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Metabolic Control Targets for Patients with Type 1 Diabetes in Clinical Practice

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1. Introduction

Diabetes and its micro- and macro-vascular complications constitute one of the principal social-health problems world-wide. It has high impact on the quality of life and prognosis of the individuals affected, as well as high direct and indirect economic costs to the Public Health Service. Following the publication of benchmark studies in the 1990s which indicated that the maintenance of glycaemia levels as close as possible to normality is associated with a lower incidence, progression and severity of the complications, the optimisation of metabolic control has been converted to a core therapeutic objective (DCCT, 1993; Herman, 1999; UKPDS, 1998). The tools for the management of diabetes have advanced spectacularly in these past few years, not only for the control of glycaemia but also for its measurement. As such, currently, there is a wide variety of drugs available with different mechanisms of action which, alone or in combination, enable a reasonable metabolic control in the majority of cases. Although insulin has been used for >80 years, the biggest advances in the mode of use have been over the last two decades. This change has been due, in great part, to: 1) development of new sources of insulin (analogues of insulin) together with the development and fine-tuning of different forms of its administration (continuous subcutaneous insulin infusion; CSII) in search of profiles of activity closer to the normal physiologic state; 2) change in philosophy in the therapeutic planning of diabetes, such that the strategies of co-responsibility and flexibility of life-style have become fundamental aspects; 3) introduction of self-control using capillary glycaemia (SCCG) in daily practice (De Witt & Hirsch, 2003); 4) recent incorporation in clinical practice of the use of glucose sensors, continuous glucose monitoring systems (CGMS) that generate the maximum information on modifications of glucose levels in plasma along the course of the whole day.
This review centres on the importance, in clinical practice, of the metabolic control targets for patients with DM type 1. Difficulties in achieving glycaemia goals using multiple insulin injection with new insulin analogues, and modern technologies such as CGMS and CSII are extensively analysed.

2. Importance of glycaemia control in the treatment of diabetes

Traditionally, the conventional therapy has been orientated towards achieving acceptable levels of glycaemia and stable clinical status in the asymptomatic patient. Intensive

treatment of diabetes, according to the protocol of the Diabetes Control and Complications Trial (DCCT), consists in a therapeutic design orientated towards achieving almost normal levels of glycaemia. Included are: a rigorous educative plan with frequent actions for a life-style change, an insulin regimen with three or more daily injections (multiple doses of insulin), or CIIS and programme of SCCG four of more per day (DCCT, 1995).

Over the past few years there have been several studies evaluating the effect on the appearance and progression of the micro-vascular complications of diabetes using a strict control of glycaemia with intensive treatment (Herman, 1999). The most significant was the DCCT study published in 1993 (DCCT, 1993). Included were more than 1000 patients with DM type I and the results demonstrated that maintaining the levels of glucose within a range closest to normality, tended to reduce the appearance of retinopathy by 76%, nephropathy by 56% and neuropathy by 60%. The DCCT established the targets of glycaemia control and of glycosylated haemoglobin (HbA1c) in patients with DM type 1, together with the need to perform measurement of capillary glycaemia as part of the intensive treatment regimen.

In DM type 2, the Kumamoto study (Shichiri et al., 2000) with a design similar to the DCCT, demonstrated that intensive treatment (target of HbA1c <7%) reduced the risk of retinopathy by 69% and nephropathy by 70%. The United Kingdom Prospective Diabetes Study (UKPDS) published in 1998, demonstrated that intensive long-term treatment of the hyperglycaemia also reduced the appearance of micro-vascular complication in patients recently diagnosed with DM type 2 (UKPDS, 1998).

These studies demonstrated definitively that the better the control of glycaemia the tighter the association with the decrease in the rates of micro-vascular complications (retinopathy and nephropathy). Follow-up studies of the DCCT (DCCT-EDIC; 2000; Martin et al., 2006) and of the UKPDS (Holman et al., 2008) have highlighted that once the intensive treatment is established in the two groups with evidence of their benefits, those that had been performed earlier retain their benefits as the product of a "metabolic legacy".

