CHARLES UNIVERSITY IN PRAGUE

**THIRD FACULTY OF MEDICINE**

**Catarina Saavedra Conde**

# Continuous Glucose Monitoring

*Diploma thesis*

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Author of diploma thesis: Catarina Saavedra Conde

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Advisor of the thesis: MUDr. Jan Brož

Department of the advisor of the thesis: second department of internal medicine

Date and year of defence: May 2010

# Written Declaration

I declare that I completed the submitted work individually and only used the mentioned sources and literature. Concurrently, I give my permission for this diploma/bachelor thesis to be used for study purposes.

In Prague on May, 2010 Catarina Conde

I would like to thank MUDR Jan Brož for accepting being my tutor for the thesis. I want to thank him to be always available to clarify all the questions I had and to help me to be successful on my thesis.
I'm gratified for observe him always dedicated to his patients and students.

# Contents

## ABREVIATION LIST

| | |
|---|---|
| CDC | Centers for Disease Control and Prevalence |
| CGMS | Continuous glucose monitory system |
| HbA1c | Glycohemoglobin |
| FDA | Food and Drug Administration |
| CGM | Continuous Glucose Monitoring |
| DM | Diabetes Mellitus |
| WHO | World Health Organization |
| MODY | Maturity onset diabetes of the young |
| FPG | Fasting plasma glucose |
| OGTT | Oral glucose tolerance test |
| HDL | High-density lipoprotein |
| ADA | American Diabetes Association |
| BMI | Body mass index |
| SMBG | Self monitoring of blood glucose |
| ISF | Interstitial fluid |
| ICU | Intensive Care Unit |

Chapter 1

# INTRODUCTION

I chose continuous glucose monitoring for my diploma thesis, based on the importance to improve diabetes care and to reduce the risk of the development and progression of complications.

The worldwide prevalence of Diabetes Mellitus has risen dramatically over the past decades. The Centers for Disease Control and Prevalence (CDC) estimated that 366 million individuals would have diabetes by the year of 2030.

Diabetes Mellitus is a multi-factorial disease, which requires intensive metabolic control to avoid the chronic complications, and this metabolic control includes the continuous glucose monitory system (CGMS) in comparison to conventional methods of metabolic control, such as glycohemoglobin (HbA1c), capillary and venous glucose determinations, lipidogram and insulin levels controls.

Devices for continuous blood glucose monitoring are currently used and they measure the glucose in the interstitial fluid (ISF) that is in equilibrium with blood glucose. These devices provide retrospective glucose values or even real time glucose values. (In this way) continuous monitoring will give multiple glucose measures not just during the day but also during the night and with possibility to predict the glucose values in the future. One of the important functions of this devices is the alarms that notify the patient if the blood glucose falls to hypoglycaemic range or if increase to hyperglycaemic range.

Until very recently, self-monitoring of blood glucose was achieved by multiple capillary blood glucose. This measurement just

provides a snapshot blood glucose concentration at that moment without predicting future glucose levels.

Food and Drug Administration (FDA) in the U.S and also by the CE marking in Europe approved five continuous glucose monitor (CGM). These devices can measure blood glucose in a minimal invasive method by a sensor in the subcutaneous tissue or in a non-invasive method of electromagnetic radiation trough the skin.

The CGMS enables the identification of physiological phenomenon such as Somogo and asymptomatic hypoglycemia that other methods cannot detect.

## Continuous Glucose Monitoring

### Definition and prevalence of Diabetes Mellitus

Diabetes Mellitus (DM) is a disease, which comprises a group of metabolism disorders resulting from the insufficient production of insulin by the pancreas and resistance to insulin action. Is characterized by hyperglycemia resulting from a deficiency in insulin secretion from the β cells of the pancreas, peripheral resistance to insulin action or both (GALINDO et al., 2006; TEIXEIRA et al., 2001).

The disease begins silently, which leads to a delayed diagnosis and increases developed chronic complications such as nephropathy, retinopathy, neuropathy and cardiovascular disease. This fact increases the morbidity of these patients.

Approximately 50% of patients with diabetes type 2 have no apparent symptoms or very mild symptoms, making it difficult to suspected diagnosis (BUSE et al., 2003, O'Connor et al., 2006).

The classic symptoms of DM are hypoglycemia, an osmotic diuresis caused by glycosuria leading to urinary frequency, polyuria, and polydipsia that can progress to orthostatic hypotension and dehydration. Other symptoms mostly caused by dehydration are weakness, fatigue, and mental status changes.

In patients with DM 2 this symptoms usually occur slowly leading to a delay in diagnose. Such patients may have delayed 5 to 7 years in the diagnosis of disease, when they can show no clinical signs of major complications diseases such as retinopathy, nephropathy or macroangiopathy and peripheral neuropathy.

The prevalence of diabetes is increasing and represents today a major impact on public health. World Health Organization (WHO)

data provide a increase of 2.8% in 2000 to 4.4% in 2030, representing an increase of 171 million diabetics in 2000 to 366 million in 2030 (WILD et al., 2004).

## Classification of Diabetes Mellitus

In Type 1 DM also named insulin dependent, insulin production is absent because of autoimmune pancreatic β- cell destruction trigged by environmental exposure. The destruction of the β- cell is done over a period of months or years until the point that insulin concentrations are no longer adequate to control plasma glucose levels. This is mainly in children and adolescents.

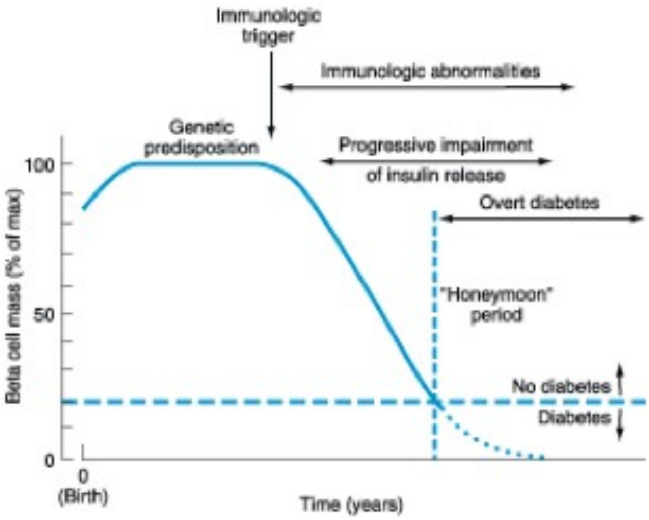



Figure 1. The downward slope of the beta cell mass varies among individuals and may not be continuous. This progressive impairment in insulin release result in diabetes when 80% of beta cell mass is destroyed. A "honeymoon" phase may be seen in the first 1 or 2 years after the onset of diabetes and is associated with reduced insulin requirements.

Inheritance can be monogenic, may be related to antigens histocompatibility HLA-, and high-risk individuals who have the DR3 - DQ2 or DR4-DQ8 and it is believed that the presence of an aspartic

acid at position 57 DQ beta chain and arginine at position 57 of DQ alpha chain, increase the risk of developing diabetes. This susceptibility is seen in more then 90% of the patients with DM type 1 and in some ethnic groups as Scandinavians and Sardinians.

