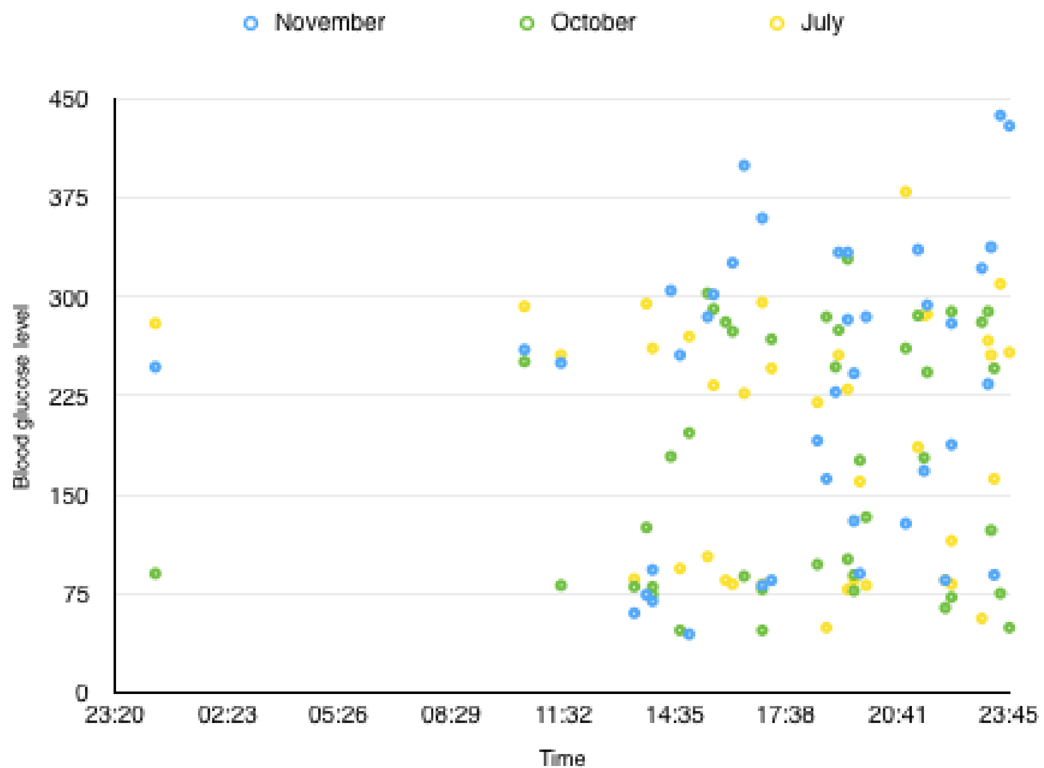

Fig. 26: Dog #1 - Alerting protocols

The main alerting time of dog#1 is between 2:30pm and midnight. This dog lives with a family, in which the diabetic attends school. During this time, the dog stays at home.

In total, they recorded 125 alerts in three months, 103 (80%) of the dog's alerts were correct, 22 (18%) wrong. He did not miss any tested hypo- or hyperglycemia.

We can see a higher alerting frequency at blood glucose levels of around 80mg/dl as well as above 230mg/dl.

Dog#2 stays with the owner the whole day. The main alerting time is between 6:00am and midnight.

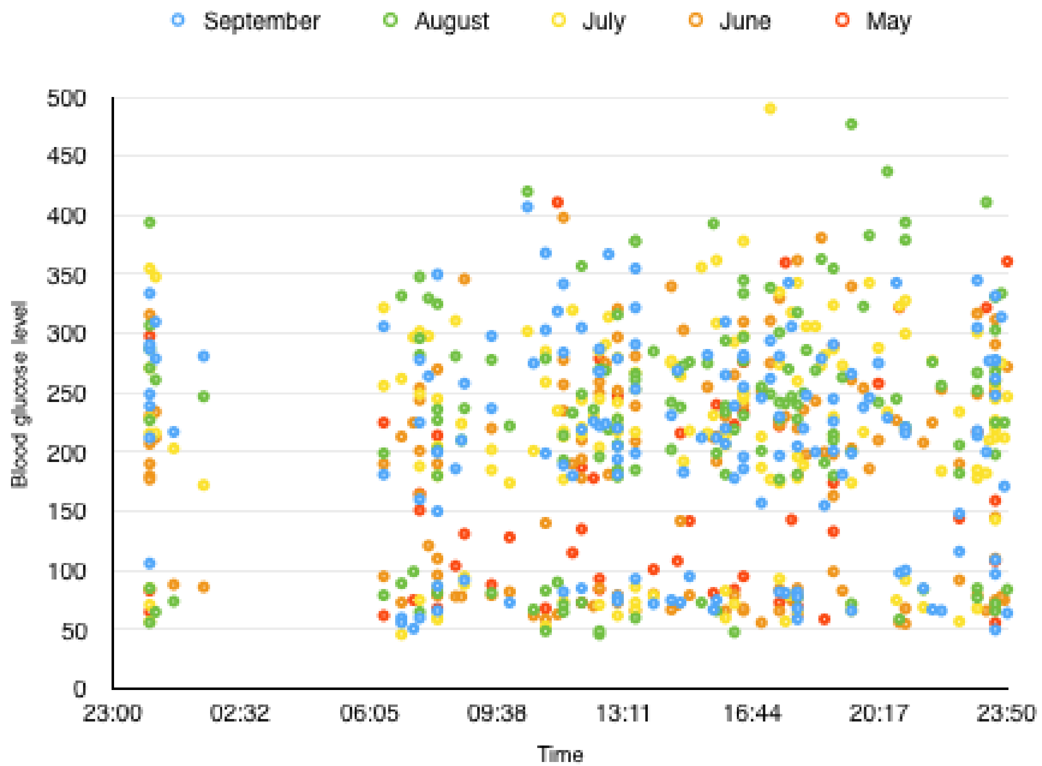

Fig. 27: Dog #2 - Alerting protocols

In this diagram the gap (normoglycemia) between the upper alerting limit (200mg/dl) and the lower alerting limit (80mg/dl) can be seen very clearly. In total, they recorded 697 alerts in 5 months, 494 of which were correct (71%), 191 wrong (27%) and 12 missed (2%).