Despite that many epidemiologic studies and meta-analyses (Selvin et al., 2004; Stettler et al., 2006) having clearly demonstrated a direct relationship between HbA1c and the incidence of cardiovascular disease (CVD), the potential of intensive control of glycaemia to reduce CVD has not been delineated, as yet. In the DCCT, no differences were observed between the groups with respect to the appearance of CVD events. However, at 8 years of conclusion of the study, the patients who had been assigned to the intensive treatment group had a 42% reduction in CVD and a 57% reduction in the risk of non-fatal myocardial infarction, stroke or death, compared to those who had been assigned to the standard treatment arm of the trial (Nathan et al., 2005). It has been demonstrated recently that, as with DM type 2, the benefit of intensive glycaemia control in patients with DM type 1 persists over decades (DCCT-EDIC, 2009).

In the UKPDS, a reduction was observed of 16% in the risk of CVD in the intensive treatment group, although this difference did not reach statistical significance. However, at 10 years of follow-up, a reduction in non-fatal acute myocardial infarction and in all-cause mortality of 13 and 27%, respectively (Holman et al., 2008) was demonstrated in the participants initially assigned to intensive control of glycaemia, compared to those assigned to conventional control. Nevertheless, the results of three large studies (ACCORD, Ismail-Beigi et al., 2010; ADVANCE, Patel et al., 2008; VADT, Duckworth at al., 2009) that had investigated the effect of glycaemia control in DM type 2, were unable to demonstrate that the intensive control of glycaemia achieved any reduction in the CVD, even though the patients were DM type 2 of long duration and with high risk of CVD.

Maintaining levels of glycaemia that are practically normal carries a series of notable risk. Among these is the increase in episodes of slight as well as of severe hypoglycaemia. The investigators in the EDIC study (Nathan et al., 2005) observed CVD benefits associated with intensive glycaemia control, but not in those with a level of HbA1c <6.5%. In the initial publications of the ACCORD study, the greater rates of mortality were produced in the 2 extreme categories of HbA1c, independently of the regimen of treatment. Also, the decreases in survival in the patients with lower HbA1c levels were related, at least in part, to the appearance of hypoglycaemia. As such, episodes of severe hypoglycaemia in patients with advanced disease need to be prevented, and not with the intention of achieving normal, or near normal, levels of HbA1c (<6.5%) in those in whom achieving normal levels safely do not appear probable.

2.1 Objectives of glycaemia control

The recommendations for glycaemia control targets in adults, in pregnant and in non-pregnant women are shown in Table 1. The recommendations are based on the blood levels of glucose which correlate with levels of HbA1c at 7%. The targets need to be individualised for each patient, and it is necessary to be assured of achieving them. In young and healthy patients that know the symptoms of hypoglycaemia and recover from them relatively easily, the targets need to approximate to the levels of glycaemia observed in persons without diabetes. However, the objectives of control are more strict during gestation, and more permissive for persons who have difficulties noting the symptoms of hypoglycaemia as well as those who present with severe hypoglycaemia or for those whose episodes of hypoglycaemia can be particularly dangerous (for example, patients with heart disease, cerebrovascular pathology or autonomic neuropathy). As such, in adults with limited life expectancy or advanced vascular disease, it would be more appropriate to have less strict targets. Post-prandial hyperglycaemia is defined as values of glycaemia >140 mg/dL at two hours after a meal. It is a frequent phenomenon that is unnoticed in the determination of HbA1c and basal glycaemia since it is already present when the levels of HbA1c are optimum. Several studies have shown that the levels of post-prandial glycaemia are strongly related to the CVD risk (Cavalot et al., 2006; Ceriello, 2005; European Diabetes Epidemiology Group, 1999;). Curiously, the contribution of post-prandial glycaemia appears to be more evident in patients with well-controlled diabetes (contribution of about 70% to the HbA1c when it is <7% and about 40% when it is >7.3%). However, the targets of post-prandial glycaemia using SCCG are controversial. In some epidemiology studies, values of elevated glucose following oral glucose load test have been associated with an increased risk of CVD, independently of the fasting plasma glucose level. Also, the phenomenon appears intimately linked with CVD such as endothelial dysfunction which is aggravated by post-prandial hyperglycaemia (Ceriello et al., 2002). The majority of authors recommend values of HbA1c <7% as the appropriate metabolic control objective (American Diabetes Association, 2011)