Autoantigens include glutamic acid decarboxylase, insulin, insulinoma-associated protein and other proteins in β- cell. Several virus such coxsackievirus, rubella, cytomegalovirus, Epstein-Barr, and retroviruses have been linked to the onset of type 1 DM. Diet is also a factor that must be considerer, infants exposure especially to cow's milk and the milk protein β casein, also high nitrates in drinking water, and low vitamin D consumption have been linked to increased risk of type 1 DM.

In Type 2 DM also named non-insulin dependent, insulin secretion is inadequate. The primary mechanism, peripheral *insulin* resistance and increased hepatic production of glucose make *insulin* levels inadequate to normalize plasma glucose levels. Due to this the insulin secretion becomes insufficient after pancreatic exhaustion. DM type 2 is mainly seen in adult, corresponds to 80-90% of cases of diabetes and occurs in 7.5% of the population. With an increase of obesity in childhood there is a new onset of DM in children that is now type 2.

The inheritance of type 2 DM may be monogenic or polygenic. Fashion monogenic is rarer and is associated with resistance to insulin action related to mutations in the receptors for insulin gene in PPAR-gamma or defects in insulin secretion, mutation in the proinsulin or insulin, mutation in the mitochondrial genes, MODY (Maturity Onset Diabetes of the Young), The form of polygenic inheritance involves genetic and environmental factors and may relate to resistance to

insulin in muscle, fat, liver, defects in beta cell response to hyperglycemia, and increased gluconeogenesis liver. Obesity and weight gain are important in insulin resistance reflecting lifestyle, exercise and diet changes. There is 90% in twin concordance in comparison to the 50% in type 1 DM.

There are other types of diabetes related to genetic defects in insulin production, such as MODY (Maturity onset diabetes of the young), diabetes produced by drugs that inhibit the production of insulin, alcohol or endocrinopathy such Cushing's syndrome and pancreatic diseases as cystic fibrosis, pancreatitis and hemochromatosis. There are cases related to rare genetic syndromes and some that develop insulin resistance in all women, but only a few developed gestational DM.

In some circumstances (diabetes with onset between 25 and 30 years, during pregnancy and in hemodialysis patients), the diagnosis of the type of diabetes is more difficult and may require the use of some laboratory methods for establish the classification of the type of diabetes. Among these are markers of autoimmunity, as the measure of autoantibody related to pancreatic insulitis and evaluation of pancreatic insulin reserve through As C-peptide and the rapid phase of insulin secretion.

| Characteristic | Type 1 DM | Type 2 DM |
|---|---|---|
| Age of onset | Mainly less then 30 years old | Mainly more then 30 years old |
| Obesity | Not correlated | Associated with obesity |
| Ketoacidosis | Yes | No |
| Twin concordance | Less then 50% | More then 90% |
| Associated with human leucocyte antigen (HLA) | Yes | No |
| Antibodies in diagnose | Yes | No |
| Istets pathology features | Insulinitis and loss of most beta cells | Amyloid deposits are common |
| Prone for complications | Yes | Yes |
| Hyperglycemia responds to oral antihyperglycemic drugs | No | Yes |

Table 1. Main characteristics between diabetes type 1 and type 2

## Diagnostic criteria for Diabetes Mellitus and impaired Glucose Regulation

The constant progress made in the control of Diabetes Mellitus and better understands the disease and its complications have led to parameters increasingly strict about the diagnosis and control of the disease.

There are 3 tests used for the diagnosis:

- A fasting plasma glucose (FPG) test measure blood glucose in a

person who has not eaten for at least 8 hours.

- An oral glucose tolerance test (OGTT) measures blood glucose after a person fasts at least 8 hours and 2 hours after the person drinks a glucose-containing beverage of 75 grams of glucose dissolved in water.
- Random plasma glucose test measure blood glucose without regard to when the person being tested last ate.

| TEST | NORMAL | IMPAIRED GLUCOSE REGULATION | DIABETES |
|---|---|---|---|
| FPG | <5.6mmol/L | 5.6-6.9 mmol/L | ≥7.0mmol/L |
| OGTT | <7.7mmol/L | 7.7–11.0 mmol/L | ≥11.1mmol/L |

Table 2. Diagnostic Criteria for Diabetes Mellitus and Impairment Glucose Regulation

OGTT is more sensitive for diagnosing DM and impaired glucose tolerance but is less convenient and reproducible than FPG. It is therefore rarely used routinely, except for diagnosing gestational DM. FPG is also preferred for diagnosis diabetes because of the low cost of the test.

Random plasma glucose test is when casual blood glucose levels are 11.1 mmol/L and with present of symptoms such increase urine output, increase thirst and unexplained weight loss, can mean a person has diabetes.

Glycohemoglobin, which shows the average blood glucose of patients in the last 2 to 4 months and fructosamine, which reflects the blood of the last 2 to 3 weeks are useful in clinical monitoring, but are

not tests of the first choice for the diagnosis of the disease. Other tests may help in clarify the etiology and stage of disease, such as insulin, C-peptide, dosages of anti-islet cell, anti-insulin and anti –GAD.

Early diagnosis of changes in glucose tolerance allows therapeutic measures that can prevent the onset of diabetes in individuals with glucose tolerance and delay the onset of chronic complications.

Screening for DM should be conducted for patients at risk of the disease. American Diabetes Association (ADA) recommend to people with more then 45 years old every 3 years, with risk factors for diabetes mellitus such as overweight Body mass index (BMI) more the 25, sedentary life, Family history of diabetes mainly first degree relatives, history of impair glucose regulation, hypertension, high levels of triglycerol and with low levels of high-density lipoprotein.

## Treatment

The treatment involves control of hyperglycemia to improve he symptoms and prevent complications while minimizing the episodes of hypoglycemia. The glucose levels in the blood must be maintained between 4,4 and 6,7 mmol/L during the day and between 5,6 and 7,8 mmol/L at bedtime. The HbA1c must be maintaining less the 7%.

All the patients must be educated; diet, exercise counseling and monitoring of glucose control are the main important elements for a good treatment.

Patients educations about Diabetes Mellitus is important and they should be aware how to perform finger-stick testing, the symptoms and sign of hypoglycemia, hyperglycemia and diabetes

complications. This education is crucial for optimizing care. Formal diabetes education program, nurses and nutrition specialists are very effective.

All diabetes need to be educated about a diet that is low in saturated fat and cholesterol and contain moderate amounts of carbohydrates and higher fiber content. Exercise must be incorporated in their habits this will protect them from vascular diseases.

Monitoring of plasma glucose, HbA1c, fructosamine levels. Self-monitoring of the whole blood glucose using fingertip blood, test strips and glucose meter are the most important. The new devices of CGM are important role to maintain the glucose levels.

Every diabetic patient should have a personalized treatment according to the type of diabetes that they present.

## Chronic complications of diabetes

The chronic complications of diabetes are frequent and associated with elevated morbidity and mortality. The main complications are retinopathy, nephropathy, neuropathy, macrovascular diseases and infections. Cardiovascular disease is the leading cause of death in both types of diabetes, accounting for 44% of all cases of death in patients with diabetes type 1, followed by renal disease. (CENTERS FOR DISEASE CONTROL AND PREVENTION., 2002, Picon et al., 2006, Castro et al., 2004)

Most of the morbidity and mortality and the cost of diabetes is a direct result of the management of complications that could be prevented. The decrease in risk diabetics develop complications of the disease requires much more than the intensive glycemic control, since

that strict control can only reduce microvascular complications of the eyes, kidneys and nerves and not the complications of macrovascular diseases such as cardiovascular system.