Main alerting time of dog#3 is between 6:30am and 10:00pm.

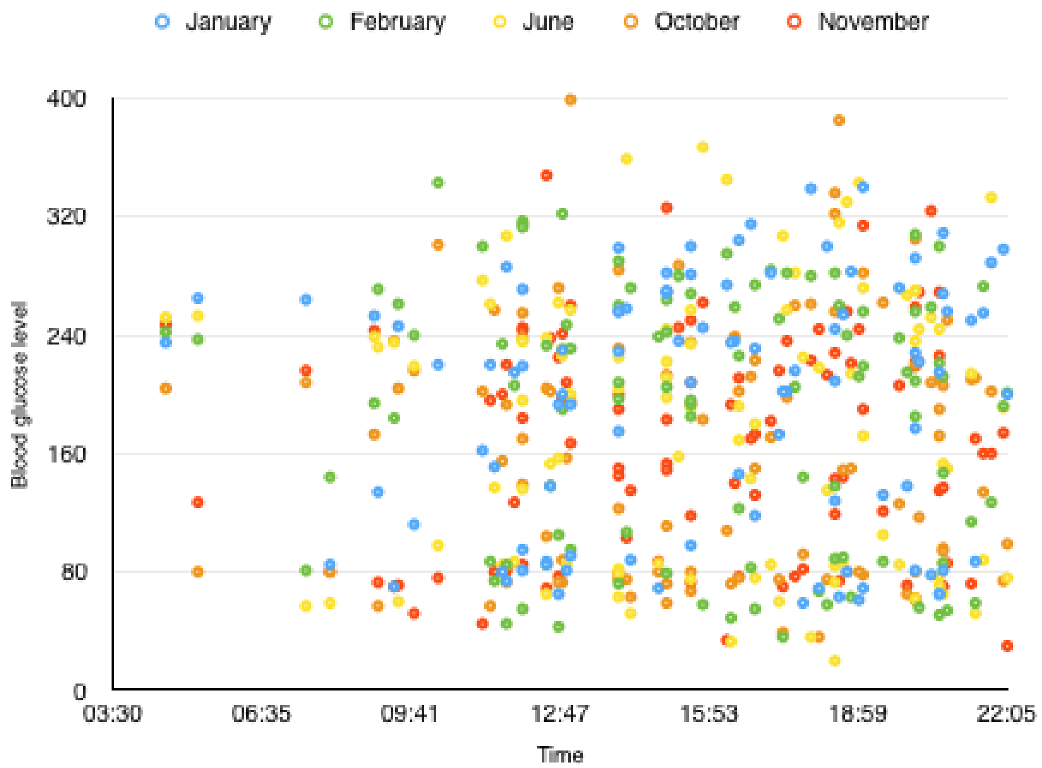

Fig. 28: Dog #3 - Alerting protocols

In total, they reported 602 alerts in five months, 469 of which were correct (78%), 120 wrong (20%) and 13 missed (2%).

Main alerting time of dog#4 is at 7:30am in the morning, at about 02:00pm and 6:30pm. The dog even alerts during the night. Just like dog#2 the empty space between 80mg/dl and 250mg/dl of normoglycemia (their upper alerting limit value) can be seen clearly.