Achieving a good metabolic control in DM type 1 is not an easy issue. Results reported in international studies on the degree of metabolic control in 13,612 patients from Sweden (Katarina et al., 2007) and 27,035 from Austria and Germany (Gerstl et al., 2008) showed that only 21.2% and 27%, respectively, of type 1 DM patients have HbA1c <7%. We studied a cohort of patients with type 1 DM (n = 489) followed-up from 2005 to 2007. During the study period, the mean HbA1c decreased from 7.78% to 7.36% and the frequency of patients with HbA1c <7% increased from 24.6% to 27.1% and those with a mean HbA1c of >8% decreased from 42.6% to 38.7% (Baena et al., 2008).

HbA1c	< 7%
Pre-prandial plasma glucose	70-130 mg/dL
Post-prandial plasma glucose	<180 mg/dL
The objectives need to be individualised based on: • Duration of the diabetes • Life expectancy • Associated co-morbidities • Known CVD or advanced micro-vascular complications • Severe hypoglycaemia, or inadvertent To improve objectives of post-prandial glucose if HbA1c was beyond the target despite pre-prandial glucose levels	
In pregnancy: HbA1c Pre-prandial plasma glucose Post-prandial plasma glucose	 6% 60-99 mg/dL 100-129 mg/dL

Table 1. Recommended objectives for glycaemia control, in patients with diabetes

3. Glucose monitoring in patients with diabetes

SCCG is an essential component of intensive treatment, and the core of the DCCT publication is the enormous increase in its diffusion and utilisation. As a result of this, the new technologies applied to these systems have evolved rapidly, giving rise to successive new measures on the market.

HbA1c is the reference pattern to assess long-term glycaemia control and, together with the measured glucose, determines the guidelines for adjustments in treatment of diabetes by the attending physician.

As we have stated earlier, in the past few years there has been in increase in the evidence showing the influence of post-prandial hyperglycaemia and glycaemia control, on the development of diabetic complications (Ceriello, 2003).

SCCG consists of determining the capillary blood glucose of the patient, using the glucometer. It carries information complementary to HbA1c levels, such as fasting and post-prandial glucose, detection of hypoglycaemia, information on the daily glucose variability, etc. This enables optimisation of treatment, above all in patients receiving intensive therapy. However, the information provided by the glucometer refers to a specific moment in time. For greater and better information on glycaemic changes there needs to be continuous glucose monitoring systems (CGMS) that perform several measurements per hour and, as such, produce averaged information over the course of the day.

3.1 Indications for self-monitoring of glycaemia in patients with DM type 1

Type 1 diabetes is characterised by frequent fluctuation in glycaemia. SCCG is the method–of-choice and the timing is decided according the needs of the individual patient as well as the targets of the therapeutic regimen. There are no studies that demonstrate the efficacy of SCCG alone in improving the glycaemia control in patients with DM type 1, but they are an integral part of the treatment. The results of the DCCT study demonstrated that intensive treatment is the most appropriate option for the majority of patients with DM type 1. The

two modalities of intensive treatment (multiple doses of insulin and continuous subcutaneous infusion of insulin) involved targets of glycaemia control close to normality, with a higher risk of hypoglycaemia (DCCT, 1993). To prevent episodes of asymptomatic hypoglycaemias and hyperglycaemias and, as such, to perform an appropriate adjustment of the insulin dose, it is necessary to frequently supervise the glycaemic levels. In the DCCT study there was a need for at least 4 SCCG measurements per day (pre-prandial and at bedtime) and post-prandial measurements were performed when the levels of HbA1c were not appropriate despite the values of the pre-prandial SCCG values being within the pre-established control targets. Further, a SCCG measurement was indicated at 3:00 a.m. once a week.