Metabolic syndrome is a clinical condition characterized by clustering of risk factors for cardiovascular disease, among them hypertension, dyslipidemias, visceral obesity, manifestations of dysfunction endothelium and the presence of insulin resistance.

It is known that the negative impact of any additional risk factor such hypertension or dyslipidemias for cardiovascular diseases is much higher in diabetic patients. And as obesity, hypertension, dyslipidemias and resistance insulin conditions are very frequent especially in diabetic patients type 2. Early detection of these risk factors and aggressive treatment of these conditions can significantly reduce the risk of cardiovascular disease in diabetic patients (Kendall et al., 2001).

Currently, the system of continuous glucose monitoring has become interesting tool for investigating the glycemic profile of patients with diabetes, as well as in other clinical conditions that develop with fluctuations blood glucose levels.

Chapter 2

# DETERMINATION OF THE LEVELS OF GLYCEMIA

The measurement of glucose levels is essential for the efficacy of treatment of diabetes. The methods for measurement of glucose can be done by: laboratory exams, self-monitoring by glucometer, sensors for continuous glucose measurement and measurement of hemoglobinemia.

## 1. Laboratory exams

Laboratory exams are traditional and typical glucose monitoring. A blood sample is taken and sent to the laboratory. At the laboratory plasma is separated by centrifugation and specific enzymes such as glucose oxidade is applied. Enzymes cause a chemical reaction leading to the degradation of glucose, with the formation of a product that is easily measured through the change of color reactions or oxi-redox reactions.

The results have a high degree of accuracy, with errors estimated at 2%. The laboratory test is considered a “gold standard” when compared to other types of monitoring. However a few hours are necessary to obtain the test results, because the necessary logistics for the transport of the samples to the lab. This makes the practical use on glycemic control difficult, which led to the development of portable devices for measuring blood glucose.

## 2. Self-monitoring of blood glucose (SMBG) by glucometer

**Continuous Glucose Monitoring**

The self-monitoring of glucose should be advised for all diabetic patients.

A small sample of capillary blood is collected through a small hole in the fingertip of the patient. The blood sample is applied to a tape that is inserted into a portable measuring device. Different methods of measurement are used in this type of device.

In general, tapes use up specific enzymes for the degradation of glucose and the device makes measurement of formed products.

The glucometer provides a reading of glucose in less than half a minute, amounting to a total time of the examination less than five minutes. Due to the speed that test is performed, the glucometer is the measurement most frequently used by diabetic patients. The patient can make measurements several times a day, which allows an adequate glycemic control.

The main disadvantage of using the glucometer is the accuracy of their measure compared to the laboratory test. Readings also depend on the ability of the person performing the examination. The diabetic patient must have an adequate training to be able to perform a good measurement with the glucometer.

**Continuous Glucose Monitoring**


Figure 2. Schematic representation of glucose measurement with a glucometer

- First step you should set up your glucometer, a test strip, a lancet and an alcohol prep pad
- Wash your hands to prevent infection
- Obtain the blood from the tip of the finger. Rub the hands together to increase blood flow on the periphery
- Turn on the glucometer and place a test strip in the machine. Watch the indicator for placing the blood to the strip
- Clean the area with alcohol where you are going to puncture and wait until the alcohol evaporates
- Pierce the fingertip and obtain a drop of blood.
- Place the drop of blood on at the side of the strip
- Write down the result that are seen on the glucometer

The frequencies recommended for blood glucose monitoring are:

• ≥ 3 to 4 times per day in patients treated with multiple injections of insulin or using an insulin pump.

• ≥ 2 times per day for patients above the glycemic targets were treated with oral agents and / or a single daily dose of insulin.

• ≥ 1 time per day with a weekly glycemic profile in patients with glycemic control and treated with single daily dose of insulin or oral agents;
• ≥ 1 time per week in patients on non-pharmacological treatment, whether or not with glycemic control.

## 3. Sensors for continuous glucose monitoring

In the last years many technological devices have been in study for the continuous glucose measurement. The Medtronic, DexCom and GlucoWatch are some of many examples of these devices.

CGM system operates by measuring the glucose levels in the interstitial fluid. The device has three components a sensor that measure glucose levels, a transmitter that is attached to the sensor and a receiver that display and stores the glucose information. The information on the receiver is then converted into estimated mean values of glucose standardizes to capillary blood glucose levels measuring during calibration.

The plastic sensor is inserted just under the skin of the abdomen and this devise can display real-time glucose values and glucose trends. These devices have incorporated an alarm or vibrate when they detect values of hypoglycemia or hyperglycemia. The receiver can store information for later use. The data must be downloaded in the computer to be able to store more information.

These devices are minimal invasive or noninvasive, usually getting the readings through skin or subcutaneous sensors, to minimize patient discomfort. These ISF monitoring technologies are defined minimal invasive because they just compromised the skin barrier but not

puncture any blood vessels.

One of disadvantages of CGM is the lack of accuracy of each single data point compared with the accuracy of SMBG mainly in the hypoglycemia range. (David C. Klonoff, 2005) Other important fact is that is devices have high cost and insurances don't cover for the technology.

4. Monitoring of glycohemoglobin

Over the years prolonged hyperglycemia leads to the development of lesions that are extensive and irreversible, affecting human eyes, kidneys, nerves, large and small vessels, as well as coagulation. Persistently increased levels of glucose in blood are toxic to the body, through three different mechanisms: through the promotion of glycation proteins by hyperosmolarity and by increasing levels of sorbitol within the cell. Is through this process of glycation of proteins that the blood glucose binds to molecule hemoglobin 2. The amount of glucose linked to hemoglobin is directly proportionate to the average concentration of glucose in blood. Since erythrocytes have a lifetime of approximately up 120 days, the measure of the amount glucose bound to hemoglobin can provide an assessment of glycemia control. This is the purpose examination of hemoglobin, the most frequent assessment hemoglobin A1C (HbA1c) 2. Traditionally, the A1C has been considered as representative of overall weighted average of blood glucose. Actually, glycation of hemoglobin occurs when throughout the lifetime of red blood cell, which is approximately 120 days.

Chapter 3

# MEDTRONIC, DEXCOM, GLUCOWATCH

The challenge of diabetes treatment is to keep the patient within the normal range, which proved to decrease the risk of secondary complications, such as impaired eye, kidneys and nerves. The treatment of diabetes is thus a work of prevention continues.

The continuous glucose monitoring system can provide over 24 hours a map so that the expert knows how treatment is indicated at night or after meals. The map allows you to adjust the treatment much more personalized to each patient.

CGMS has the advantage of adjusting the doses of patients using insulin infusion pump, but not yet adequate in children with nocturnal hypoglycemia. CGMS allows the physician to have a more realistic view of what happens in terms of glycemic variation on the person with diabetes, allowing it to become more capable of handling other cases.