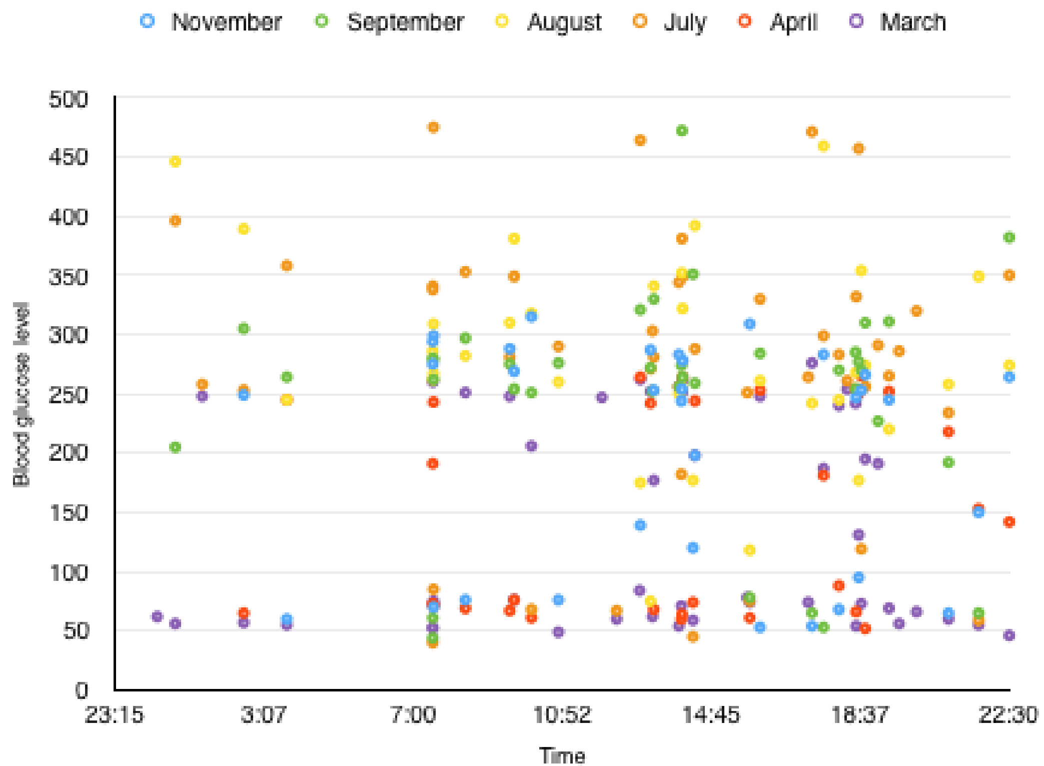

Fig. 29: Dog #4 - Alerting protocols

In total, they reported 289 alerts in 6 months, 252 (87%) of which were correct, 34 (12%) wrong and 3 (1%) missed.

As Fig. 30 exhibits, dog#5 displays a strong alerting behaviour at night. Main alerting time is at 8:00pm and between midnight and 3:30am. The gap between 8:00am and 2:00pm indicates the time in which the child is at school.

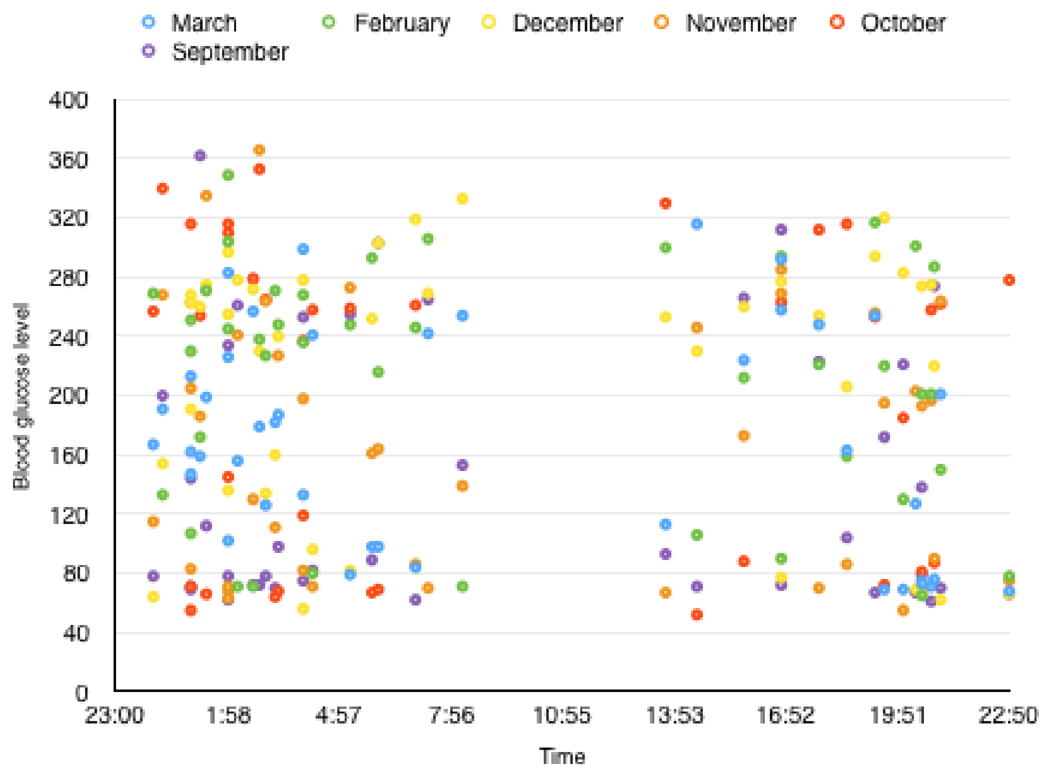

Fig. 30: Dog #5 - Alerting protocols

In total, they reported 273 alerts in 6 months, 171 (63%) of which were correct, 76 (28%) wrong and 26 (10%) missed.

Main alerting time of dog#6 is between 12:00am and 5:00pm, however he alerts at night as well. The alerting range for this dog is above 180mg/dl and under 75mg/dl. The owner of the DAD is able to keep tight glycemic control.