It is not clear what would be the optimum frequency of the capillary glucose measurements in patients with DM type 1, although there are various studies that have demonstrated that the increase in the self-control of glycaemia improves the metabolic control in these patients Currently, the majority of patients with DM type 1 and with gestational diabetes treated with insulin need to have at least 3 SCCG per day (ADA, 2011) (grade A evidence), which should be individualised according to the characteristics of the patient and the therapeutic targets. In general, it is recommended that measurements regularly before meals and, on occasions, one or two hours after, and at night-time, provide information that is very useful for therapeutic optimisation (Bergenstal & Gavin, 2005).

The latest clinical practice guide of the American Diabetes Association (ADA) establishes the following recommendations based on the scientific evidence (ADA, 2011):

- Achieving a strict glycaemia control requires SCCG as an integral part of the therapeutic strategy (grade A evidence).
- The patients treated with multiple doses of insulin need to perform SCCG 3 or more times a day (grade A evidence).
- In patients treated with les than 3 doses of insulin, oral agents or single diabetic treatment, the SCCG is useful in achieving glycaemia control targets within the context of a specific educative program (grade E evidence).
- To achieve the targets of post-prandial glycaemia control there needs to post-prandial SCCG performed (grade E evidence).
- There is a need to instruct the patient on the usefulness of the SCCG, and to evaluate the technique and its use regularly so that the data obtained can be used in treatment adjustment (grade E evidence).

3.2 Modalities of self-monitoring of glycaemia

3.2.1 Self-monitoring the level of blood sugar using the glucometer

SCCG requires a capillary blood sample obtained, usually, from finger-prick using a micro-lancet and using a glucose meter. The majority of glucose meters currently available generate plasma values by the device reader, or directly in plasma, or by multiplying the whole blood value by 1.12 so that the value is comparable with that from the laboratory (Valeri et al., 2004).

The measurement of glucose using the modern enzymatic methods (hexokinase or glucose oxidase) generates a rapid, reliable and precise measurement. The strips impregnated with these enzymes collect the blood sample and are read by the device in a short period of time (Goldstein et al., 2004).

The majority of machines have a memory to save the previous results, and some even have the option of downloading to a computer and with printer graphics to enable the analysis of the data and to optimise the metabolic self-monitoring. Some devices enable patients to

record data such as the medication dose or the presence of symptoms. The most recent are smaller sized and require less quantity of blood for the analysis. For patients with impaired sight, there are devices that can adapt to voice synthesizer to deliver an audible version of the result. Most results can be obtained within about 5 seconds, depending on the characteristics of the apparatus (Bode et al., 2001).

In some countries such as the USA, there are currently available certain glucometers that use other different sites than that of the finger to obtain the blood sample, in an attempt to reduce the discomfort of the finger-prick. In a study performed on one of these devices that obtained blood from the arm it is noted that reliable results were obtained that were less painful than the finger prick (Fineberg et al., 2001).

3.2.2 Continuous monitoring of glucose - glucose sensors

Over the last decade the SCCG system has been the only measurement available for the monitoring of glycaemia levels. Despite its unquestioned usefulness, it is an invasive technique, tedious for the patient, generates limited information at any specific time, and without additional information to establish trends.

The concentration of glucose in the interstitial tissues is reflected in its concentration in capillary and venous blood, since the glucose diffuses into interstitial tissue to equilibrate both compartments. Based on this, the CGMS measures the glucose concentration in the interstitial liquid of the subcutaneous cellular tissue in a minimally invasive manner, using a sensor subcutaneously located. The CGMS can detect glycaemia oscillations continuously, such that maximum information can be generated on the direction, magnitude, duration, frequency and possible causes of the fluctuations of glycaemia over the long-term course of the day. Hence, it is very useful in optimising the treatment of patients with diabetes (Maran et al., 2005) (Garg, 2009). It precludes the limitations of information of the CGMS system of intensive treatment in the cases of detection in periods of inadvertent hypo- and hyperglycaemia (Klonoff, 2005). However, the sensors currently available do not have the precision of capillary glucometers and, hence, the use is approved as a complement, and not as a substitution, for SCCG.