## Indications and contraindications for the use of CGMS

The CGMS is suitable for all types of diabetes, especially for those with inadequate glycemic control. Diabetics with busy lifestyles and irregular hours have a greater propensity for both hyperglycemia and to hypoglycemia, which often are sudden and often asymptomatic even during sleep. These events of glucose can be analyzed in detail from this procedure facilitating treatment planning. This examination may be accompanied by several meals, serving as support for dietary

guidance and for the exercise. Capillary blood glucose meter is a static measurement of that moment of glycemic control, where CGMS measures glucose values for 24 hours, allowing a more detailed understanding of diabetes control. This test is extremely useful in comparison to choose the best type of insulin and their ways of using them in the treatment of diabetes.

Patients should be more then 18 years old and the used of these devices should be contraindicated in patients that are unwilling to performed minimally two blood glucose measurements per day.

The therapy adjustments should be based not just from the parameters from the continuous glucose monitoring but also from the self-monitoring glucometer.

Continuous glucose monitoring is acceptable for patients:

- Replacement of insulin by rapid insulin analogue ultra-rapid or addition of additional applications of rapid-acting insulin or insulin analog ultra-fast action
- Replacement of Neutral protamine human (NPH) insulin by an insulin analogue of long-term or adding additional applications of NPH
- Adjustments of doses of basal insulin and glucose
- Changes in the composition of carbohydrates in the diet
- Changes in blood glucose for the ideal pre-or postprandial.
- Quantification of the response to an oral glucose agent
- Evaluation of the impact of changes in lifestyle over the control glucose.
- Monitoring of conditions in which an intensive glycemic control is desired mainly in Gestational Diabetes, Diabetes in Children and patients in the intensive care unit (ICU)

**Continuous Glucose Monitoring**

- Diagnosis and prevention of hypoglycemia and nocturnal hypoglycemia

In conclusion the CGM gives continuous awareness of the current glucose levels and protect the patient from states of hyperglycemia and hypoglycemia. This leads to a better treatment and prevention of Diabetes.

**Components of the minimal invasive devices**

- **Monitor** shows real time glucose measurements and tells about the changes of glucose levels. They differentiate according to the type of the device. This devices can be put in the belt, pocket or under the clothes.


Figure 3. DEXCOM

**Continuous Glucose Monitoring**


Figure 4. MEDTRONIC

- **Sensors** there are two different types of sensors in these devices. All this devices where approved to be used in the patient by the FDA.

The Guardian REAL-time, Seven Plus and MiniMed Paradigm and seven plus have enzymatic sensors. The enzyme sensor consists of an electrode covered by a layer enzyme. This sensor has the form of a needle being that is inserted through the skin to subcutaneous. The sensor stay in contact with the interstitial fluid. Thus, by measuring the electric current generated, the device can estimate the concentration of glucose in interstitial fluid and therefore in the blood, assuming that the interstitial glucose concentration is equal to the blood glucose. This sensors test the glucose values every 5 minutes.

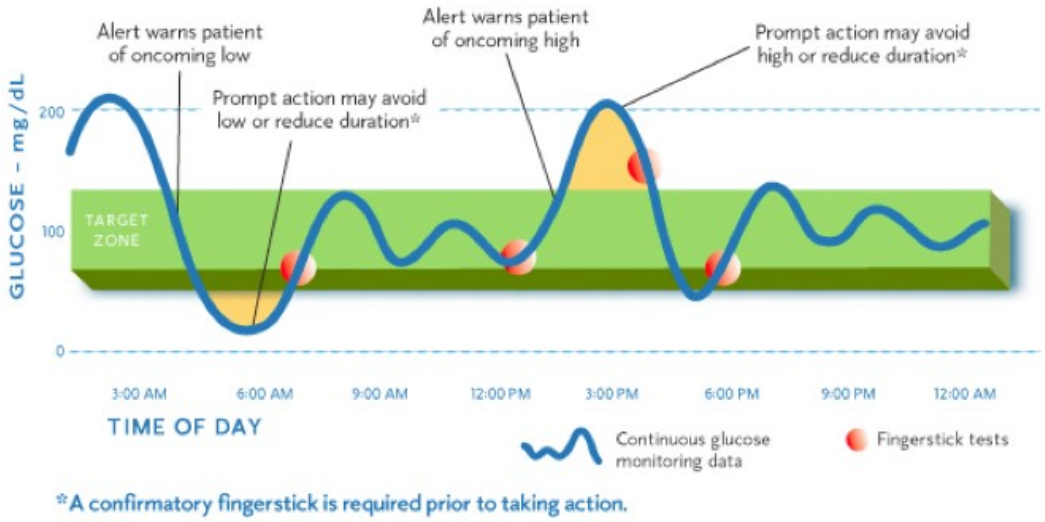
Another mechanical sensor is the reverse iontophoresis, which is in the GlucoWatch G2. Two electrodes apply an electric voltage on

the skin of the individual. The applied voltage creates a flow of interstitial liquid to the surface of the skin. The liquid thus extracted contains interstitial glucose, which is then measured hen is an enzyme sensor.

The sensor of DexCom has a life spam of a week in comparison to the sensor of Medtronic that need to be substituted every 72 hours. Also some patients refer that the sensor of DexCom is easier to be inserted then the Medtronic.

- **Transmitters** are usually small and are rechargeable devices. They connect to the sensor that is inserted subcutaneously.
- **Calibration** procedure can be performed by means of conventional capillary blood glucose measurements in order to transform the sensor signals obtained from the interstitial fluid into "blood" glucose values. The ideal time for calibration is either after fasting or at least three hours postprandial. This calibration must be done at least every 12 hours
- **Software** The seven plus stores up to 30 days of information, which after must be downloaded to the computer using the DexCom Data Manager software. Medtronic uses Comlink 90 days. The data that is stored in the computers helps the patient and also the Doctor to evaluate and then make adjustments on the treatment. Creates customizable charts to clearly display the glucose and gives short and long trends of the treatment.
- **Alarm** the most important use of an alarm is to detect unsuspected hypoglycemia as between 2-3 AM so that glucose can be administered to prevent brain damage. This also will prevent the hyperglycemia that is seen in the morning in patients that didn’t have enough insulin during the night.

**Continuous Glucose Monitoring**




Graphic 1. Glucose rates on continuous glucose measurement device

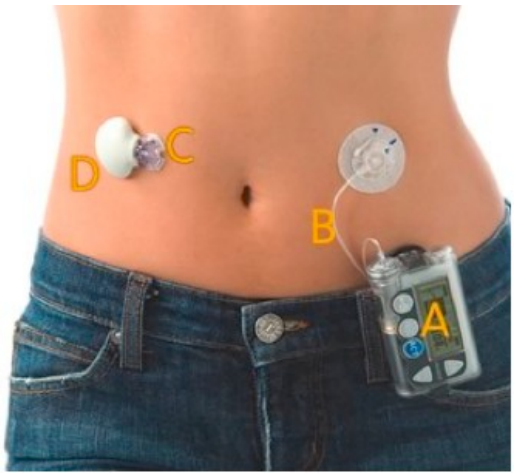
**Continuous Glucose Monitoring**

## MiniMed Paradigm REAL-time

A new Medtronic device that was approved by FDA is the MiniMed Paradigm REAL-time.

For the first time, a technology system integrates insulin and continuous glucose monitoring. This advanced technology combines a "smart" insulin pump with the new benefit of continuous glucose monitoring in Real time. The delivery of insulin is made in multiple basal rates with low units per hour. Is part of the Integrated System: the insulin pump Paradigm REAL-Time and a transmitter connected to a glucose sensor. The transmitter is a key component in the transmission to glucose in Real Time. User of the system will be integrated with a cannula in the subcutaneous infusion of insulin and a sensor in another location, subcutaneous, for the reading of glucose concentration. This system provides direct access to users to its own standards of glucose.