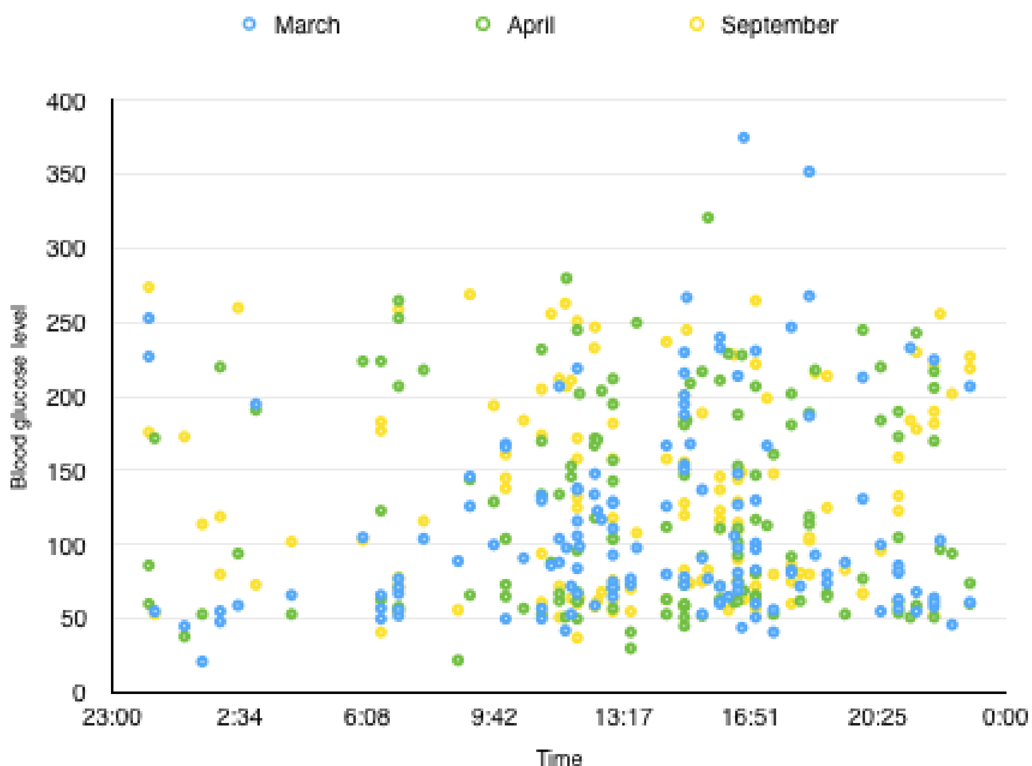

Fig. 31: Dog #6 - Alerting protocols

In total, they reported 487 alerts in three months, 253 (52%) of which were correct, 175 (36%) wrong and 59 (12%) missed.

4 Discussion

Dogs have long been known to be humans' best friends. Over the years, mankind discovered that they can even help with many different issues, such as drug tracking and detecting explosives. In recent years, dogs have been found useful in the medical sector as well. They help blind people to manage their life and help old and handicapped people to regain mobility. In all these cases, the psychological and emotional factors play a major role.

According to conducted surveys, diabetic alert dogs can be valuable emotional and medical assistance to their owners. By means of our questionnaire, we wanted to find out further details of benefits and disadvantages of the companionship with this kind of specially trained dog.

We made the distinction between over and under one year according to the experience of the Animal Training Center. Although there are significant differences, it would be interesting to follow up in a few years to see, if there is a change and further differentiation into under one year, between one and three years, between three and five and over five years. For this kind of detailed analysis, however, a higher number of participants is essential. Our results are quite positive concerning the initial hypothesis, but it is important to keep in mind that the number of participants for this questionnaire was rather small. Therefore, we have the problem of limited reliability. The one year line is drawn by choice. There is no guarantee that a nine months companionship is still a rookie team nor that it is a well-functioning team if the dog stayed with the owner for one and half years.

To assess a higher number of existing teams, it would either be possible to wait until the ATC has been training many more dogs over the years, or to include different diabetic alert dog training centers. In the latter case, it would be interesting to know, if different training approaches lead to different degrees of satisfaction and quality of life among the future dog owners.

A diabetic alert dog is not just for medical assistance. It helps the owner to ease his/her (or the family's) fears and therefore improve the quality of life significantly.

We asked about the feeling of exposure due to having the dog. In contrast to the written answers inside the original questionnaire, we received side-notes and comments written by the parents that their children are proud to have their special dog just for them. They would feel unique because of their DAD and that the dog would be their hero.

As shown in the analysis of the full questionnaire, 45% of participants have only few problems managing their disease, 46% feel even better with the dog. The resulting question is: Does a DAD benefit the already well managing patients with diabetes in getting even better or can it help to improve the quality of life of those with problems?

Not all changes of HbA1c can be traced back to the dog's ability to detect and alert blood glucose issues only. Increased interest in the disease, caused by the presence of the DAD or new measuring instruments alone can lead to improvement. The HbA1c is a snapshot of the glycemic control of the last 12 weeks; it would be interesting, if a diabetic with a low HbA1c can continue with a good glycemic control. In many cases a low HbA1c is achieved through recurrent hypoglycemias during the night. Can the low HbA1c be achieved by good glycemic control with the help of the DAD and other devices or can it be achieved just at the expenses of hypoglycemia?

An increased worry for hypoglycemia during nighttime can originate from the tighter glycemic control during daytime. Many parents or patients with diabetes adjust their blood glucose level to a higher concentration during nighttime in order to prevent unrecognized hypoglycemia during sleep, despite the long term consequences. Because of the dog's alerting, the glycemic control improves during the daytime and in the evening, the insulin has not been faded and can work on. The diabetic alert dogs are trained to alert even during the night, but there is no guarantee. So the fear of hypoglycemia can increase during nighttime with the dog.

We summed up adults and children alike. The children have their families to take care of the dog and react to the alerting. They do not have all the responsibility. It would be interesting, if there is a difference between children and adults in the alerting behavior. Even in bad mood the diabetic has to react friendly towards the

dog, while in case of children there is the family to buffer the emotions a child might direct towards the dog.

We interpreted the questions as described in the methods. There is the possibility to rearrange them and to imply a different meaning.