The invasive intravascular sensors measure plasma glucose directly and has been used to monitor hospitalised patients. However, there have not been any studies published on their functioning and usefulness in extended groups of patients (Klonoff, 2005).

3.2.2.1 Types of glucose sensors

Continuous monitoring of glucose was introduced in the 1970s, with a complex system termed biostator or artificial pancreas. Subsequently, new generation sensors appeared, with mixed results.

Currently, there are 4 types of CGMS approved by the FDA available on the international market: CGMS® (Continuous Glucose Monitoring System) such as the Guardian®, the Guardian Real Time®, the Paradigm Real Time® (Medtronic MiniMed, Northridge, CA, USA); the GlucoDay® system (Menarini Diagnostics, Florence, Italy); the Seven® system (DexCom Inc., San Diego, CA, USA); and the Freestyle Navigator® monitor (Abbott Laboratories, Alameda, CA, USA) (Gross et al., 2000). Table 2 compares the main features of the currently available systems.

CGMS, approved by the FDA in 1999 was the first generation of sensors commercialised and, as such, the most widely used and, for which, there is the most clinical experience available. It is composed of a subcutaneous sensor and an external monitor. It needs to be

	Guardian, Guardian RT, Paradigm RT	**Glucoday**	**Freestyle Navigator**	**Seven System**
Range of glucose values (mg/dL)	40-400	40-400	20-500	40-400
Life-span of sensor (days)	3 in USA/ 6 in Europe	2	5	7
Warm-up period (hours)	2	2	10 (1 for latest system)	2
Calibration frequency	Every 12 h	One point	Post-insertion: -10, 12, 24, 72h -1, 2, 10, 24, 72h (latest system)	Every 72 hours
Sensor device	Amerometric sensor	Microdialysis glucose	Amperometric sensor	Amperometric sensor
Results timing	Retrospective	Retrospective and Real time	Real Time	Real Time
Sensor site	In situ	External	In situ	In situ
Frequency of blood glucose display (min)	5	3	1	5
Rate-of-change arrows	Yes	No	Yes	Yes
Integrate with pump	Yes (Paradigm RT)	No	No	No
Accuracy (error grid) (%)	61.7-76.3	64-88	76.3-81.7	70.4
Limitations	- Life span of 3 days (USA) - Update glycaemia data on the screen every 5 minutes - Calibrations are required every 2- 3 days	- Large system - Life span of 2 days - Skin irritation - No rate- of-change arrows	- Large sensor and transmitter - Warm- up period of 10 hours (first sensor)- - Calibration time programming required - Must use Freestyle strips for calibration - High cost	- Update glycaemia data on the screen every 5 minutes - Does not permit selecting specific points above

Table 2. Main features of the currently available CGMS devices (Torres et al, 2010)

calibrated a minimum of 4 times a day using measured capillary glucose levels, presenting an out-of-phase between the level of glycaemia and the sensor signal of about 4 minutes (Gross et al., 2000).

In the past few years, progressively improved new models have been developed. In 2004, the FDA approved the Guardian Monitor®, with improvements on the previous system that included an alarm not only to signal hyperglycaemia but also for hypoglycaemia. One year later the Guardian MiniMed Real Time® appeared on the market: It was the first continuous

glucose monitor that provided the measurements of glucose in real time, every 5 minutes, and with direct connection to a CSII. The Paradigm Real Time® was approved in 2006 as the first sensor integrated with a CSII (Paradigm REAL-time 522/722) enabling it to create a closed circuit. More recently, MiniMed Paradigm Veo® system has been commercialised. It includes CSII with a CGMS with a mechanism that enables the infusion of insulin to be delayed when the levels of glucose are below the specified range. All these systems require at least 2 calibrations per day.