Figure 5. MiniMed Paradigm REAL-time




A- Insulin pump

B- A cannula that sits under the skin for 3 days and delivers insulin

C- Glucose sensor for continuous glucose monitoring

D- Transmitter that sends glucose data to the insulin pump

| | *Medtronic Guardian REAL-Time* | *DexCom SEVEN PLUS* |
|---|---|---|
| **FDA approval** | Children 7-17 and Adults in June 2006 | Older then 18 years old in March 2006 |
| **Price** | System $1,339 System + $35 with 10 sensors | System $1248 and $240 with 4 sensors |
| **Accuracy** | Error Grid: 98.9% | Error Grid: 97% |
| **Sensor life** | 72 hours | 7 days |
| **Start up initialization Time** | 2 hours | 2hours |
| **CalibrationEvery** | Every 12 hours | Every 12 hours |
| **Alarm** | Yes | Yes |
| **Dispay glucose number** | Every 5 minutes | Every 5 minutes |
| **Alarm set** | 8 different thresholds | One high and two lowers |

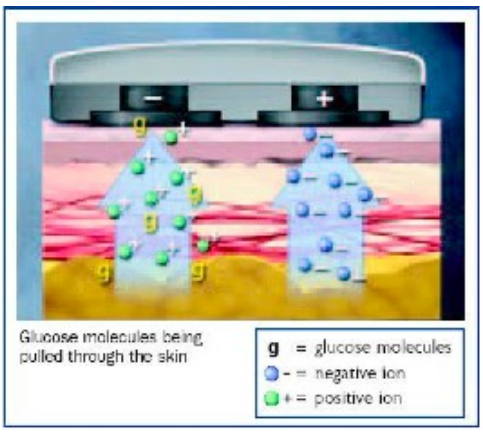
Table 3. Comparison between Medtronic Guardian REAL-Time and DexCom SEVEN PLUS

## Continuous Glucose Monitoring

### GlucoWatch

GlucoWatch is a noninvasive automatic device approved by the Food and Drug Administration (FDA) of the United States. It works like a watch around the wrist and pulls glucose through the skin by applying a potential, iontophoresis, measuring glucose in the sample extracted by an enzymatic electrochemical sensor. The extraction and reading takes 20 minutes and can be downloaded and viewed on the display until 3 measurements per hour. The area where the arm is placed on the watch must be shaved, it is necessary to restore a gel sensor and change the device arm every 12 hours and make new calibration. To prevent skin irritation topical corticosteroids can be applied.

Figure 6. Relation between the GlucoWatch and skin




- Two electrodes that must be change every 12 h
- Mechanism of the sensor is iontophoresis
- Calibration of 3 hours
- Measurement of glucose is done every 10 min for 12 hours
- Alarm is incorporated
- Disadvantages is skin irritation and measurement can be change by the sweat

**Continuous Glucose Monitoring**


Figure 7. GlucoWatch G2

**Problems with continuous glucose monitoring**

An important limitation on the CGM is that the measurements are made from the interstitial fluid, not from blood. Assuming that the concentration of glucose in the ISF is identical to the concentration of glucose in blood. However, this hypothesis is not entirely correct and the relationship is not well understood. The glucose in the blood passes into the interstitial fluid in a continuous process of diffusion. So when the concentration of glucose in the blood is constant, the concentration of glucose in the ISF is also constant. However if there are changes in the concentration of glucose in the blood will also be changes in the ISF. This can be seen after a meal, because at that time there is an increase in blood glucose and glucose in the ISF is still constant. After applying a dose of insulin, there is a greater absorption of glucose in the liver and increasing glucose uptake by cells. Therefore insulin leads to a decrease in blood glucose in the blood and

also in the ISF.

In this both situations there is a difference between the blood glucose and interstitial that is read. The difference between these values influence the process of calibration of sensors, calibration allows for a relationship between glucose in the blood, which is measured by the glucometer and glucose concentrations in ISF taken through the sensors. These limitations presented by CGM sensors cause a reduction in the accuracy of readings. Although the currently available data suggest limited accuracy of these devices compared to capillary blood glucose measurement (especially in the hypoglycemic range) and point to the need for improvement in the technology, it is important to remember that both CGM and capillary measurement have limitations and that both provide estimates of plasma glucose concentration as determined by a gold standard assessment.

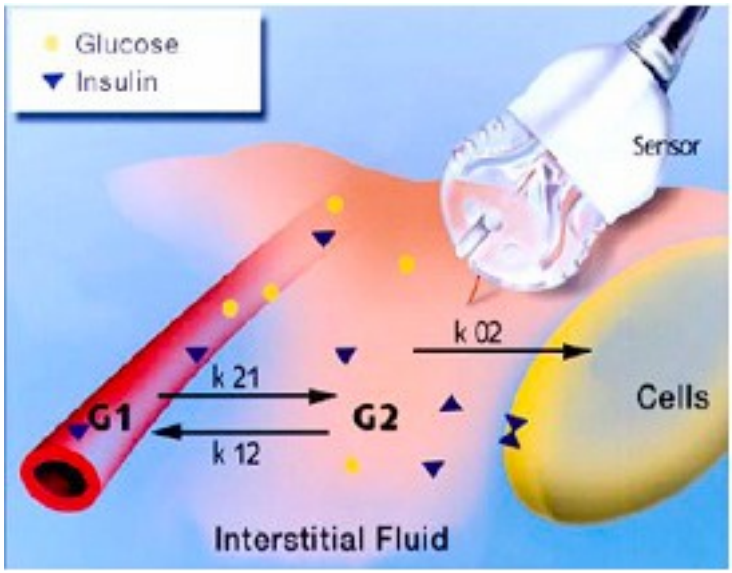



Figure 8. This picture shows in a simplified way the relation between a blood vessel and a cell. The transport of substances as glucose is made first from the interstitial fluid. When we use a glucometer to measure the glucose we are measuring the concentration of glucose in the blood vessel. The sensor from the CGM measures the concentration of glucose in the interstitial fluid.

Other problem related to the continuous glucose measurement is the lack of accuracy compared with the self-monitoring by glucometer. This lack of accuracy is mainly seen in relation with period of hypoglycemia. The alarm setting should be chosen carefully so as not to incur too many false alerts while still allowing enough time to verify that blood glucose values are actually low before acting to correct the hypoglycemia.

The costs for CGM are substantial and are currently a major barrier to its widespread use. The systems and the accessories are very expensive for the patient to be able to afforded. The insurances don't cover the system for the entire patient. In this point the physician has a main role where he must specify that the patient will benefit from the used of CGM. Many

## Conclusion

The FDA advise that the use of Continuous Glucose Monitoring is not intended to replace home blood glucose monitoring but should be used in conjunction with self-monitoring for a better regulation of glucose levels.

The continuous glucose monitoring system is a minimal invasive method that analyses the glucose concentration in the interstitial fluid for 24 hours. This represents an important evaluation for the different values of glucose during the day and night. The real-time monitoring leads to a better and faster response according to the values that are seen on the system. The connection between the device and the software uses leads for a rapid transmission and visualization of information. This information is registered and used to adjust the treatment.