The notification protocol was implemented by the Animal Training Center to be able to keep track on the alerting behavior of their dogs and support the owners in case of questions and uncertainty. The families have to record date, time, alerting behavior, blood glucose level, special notes and if the dog was rewarded for its actions. They also have to record, if the dog missed a hyper- or hypoglycemia. The families have to record the protocol after taking over the dog until the dog alerts to their satisfaction as well as in special times of need.

The dogs are able to detect the scent of hypoglycemia. By evaluating the notification protocol we were able to analyze the alerting behavior within specific teams under real life conditions for the first time.

All diabetic alert dogs trained by the ATC learn to alert blood glucose levels under 80mg/dl. When the dogs move to their families, the families decide their own required limit values and the dogs adjust themselves to it. We did not summarize all DADs in one legend due to this fact of changing alerting limit values.

The dog is able to detect high blood glucose levels on his own, even without being trained explicitly. Many dogs alert rising and falling glucose levels. Therefore, in the diagrams it seems that there are many wrong alerts.

Example: 7:30pm - glucose level: 133mg/dl; 8:10pm - glucose level: 77mg/dl. Or 4:20pm - glucose level: 149mg/dl falling to 34mg/dl at 4:55pm. All these „wrong“ alerts are also displayed in the legend.

Furthermore, it has to be taken into account that in some notification protocols there is a differentiation between spontaneous and motivated alerting behavior. We did not make this differentiation. We counted motivated alerting behavior as missed.

As already mentioned, DADs are not trained to detect hyperglycemia. According to their paper, Neupane et al. found increased amount of Isoprene in the breath of patients with diabetes exhibiting hypoglycemia (45). If the dog reacts to

hyperglycemia on its own - is it the same substance as when a diabetic has an elevated glucose level?

The same question comes in handy with illness, as DADs react differently in case of the diabetic being sick.

Another interesting question is, if the dogs will still find their place between all the new technologies. A DAD is able to medically detect hypo- and hyperglycemia.

However, a dog is no „working technology", and the accuracy of the alerts cannot be ensured. Although a DAD is able to detect hypo- and hyperglycemia, it is impossible to predict every mood and behavior. A dog will never act like a machine. The DAD works perfectly as additional help and support, but it is not a „tool" to simply hand responsibility over to. A specially trained dog is not just help, it is also a challenge. The training is continuous, even in bad days, which presents a major difference to having a „normal" dog. Any alerting demands attention and approval, despite the mood of the patient. Before thinking about applications it should be made clear, if the patients and families are willing to accept the DAD as a normal dog with special needs.

Even if once there might be technological solutions that were able to manage the glucose-system for a diabetic as good as possible, those technologies will most likely still be subject to failure and malfunction due to the complex nature of the whole glucose-system. Those failures can hardly be prevented. Exactly for those insecurities a DAD will be able to provide for an additional security-net.

The emotional and psychical benefit is considerable and can never be eased by technology. Last but not least, patients with diabetes have to go for walks with the dog, therefore they do sports regularly. With the last three points it is the question, if a „normal" dog would have the same effect due to these problems.

Concerning the participation in this questionnaire, 52% of participation was less than expected. The total number of possible participants was limited due to the eligibility requirements. The fill-in and sending-back of the questionnaire was associated with effort, while the attendance was voluntary; the participations did not get anything out of it.

The final mentioning belongs to some special notes on the notification protocols. The families described „distant alerts“, a special alerting event during which the dog alerts hypo- or hyperglycemia without the patient being in close physical proximity to the DAD. Three of the six DAD notification protocols show these special notes. After inquiries of the ATC the trainers told us that up to 50% of their trained dogs develop this kind of ability. These notes and the empirical knowledge of the ATC would be an interesting opportunity for further scientific investigation.

On the last page of the questionnaire we asked for opinions, translated freely from German:

- *„I have my dog for one year now. Since my pregnancy I don't feel my hypoglycemias anymore, especially at night. Because of my dog I am not afraid anymore to go to bed in at night. Before I got her I had four serious hypoglycemias at night, with cramps, unconsciousness and waiting for hours until help arrives. My dog took all this fear from me. My dog enriches my life and helps my with my glycemic control. She even alerts strongly rising and falling blood glucose levels. She alerts with other patients with diabetes too. She is my life saver on four paws!"*
- *„A diabetic alert dog is a big relief in the life of a diabetic. Not just for the sugar, it is a comforter for the soul and companion too! We don't want to hand her over anymore!"*
- *„P. was 7 years old and filled in a book of friendship. He asked me what his biggest wish was. My guess was not having diabetes. He answered: Oh, it's not so bad- otherwise we wouldn't have our dog!"*
- *„One month ago I told my son happily about the new healing approaches. He said: That's not possible! We would have to give away our dog! When I explained that all patients with diabetes would be cured and our dog would be allowed to stay with us, it was fine again."*
- *„Since having the diabetic alert dog, the burden of diabetes has decreased for my son. I would do it again, just for his psyche I would do it again. He feels special because of the dog.*
  I feel better too. Even with four kids I am able to go for a walk without feeling guilty. I don't have to keep an eye on him the whole time. P. feels the hypoglycemia between 40-50, the dog recognizes it much earlier. He even alerts strongly falling glucose levels. P. don't recognize high levels, the dog does. Sometimes the dog alerts falsely, but he nearly doesn't overlook something. The dog wakes me even at night!"
- *„Our dog alerted persistently tree times in the mid-morning, when J. was in school, 2km away from our house. We inquired- she was right! Hypoglycemia!"*