Another type of sensor known as the GlucoDay® system became available on the market in 2002. Its system is based on the technique of micro-dialysis applied to the interstitial fluid that, as has been commented-upon above, provides a reading of the glucose concentration in the subcutaneous cellular tissue that is very similar to the plasma value (Poscia et al.,2003; Varalli et al., 2003). The data collected can be visualised permanently in real time and to be used subsequently for different analyses regarding the behaviour of the glucose concentrations, such as its graphic representation. This system shows high precision and reliability, including at low glucose concentrations (Maran et al., 2002).

The Seven System® was approved by the FDA in 2007. It enables real time readings with measurements performed every 5 minutes and with a latency of 12 hours. It is the only one proven for use over a period of 7 days. The results can be stored for subsequent analyses. The system includes alarms that can be programmed not only for hyperglycaemia but also for hypoglycaemia. It needs to be calibrated every 12 hours with capillary glucose values. A new version is the Seven Plus System® which has improved not only the functionality but also has many additional functions included.

The latest system approved by the FDA in 2008 is the Freestyle Navigator® which has introduced important improvements to the CGM system (McGarraugh, 2009). It enables readings in real time following a latency period of 10 hours (1 hour in the more advanced versions). The concentration of glucose is measured every minute and enables analyses to be made every 10 minutes. The calibration requires capillary glucose measurement (only 4-5 in the first period). It has alarms not only for excessively elevated glucose levels but also for glucose decrease.

3.2.2.2 Clinical indications for continuous glucose monitoring (CGM)

The clinical applications for continuous glucose monitoring (CGM) have not, as yet, been well established. The system can be useful in determining patterns of glycaemia over a 24h period and to detect inadvertent hypoglycaemia. However, its role in improving control of diabetes is, as yet, unclear.

Currently, there are studies and preliminary data on the possible uses; the most extensive studies have focused on the detection of asymptomatic hypoglycaemia. Several studies show an elevated frequency of asymptomatic hypoglycaemia, especially during the nocturnal period and, above all, in patients with DM type 1, detected using CGMS, which have been underestimated with the conventional self-monitoring systems (DeVries et al., 2004). The CGMS also captures values of glucose which can change over a short period of time and, for which, it is not always practical to wait months to evaluate the reductions in the levels of HbA1c. CGM can show the time during which the patients remain in the glucose range that is normal, low or elevated. These values can be more useful than a single point when integrating the data such as the HbA1c levels. Prolonged exposure to intermediate levels of glucose may be preferred in some patients compared to the frequent peaks of hyperglycaemia and hypoglycaemia. This can obviate therapeutically targeting different HbA1c levels in response

to oscillating levels of glucose. The CGMS can detect these oscillations as well as measure the mean amplitude and the index of variability of the glycaemia. As such, predictive information on trends during the different times of the day can be obtained (Manuel-y-Keenoy et al., 2004).
The CGMS can also be used to evaluate the response of the glycaemia profile to specific treatment or therapeutic modalities such as, for example, the use of multiple doses of insulin vs. the CIIS (Weintrob et al., 2004). There are several studies that show the usefulness of CGMS in modifying treatment and achieving better metabolic control (Edelman et al., 2009; Hirsch et al., 2008; Leinung et al., 2010). Some authors consider this its most important use. In adolescents, apart from being a useful tool to improve glycaemia control, it also promotes communication and motivation of the patient (Schaepelynck-Bélicar et al., 2003) .
According to the data available, beneficial effects in metabolic control can be exercised in pregnant women with diabetes, but more studies are necessary to evaluate the reality of reducing perinatal complications (Festin, 2008).
As such, the possible indications of CGM comprise those situations that require detailed information on the fluctuations of glycaemia: diagnostic confirmation and management of hypoglycaemia (undetected hypoglycaemias or nocturnal hypoglycaemias); therapeutic adjustments in patients who do not achieve the control targets (discrepancy between HbA1c and capillary glycaemia, pregestational diabetes); diabetic educational tool (impact of intake on the glycaemia profile), physical exercise, intercurrent situations; diabetes and hospitalisation (unit for the treatment of the critically-ill patients and/or intensive coronary care), pancreatic tissue transplant and clinical investigation.
According to the recommendations of the American Diabetes Association (ADA, 2011), the CGM can be indicated in selected adult patients with DM type 1 on treatment with intensive insulin therapy to decrease the level of HbA1c (recommendation grade A). As well, CGM can be indicated in children, adolescents, and young adults in whom the adherence to treatment would be high (recommendation grade C). In patients with inadvertent hypoglycaemias, the CGM would be indicated as a complement to the SCCG.