The CGM is mainly important for nocturnal hypoglycemia control, because it cannot be detected by self-monitoring. The presence of nocturnal hypoglycemia is an indication for prescribing CGM to the diabetic patient. These devices have an important role in postprandial hyperglycemia.

The continuous glucose monitoring represents a big advantage in improving HbA1c values and avoids the occurrence of disruptive hypoglycemia. Throughout the years this improvement of HbA1c represents a better control of glucose values and this means that less long-term complications will develop.

These devices may be the future for a better treatment and care of the diabetic patient and will decrease the associated chronic complications and improve the prevalence of this disease.

# PATIENTS METHODS

## Patient presentation

First patient:

Patient was brought by ambulance to the hospital to the dialectology department. Patient presented increase thirst, polyuria but without dysuria and hyperglycemia, 24mmol/L.

Knowing the result from the laboratory examinations it was confirm that patient is diabetic type 2.

The treatment started with education of the patient about the disease and changes about the diet. Due to his high glucose levels insulin was given to decrease the glucose values to a normal range.

For a better treatment of the patient started with CGM DexCom. The importance of using this mechanism is to maintain the glucose levels in a normal range.

DexCom was used from 09/03/10 until 13/03/10, and all the dates are seen below.

## Continuous Glucose Monitoring

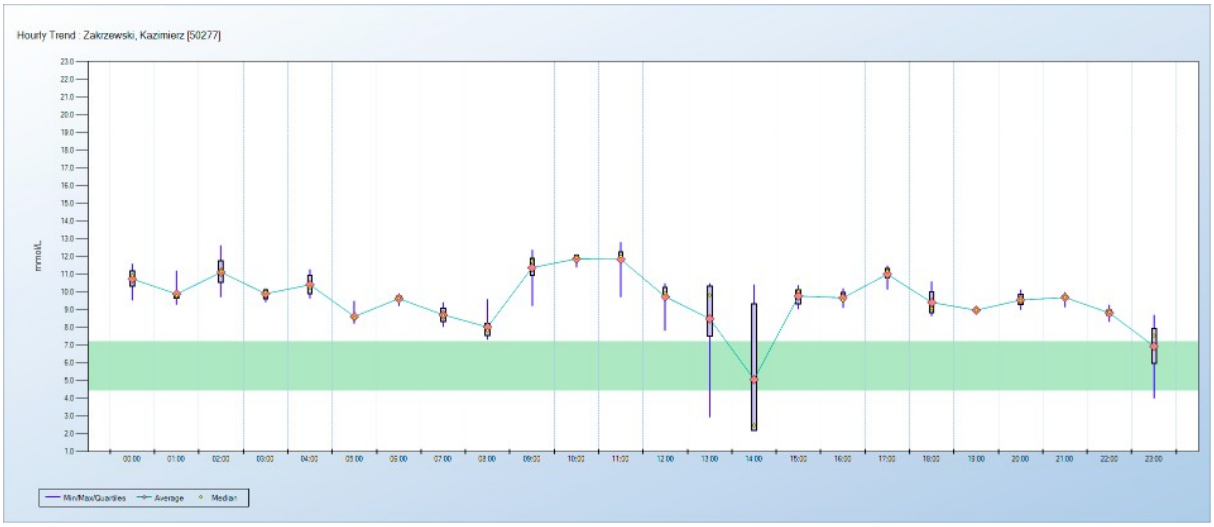
Hourly Trend from 09/03/2010 00:00 to 10/03/2010 00:00.


The glucose was measured from 12:30 until 22:30. During these 10 hours the patient presented hyperglycemia and the glucose values where not stable.

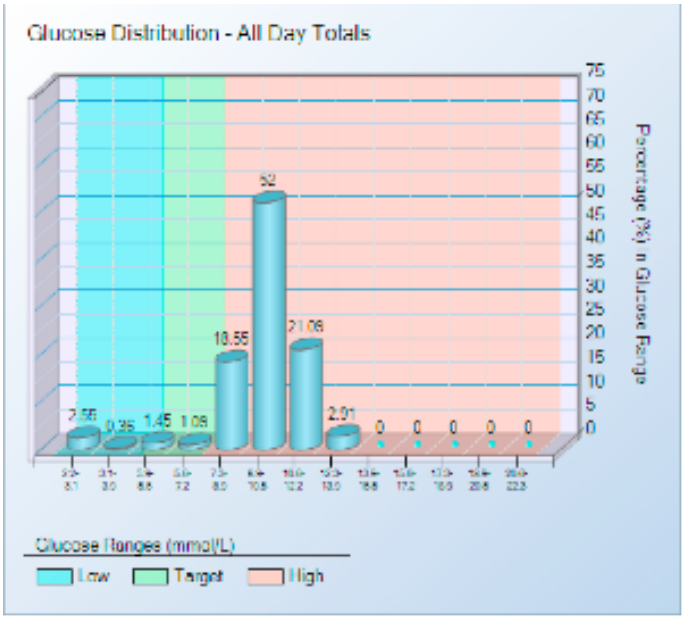

This graphic shoes an average of glucose levels above 9,9 mmol/L

## Continuous Glucose Monitoring

Hourly Trend from 10/03/2010 00:00 to 11/03/2010 00:00




The glucose was measured from 00:00 until 23:00. During these 23 hours the patient was also most of the time in hyperglycemia but he had periods of normal glycemia. From 14:00 o'clock we can see that the glucose values are more stable and more close to the normal value.

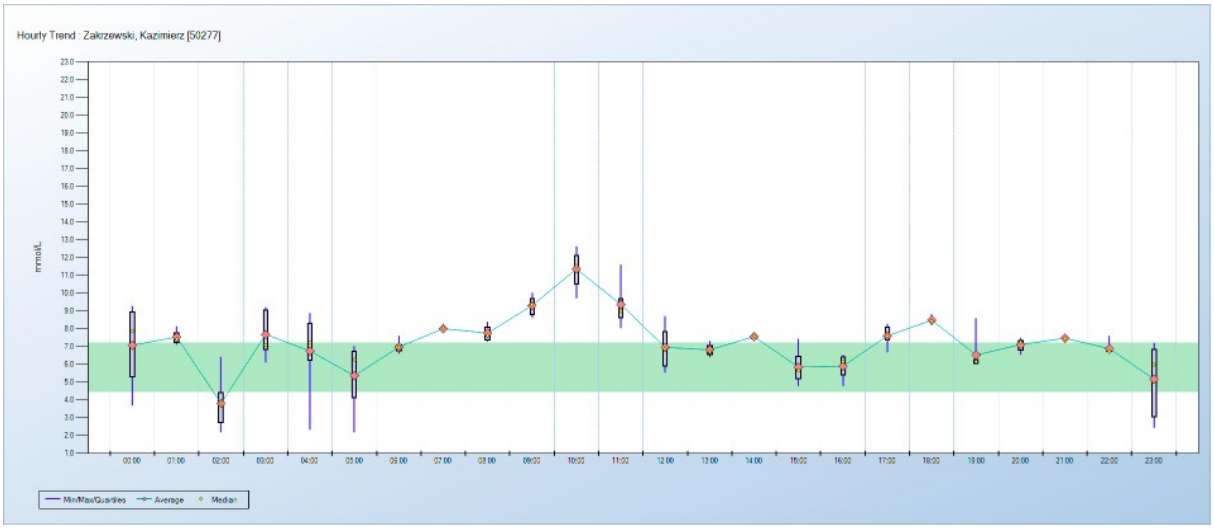



In this graphic there is a increase percentage of glucose values between 7,3 and 8,9