- *„Our son loves to play and train with the dog. Once he was in the garden with her, our diabetic daughter in her room and I was in the kitchen. Suddenly he came in and told me: Mum, L. has to measure her blood glucose! The dog alerted!*
  She was right! 70mg/dl. Thanks to her we could avoid an oncoming hypoglycemia."
- *„Our daughter had a sleepover with a friend of hers, they went to her house in the afternoon (4km away). In the evening, we were sitting on the couch, our dog got nervous, ran around, looked at us in her special way and gave her paw. She became more and more energetic and wouldn't leave us alone.*
  When I got up she barked at me, raised up on her hind-legs and even scratched my tight. We called our daughter, her blood glucose was by 50mg/dl! Our daughter nearly not recognizes hypo- or hyperglycemia and without our wonderful dog her glucose would have fallen even more. It was already after the evening meal and the girls would have gone to bed in a few minutes!
  Every time I think about this incident still I feel goosebumps und get emotional."
- *„One time our daughter wanted to go to her friend. Before going, we measured 86mg/dl. To be safe, she got some sweets with her. 5 Minutes after she left our dog came and looked at us in her special way and raised on her hind-legs. We called our daughter, et voilá: 71mg/dl."*
- *„Our daughter went to bed after dinner. The dog came along. In front of the bed, she looked at us in her special way and after questioning her, she barked quietly. Okay, let's measure. 70mg/dl. Good girl. So we gave our daughter 1 BE to drink and then let's go to bed.*
  10 minutes later the bell rings. Our dog has the possibility to press a button beside our daughter's bed to alarm us. We thought that maybe our daughter got up once more and accidentally pushed the button. But to be sure I went to her room.
  But no, our daughter was fast asleep and the dog sat beside her bed and looked at me like 'are you already coming?'

I measured her blood glucose. 54mg/dl!! Despite her earlier drink her glucose level dropped even further! Never ever I would have controlled her this evening! I was sure, that everything was okay with the juice!“

- *„Another positive side effect: Since our son was small he was always rather carful and kept the distance if he didn’t know something. Since getting the dog he became much more open and social. He is not suspended anymore getting to know new things because his friend and protector is always with him.“*
- *„The improvement of HbA1c was clearly recognizable after switching from pen to pump and since having the DAD (more frequent measurements). The dog is great social component for us: not being alone, taking care, having a task (going for a walk) and an additional security-net.“*
- *„Our DAD has problems with other dogs- otherwise he would be perfect!“*
- *„Our dog is a great assistance not only in everyday life and during the night, but also comforter for the soul and best friend.“*
- *„My daughters dog comes to action in every possibility: for school work, for the painting competition, arts at school,… The dog is her hero.“*

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Appendix A: Diabetikerwarnhunde Fragebogen

Teil 1: Auswirkungen und Zufriedenheit

Vielen Dank für die Teilnahme an dieser Umfrage und der damit verbundenen Zeit und Mühe. Ihre Meinung ist sehr wertvoll für uns und wir hoffen, Sie helfen uns zu verstehen, wie ein Diabetikerwarnhund Ihren Alltag beeinflusst.

Der Fragebogen ist anonym und es werden keine sensiblen Daten gespeichert. Er dient dazu, Diabetikerwarnhunde als bisher unbekannte Größe wissenschaftlich einordnen zu können.

Nachfolgend finden Sie einige Fragen über Ihre Lebensumstände und inwieweit Ihr Hund auf soziale und medizinischen Belange Einfluss nimmt.

Bitte kreuzen Sie nach bestem Wissen und Gewissen an, sollten Fragen entstehen, stehe ich gerne jederzeit für Rückfragen zur Verfügung.

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DIE NACHFOLGENDEN DATEN SIND BITTE VOM DIABETIKER/ VON DER DIABETIKERIN SELBST, ODER GEMEINSAM MIT EINEM ERZIEHUNGSBERECHTIGTEN AUSZUFÜLLEN.

Geschlecht m ☐ w ☐

Alter
(Zutreffendes bitte ankreuzen)

0-2 Jahre	
2-5 Jahre	
5-10 Jahre	
10-15 Jahre	
15-20 Jahre	
> 20 Jahre	

In welchem Alter wurde die Diagnose „Diabetes mellitus Typ 1“ gestellt? ______________________________

Langzeitzuckerwert:

Wie hoch war der HbA1c bevor sie den Hund bekommen haben? ______________________________

Wie hoch ist der aktuelle HbA1c? ______________________________

Seit wie vielen Jahren haben Sie den Hund? ______________________________

Wir erfragen folgendermaßen Probleme, die Sie in Ihrem Alltag mit Diabetes betreffen und durch die Anschaffung des Diabetikerwarnhundes besser oder schlechter gelöst werden können.

Für jede Frage kreuzen Sie bitte die Zahl ein, die Ihr Problem DERZEIT am besten beschreibt. Anschließend kreisen Sie die Zahl ein, die am besten beschreibt, wie sich Ihr Problem im Vergleich zu VOR DEM HUND verändert hat.