3.2.2.3 Inconveniences

Currently, the CGMS is approved for the use in supplementing SCCG due to the inherent problems: limited level of precision for the isolated measurement of glucose, above all, at decreased levels (Klonoff, 2004); the need to calibrate the sensor several times a day using capillary measurements; short period of use (2-7 days) (Kovatchev et al., 2008).
Minimally invasive CGMS can present secondary effects related to the continuous measure of interstitial fluid. It can cause slight local distress at the site of catheter insertion which can occur on rare occasions. Further, because of its complicated technique, these systems require help from the health-care professional team (Tanenberg et al., 2004).
The major limitation of CGMS is, however, the current absence of scientific evidence of its usefulness. Methodologically appropriate studies are necessary to evaluate precisely the impact of these systems on improving the metabolic control in patients with diabetes, and their effect on hypoglycaemia decrease. The use can be extended in the future but CGMS needs to be improved with respect to the accuracy of glucose measurement, convenience for the patient, integration with other technologies such as CIIS.

4. Treatment of diabetes

As commented-upon earlier, intensive therapy of DM type 1 has been consolidated as the therapeutic strategy of choice since it has been demonstrated to delay the appearance and

progression of the chronic complications (DCCT, 1993; Nathan et al., 2005). This strategy consists of multiple daily subcutaneous injections, or the use of CIIS with adjustment of insulin according to the intake of carbohydrates and the level of glycaemia (ADA, 2011).

4.1 Treatment with multiple doses of insulin

The objective of intensive insulin therapy is to arrive at levels of glycaemia close to that of normal, using a regimen of insulin similar to physiological conditions. To achieve this, basal insulin treatment (1 or 2 doses per day with intermediate or low insulin) is accompanied by pre-prandial bolus of quick-acting insulin which is adjusted according to the pre-prandial glycaemia and the intake of carbohydrates. To correctly fulfil this type of therapy, collaboration on the part of the patient is necessary and can be achieved with motivation and information using an appropriate program of diabetes education. As has been highlighted earlier, this type of treatment needs to be accompanied with frequent monitoring with capillary measurements.

Intensive therapy is associated with more frequent hypoglycaemias. Since the DCCT publication, analogues of fast- and slow-acting insulins have been developed which, currently, form the basis of intensive treatment with multiple doses of insulin. These insulin analogues have been associated with a lower risk of hypoglycaemias, and a comparable decrease in HbA1c. Among the analogues of slow-acting insulin are glargine and detemir. Glargine insulin is almost identical to human insulin, except for certain modifications in the molecular structure that enables delaying the absorption in subcutaneous tissue resulting in prolonged duration without peaks of activity. It can be administered at any time of the day without impairing its effectiveness. Detemir insulin is another slow-acting analogue that has a fatty acid in its structure that enables it to bind to albumin in the subcutaneous tissue and its slow release prolongs its action in the blood stream. Both insulins, glargine and detemir, have similar efficacy, similar to the NPH, and are especially indicated in patients with recurring hypoglycaemias (Sing et al., 2009).

The fast-acting insulin analogues have modifications in the molecular structure which facilitate more rapid absorption into the bloodstream. Currently, there are three fast-acting analogues (lispro, aspart and glulisine) whose duration of action and effects are similar. They commence action within 5-15 minutes of subcutaneous administration, with a maximum peak at 30-90 minutes and a duration of 2-4 hours. Compared to standard insulin that begins its effects at 30-45 minutes from injection and has a duration of 4-6 hours, the new fast-acting analogues decrease the post-prandial glucose peak more quickly, can be injected immediately before meals, and decrease hypoglycaemias (Plank et al., 2005; Porcellati et al., 2008). The election of one or other insulin for multiple dose therapy would depend on the characteristics of the patient. No one type of insulin has been elected as treatment-of-choice because a clear benefit on metabolic control has not as yet been demonstrated in a generic manner.