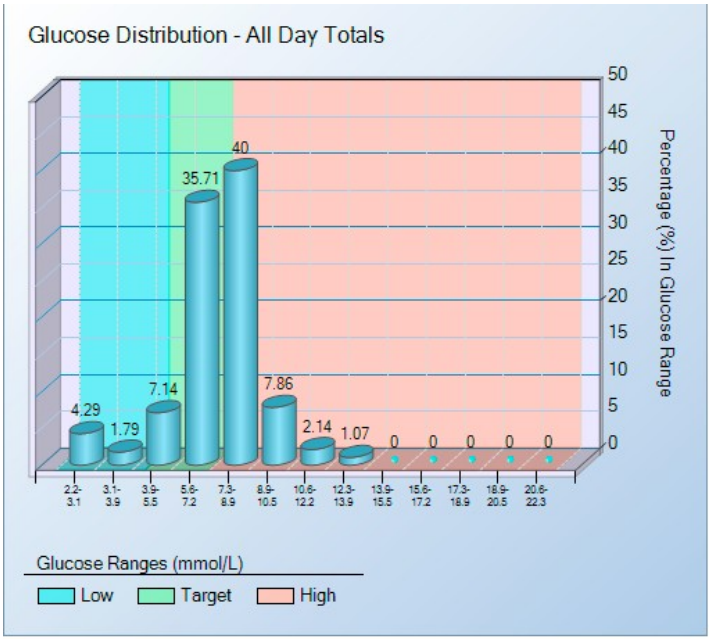
## Continuous Glucose Monitoring

## Continuous Glucose Monitoring

Hourly Trend from 11/03/2010 00:00 to 12/03/2010 00:00.



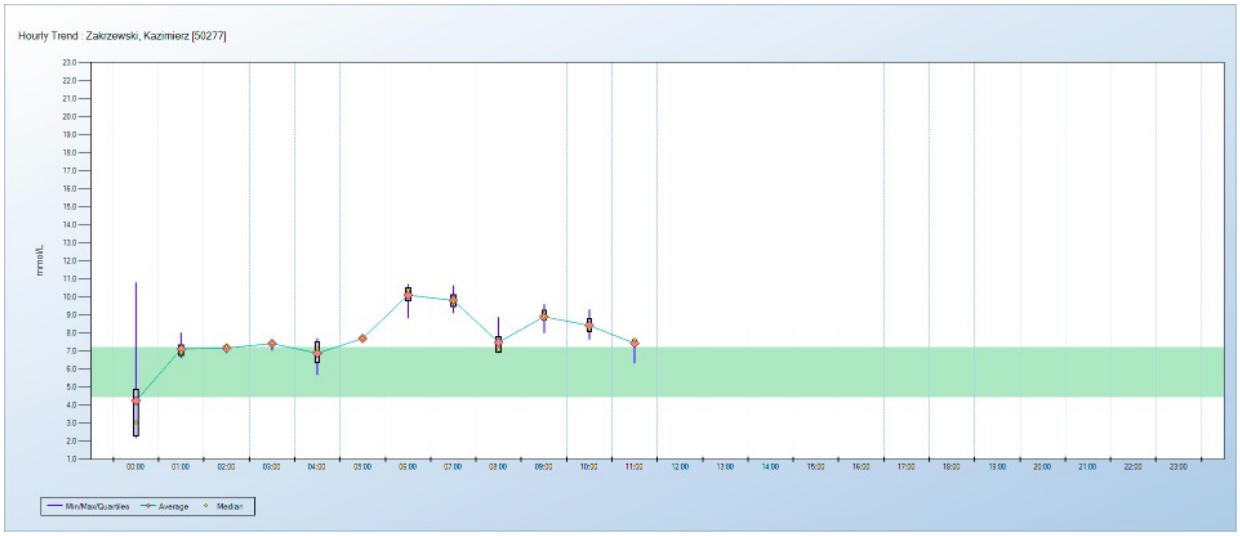

After a change of the treatment (Adding sitagliptine) of the patient we can see already changes at glucose values. In this situation the patient was almost all the time with a normal range of glucose.



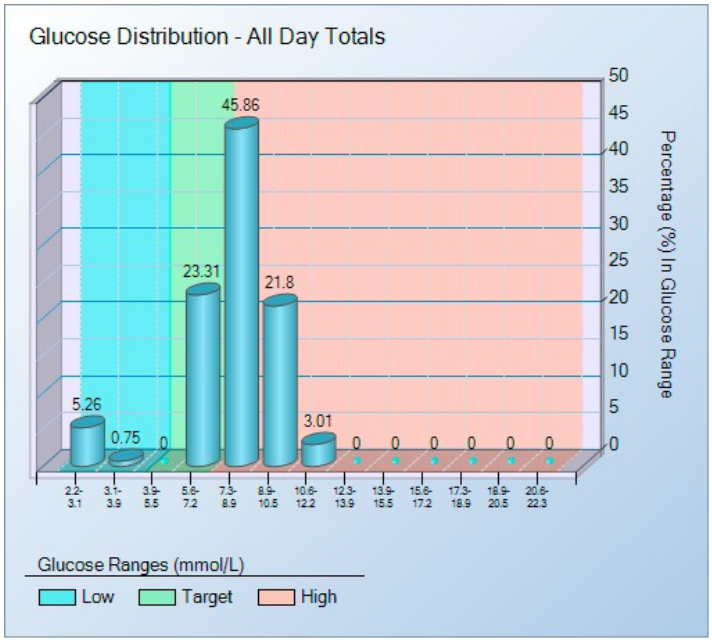

In this graphic 36% of the concentration of glucose is at target zone

## Continuous Glucose Monitoring

Hourly Trend from 12/03/2010 00:00 to 13/03/2010 00:00.




At this graphic there is a slight increase on glucose concentration but this is mainly do to lack of compliance of the patient. A good comprehension is important but sometimes difficult to achieve.




A slight decrease on the performance compared with the graphic from the day before but still better then the first days

## Continuous Glucose Monitoring

## Patient presentation

Second patient:

This patient was diagnosed with Diabetes type 1 in 1981 and he goes to the diabetology department frequently to be evaluated. The patients use self-monitoring with a glucometer and for the treatment insulin pump every day. His glucose regulation is good because almost 20 years past and he has no complications from diabetes mellitus.

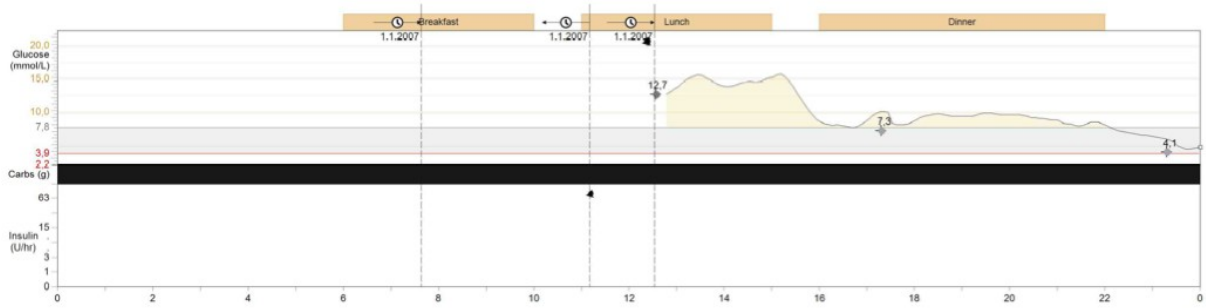
The patient was diagnosing with a craniopharyngioma and surgery was performed in 2001.