	Ist das JETZT ein Problem?					Wie hat es sich im Vergleich zu VOR dem Hund verändert?				
	Sehr stark	Ziemlich stark	Etwas	Nicht sehr	Gar nicht	Viel schlechter	Etwas schlechter	Gleich	Etwas besser	Viel besser
1. Sorge oder Angst über hohen Blutzucker	1	2	3	4	5	1	2	3	4	5
2. Die Bemühung keinen zu niedrigen Blutzucker zu bekommen	1	2	3	4	5	1	2	3	4	5
3. Sorge oder Angst vor zu niedrigem Blutzucker während des Schlafs	1	2	3	4	5	1	2	3	4	5
4. Das Gefühl sich von anderen zu unterscheiden	1	2	3	4	5	1	2	3	4	5

	Ist das JETZT ein Problem?					Wie hat es sich im Vergleich zu VOR dem Hund verändert?				
	Sehr stark	Ziemlich stark	Etwas	Nicht sehr	Gar nicht	Viel schlechter	Etwas schlechter	Gleich	Etwas besser	Viel besser
5. Die Menge an Zeit über Diabetes nachzudenken	1	2	3	4	5	1	2	3	4	5
6. Nicht zu wissen, wie Essen den Blutzucker beeinflusst	1	2	3	4	5	1	2	3	4	5
7. Die Menge an Zeit oder Bemühungen von meiner Familie oder mir, die aufgrund von Diabetes entsteht	1	2	3	4	5	1	2	3	4	5
8. Sorge oder Angst über den langfristigen Gesundheitszustand	1	2	3	4	5	1	2	3	4	5
9. Sorge oder Angst über zu niedrigen Blutzucker während des Tages	1	2	3	4	5	1	2	3	4	5
10. Die Bemühungen keinen zu hohen Blutzucker zu bekommen	1	2	3	4	5	1	2	3	4	5
11. Schmerzen oder Beschwerden beim Fingerstechen (erhöhte/erniedrigte Stichfrequenz)	1	2	3	4	5	1	2	3	4	5
12. Sorgen oder Argumente der Familienmitglieder aufgrund Diabetes	1	2	3	4	5	1	2	3	4	5

	Ist das JETZT ein Problem?					Wie hat es sich im Vergleich zu VOR dem Hund verändert?				
	Sehr stark	Ziemlich stark	Etwas	Nicht sehr	Gar nicht	Viel schlechter	Etwas schlechter	Gleich	Etwas besser	Viel besser
13. Schlafstörungen des Verantwortung Tragenden	1	2	3	4	5	1	2	3	4	5
14. Strenge beim Mahlzeitplan	1	2	3	4	5	1	2	3	4	5
15. Die Krankheitsbewältigung während der Arbeit, Schule, Kindergartens	1	2	3	4	5	1	2	3	4	5
16. Trotz Diabetes an Sport oder Bewegung teilzunehmen	1	2	3	4	5	1	2	3	4	5
17. Wissen, wie viel Insulin man nehmen soll	1	2	3	4	5	1	2	3	4	5
18. Freundschaften mit Freunden oder Kollegen halten, die nicht an Diabetes erkrankt sind	1	2	3	4	5	1	2	3	4	5
19. Auf alle Blutzuckerergebnisse reagieren	1	2	3	4	5	1	2	3	4	5

	Ist das JETZT ein Problem?					Wie hat es sich im Vergleich zu VOR dem Hund verändert?				
	Sehr stark	Ziemlich stark	Etwas	Nicht sehr	Gar nicht	Viel schlechter	Etwas schlechter	Gleich	Etwas besser	Viel besser
20. Der Umgang mit anderen, die über Diabetes fragen	1	2	3	4	5	1	2	3	4	5
21. Mein Maß an Verantwortung, mit Diabetes umzugehen	1	2	3	4	5	1	2	3	4	5
22. Sicher zu sein, ob Insulin das vor der Mahlzeit genommen wurde, die Menge an gegessenen Kohlenhydraten deckt	1	2	3	4	5	1	2	3	4	5
23. Auf alle Anzeigen des Hundes zu reagieren	1	2	3	4	5	1	2	3	4	5
24. Die richtige Menge an Insulin nehmen, wenn man krank ist	1	2	3	4	5	1	2	3	4	5
25. Das Gefühl, dass der Hund mein Leben bestimmt	1	2	3	4	5	1	2	3	4	5
26. Die richtige Menge Insulin nehmen, wenn man unüblich viel Sport gemacht hat	1	2	3	4	5	1	2	3	4	5
27. Das Gefühl, aufgrund des Diabetes und des Warnhundes anders auszusehen	1	2	3	4	5	1	2	3	4	5

Teil 2: Eignung und Aufwand

Wir würden gerne Ihre Meinung hören, wie der groß der Aufwand und die Umgänglichkeit ist, die ein Diabetikerwarnhund am Beginn darstellt.

	Sehr schlecht	Schlecht	Befriedigend	Gut	Hervorragend
Größe, Gewicht, optische Erscheinung	1	2	3	4	5
Umgang mit dem trainierten Hund BIS zur Übernahme, Einfachheit/ Leichtigkeit des Umganges	1	2	3	4	5
Umgang mit dem trainierten Hund NACH der Übernahme, Einfachheit/ Leichtigkeit des Umganges	1	2	3	4	5
Vielfalt und Flexibilität des Hundes	1	2	3	4	5
Warn- Anzeigeverhalten des Hundes	1	2	3	4	5
Aufmerksamkeit und Einsatz bei Sport, körperlicher Betätigung, Baden	1	2	3	4	5
Genauigkeit und Zuverlässigkeit des Anzeigeverhaltens	1	2	3	4	5
Unterstützung und Anleitung durch das AnimalTrainingCenter während der Trainings- und Übergabezeit	1	2	3	4	5
Unterstützung und Anleitung durch das AnimalTrainingCenter bei alltäglichen Problemen	1	2	3	4	5

Wenn Sie uns noch etwas Persönliches, Erfahrungen oder Anmerkungen zukommen lassen wollen, steht Ihnen die Box (und alle unbeschriebenen Rückseiten) natürlich gerne zur Verfügung :)

DANKE VIELMALS FÜR IHRE BEMÜHUNGEN!