Patient stared to used continuous glucose monitoring for a better regulation of the glucose values. He is using a Medtronic device for CGM.

This patient used Medtronic from 01/07/2009 to 03/07/2009. During this 3 days the insulin was changed according to the values of CGM and from the concentration of glucose from the capillary by glucometer. After this changes in the insulin the glucose concentration was between the normal range.

**Continuous Glucose Monitoring**

**Wednesday 1.7.2009**

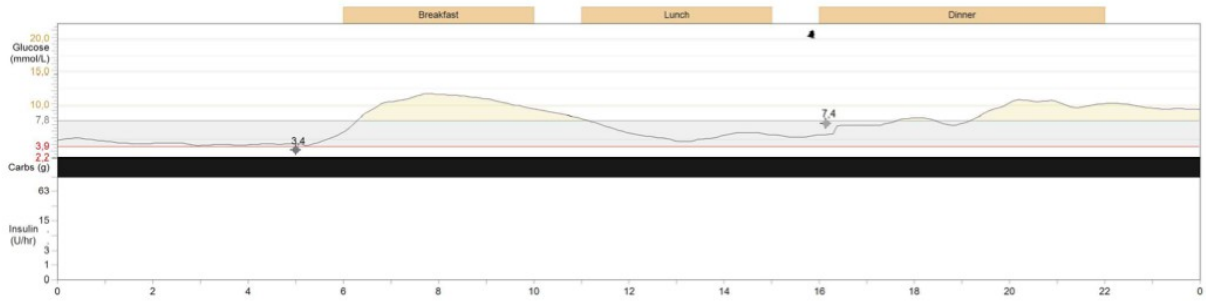



This graphic shoes the concentration of glucose of the patient. In the beginning the values are at hyperglycemia and then stat to decrease.

| Statistics | 1,7 | | 20,6-3,7 | |
|---|---|---|---|---|
| **Avg BG (mmol/L)** | **8** | | **7,9 ± 3,4** | |
| BG Readings | 3 | | 8 | 2,5/day |
| Reading Above Target | 1 | 33 % | 3 | 38 % |
| Reading Below Target | - | 0 % | 1 | 12 % |
| Sensor Avg mmol/L | 10,0+/-3,0 | | 8,7+/-2,9 | |
| Avg AUC more 7,8 mmol/L | 2,43 | 0d 11h | 1,74 | 2d 11h |
| Avg AUG less 3,9 mmol/L | - | 0d 11h | - | 2d 11h |

**Continuous Glucose Monitoring**

**Thursday 2.7.2009**

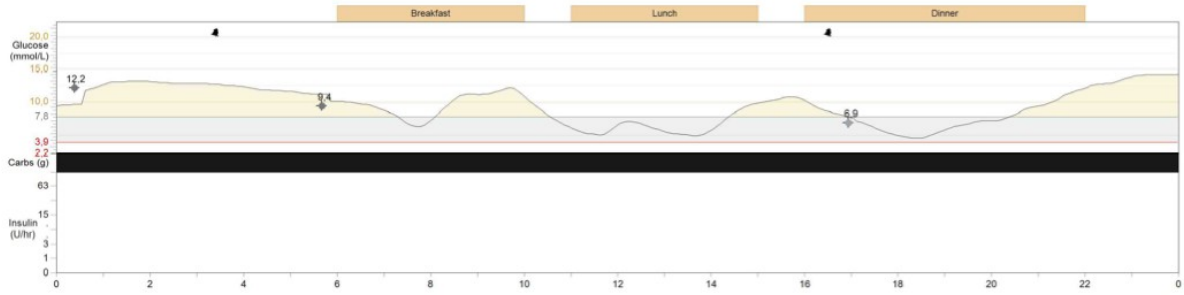



The glucose concentration was higher in the morning and at night but during the rest of the day was manly on the target values.

| Statistics | 2,7 | | 20,6-3,7 | |
|---|---|---|---|---|
| **Avg BG (mmol/L)** | **5,4** | | **7,9 ± 3,4** | |
| BG Readings | 2 | | 8 | 2,5/day |
| Reading Above Target | - | 0 % | 3 | 38 % |
| Reading Below Target | 1 | 50 % | 1 | 12 % |
| Sensor Avg mmol/L | 7,4+/-2,5 | | 8,7+/-2,9 | |
| Avg AUC more 7,8 mmol/L | 0,92 | 1d 0h | 1,74 | 2d 11h |
| Avg AUG less 3,9 mmol/L | - | 1d 0h | - | 2d 11h |

**Friday 3.7.2009**

## Continuous Glucose Monitoring




The variability of the concentration of glucose is not accentuated.

| | | | | |
|---|---|---|---|---|
| Statistics | 3,7 | | 20,6-3,7 | |
| **Avg BG (mmol/L)** | **9,5** | | **7,9 ± 3,4** | |
| BG Readings | 3 | | 8 | 2,5/day |
| Reading Above Target | 2 | 67 % | 3 | 38 % |
| Reading Below Target | - | 0 % | 1 | 12 % |
| Sensor Avg mmol/L | 9,5+/-2,8 | | 8,7+/-2,9 | |
| Avg AUC more 7,8 mmol/L | 2,24 | 1d 0h | 1,74 | 2d 11h |
| Avg AUG less 3,9 mmol/L | - | 1d 0h | - | 2d 11h |

## Conclusion of patient's evaluation

This two patient's were evaluated to exemplify the importance of CGM in diabetic patients with type 1 and type 2.

First patient:

During the first 33 hours the values of glucose concentration where elevated. According to the results, treatment was changed by adding sitagliptine on 11/03/2010, we can observe that the glucose concentration is now at the target values.

Second patient:

With this diabetic type 1 the treatment was also changed in according to the results seen on CGM. The basal rates of insulin pump were changed for a better target of glucose.

In conclusion the CGM has benefits for both diabetic patients, to achieve the glucose concentration values necessary for the patient.

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MEDTRONIC CENTER http://www.medtronicdiabetes.com/products/

Figure 1 HARRISON'S, Principles of internal medicine, 17th Edition 2008, Chapter 338 Diabetes Mellitus- Alvin C. Powers

Figure 2 adam.about.com

Figure 3 DEXCOM CENTER http://www.dexcom.com/200-dexcom-products.aspx

Figure 4 MEDTRONIC CENTER http://www.medtronicdiabetes.com/products/

Graph 1 MEDTRONIC CENTER http://www.medtronicdiabetes.com/products/

Figure 5 Medtronic-diabetes-me.com

Figure 6 Biomed.brown.edu

Figure 7 Endotext.org

**Continuous Glucose Monitoring**

Figure 8 diabetescareonline.in

## Pictures, tables and graphs

## Continuous Glucose Monitoring