Appendix B: Votum of the ethics commission

Ethikkommission

Medizinische Universität Graz

Auenbruggerplatz 2, A-8036 Graz
ethikkommission@medunigraz.at
Tel.: +43 / 316 / 385-13928, Fax: -14348

VOTUM
gültig bis 27.04.2017

EK-Nummer:	28-352 ex 15/16
Studientitel:	Diabetic alert dogs- medical and social assistance for patients with DM1 - a questionnaire based survey
Prüfer:	Priv. Doz OA Dr. Gerd Köhler Medizinische Universität Graz, Abteilung für Endokrinologie und Diabetologie
Sponsor:	Medizinische Universität Graz, Abteilung für Endokrinologie und Diabetologie
Ansprechpartner:	Priv. Doz OA Dr. Gerd Köhler, 8036 Graz, Auenbruggerplatz 15
CRO:	-
Antragsteller:	Medizinische Universität Graz
Ansprechpartner:	Sarah Sutter

Die o.a. Studie wurde von der Ethikkommission erstmals im 'expedited Review' am 24.03.2016 behandelt. Die Ethikkommission ist zu folgendem Schluss gekommen:

Es besteht kein Einwand gegen die Durchführung der Studie in der vorliegenden Form.

Kommissionsmitglieder, die für diesen Tagesordnungspunkt als befangen anzusehen waren und daher gemäß Geschäftsordnung an der Entscheidungsfindung und Abstimmung nicht teilgenommen haben: keine

Zur Beurteilung vorliegende Dokumente:

Dokumente eingegangen am 18.03.2016, begutachtet im 'expedited Review' am 24.03.2016	
✓ Cover Letter Ethikkommissionsschreiben 1	17.03.2016
✓ Antragsformular ECS	18.03.2016
Originalprotokoll Protokoll_Sutter 1	03.11.2015
✓ CV CV_GerdKoehler 1	01.06.2015
✓ CV CV_VeraHoeller 1	03.06.2015
✓ CV CV_SarahSutter 1	17.03.2016
✓ Sonstiges: DWH_Fragebogen 1	10.03.2016
Dokumente eingegangen am 07.04.2016 (in der nächsten Begutachtung mitbegutachtet)	
✓ Antragsformular ECS unterschrieben	18.03.2016
✓ Originalprotokoll 2.0	04.04.2016
Informed Consent Form 1.0	04.04.2016
✓ Sonstiges: Stellungnahme zur Bearbeitungsmitteilung	06.04.2016
Dokumente eingegangen am 25.04.2016, begutachtet im 'expedited Review' am 27.04.2016	
✓ Informed Consent Form 2.0	

Die Ethikkommission geht - rechtlich unverbindlich - davon aus, dass es sich um keine klinische Prüfung nach AMG bzw. MPG handelt.

Es handelt sich um eine Studie im Rahmen einer Diplomarbeit.

Das Votum der Ethikkommission berührt in keiner Weise die alleinige Verantwortung der Prüferin / des

EK-Nummer: **28-352 ex 15/16** Votum (27.04.2016) Seite 1 von 2

Medizinische Universität Graz, Auenbruggerplatz 2, A-8036 Graz. www.medunigraz.at
Rechtsform: Juristische Person öffentlichen Rechts gem. Universitätsgesetz 2002. Information: Mitteilungsblatt der Universität und www.medunigraz.at. DVR-Nr. 210 9494. UID: ATU 575 111 79. Bankverbindung: Bank Austria Creditanstalt BLZ 12000 Konto-Nr. 500 948 400 04, Raiffeisen Landesbank Steiermark BLZ 38000 Konto-Nr. 49510.

Prüfers / der Prüfer für die ordnungsgemäße Durchführung der Studie unter Einhaltung aller einschlägiger gesetzlicher Bestimmungen und Richtlinien.

Weiters machen wir darauf aufmerksam, dass der Kommission unverzüglich zu melden sind:

- Abweichungen vom Protokoll aus Sicherheitsgründen oder Protokolländerungen

- Änderungen, die das Risiko der Teilnehmer/-innen erhöhen oder die Durchführung der Studie wesentlich beeinflussen

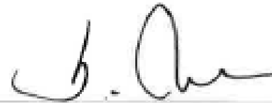
- Mutmaßliche unerwartete schwerwiegende Nebenwirkungen - SUSARs (AMG-Studien ab 1.5.2004) oder schwerwiegende unerwünschte Ereignisse - SAEs (andere Studien)

- Jegliche Information über sonstige Umstände, die die Sicherheit der Teilnehmer/-innen oder die Durchführung der Studie beeinträchtigen können

Dieses Votum gilt für ein Jahr ab dem Datum der Ausstellung. Bei längerer Studiendauer ist rechtzeitig vor Ablauf der Gültigkeit des Votums ein Zwischenbericht vorzulegen (Berichtsformular), um eine etwaige Verlängerung zu erlangen.

Graz, 27. April 2016

Univ.Prof.DI Dr.Josef Haas
Vorsitzender



Univ.Prof.Dr.Hermann Toplak
Stv. Vorsitzender

Achtung: Bitte bei allen das Projekt betreffende Schreiben oder telefonischen Anfragen die EK-Nummer angeben!

Medizinische Universität Graz, Auenbruggerplatz 2, A-8036 Graz. www.medunigraz.at

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