4.2 Continuous Insulin Infusion Systems (CIIS)

Pumps for CIIS are electro-mechanical, portable and small, with the administration of insulin from a reservoir at a programmable rate via a flexible catheter through a cannular inserted subcutaneously. This system delivers insulin continuously at a rhythm that is termed “basal rate” and which can be increased or decreased according to the requirements of the patient. In basal rate, the control of hepatic production of pre-prandial and overnight glucose is an objective. Further, the pump can provide specific amounts of extra “bolus”

insulin which can administered before the intake allows the post-prandial glycaemia to become elevated. It can, as well, correct specific increases in glycaemia caused by other circumstances. Insulins used in the CIIS are exclusively fast-acting. Standard human, and preferably, the analogues lispro, aspart and glulisine, are used since these offer less variability in absorption, and show a pharmacokinetic profile closer to that of the physiologic state (Hirsch, 2005; Radermecker & Scheen, 2004).

Using CIIS in patients with DM type 1 began in the decade of the 1970s but, despite being effective in metabolic control, the initial devices had high risk of sepsis and thrombosis. At the start of the decade of the 1980s, evidence was communicated of an increase in mortality in patients having the CIIS; data that were not subsequently confirmed (Teutsch et al., 1984). The use of CIIS does not perform very well against the possibility of severe hypoglycaemia (Lock & Rigg, 1981) and frank ketoacidosis which was highlighted in some articles (Home & Marshall, 1984). The impact of the results of the DCCT became decisive for the widespread use of insulin pumps. The study highlighted a significant reduction in the levels of HbA1c in patients treated with CIIS compared with those who received multiple daily doses of insulin (DCCT, 1995). Since then, the use of CIIS has accelerated exponentially, and what was a research tool has become an established type of treatment for selected patients with DM type 1 (Cummins et al., 2010). On the other hand, the important technological development over the past few years has been to reduce the size of the pump considerably, to increase the benefits and to improve their safety. In the past decade, several studies have confirmed that therapy with CIIS has advantages in metabolic control while achieving greater decreases in the levels of HbA1c (Cummins et al., 2010; Pańkowska et al., 2009; Pickup & Sutton, 2008; Torres et al., 2009). Further, this improvement in glycaemia control is achieved with a lower quantity of insulin (Jeitler et al., 2008; Torres et al., 2009). Hence, CIIS has become established as the preferred modality of treatment, and an alternative to the multiple doses of insulin for those selected patients who do not achieve the target of glycaemia control with multiple injections of insulin (Bruttomesso et al., 2009).

The patients with DM type 1 treated with multiple injections of insulin frequently present with the "dawn phenomenon" which consists of a sharp increase in glucose in the small hours of the morning; increase due to the increase in the counter-regulatory hormones that occur during this period and which are not sufficiently counteracted by long-acting insulin administered at bedtime. The therapy with CIIS, enables basal infusion to be anticipated and programmed, which can be useful in controlling this phenomenon by increasing the basal rhythm to that suitable for the individual's needs (Bruttomesso et al., 2009; Cummins et al., 2010).

When CIIS therapy was used initially, there were cases of severe hypoglycaemia reported which brought the safety of the system into question (Lock & Rigg, 1981). In the subsequent years, the devices available were safer and used fast-acting analogues of insulin which resulted in reduction in the frequency of the severe hypoglycaemias. This form of treatment can achieve and maintain a grade of better metabolic control than can be achieved with multiple doses of insulin; the incidence of hypoglycaemia being significantly less, including at night (Pickup & Sutton, 2008; Torres et al., 2009). Brittle diabetes, with frequent and unannounced glycaemia oscillations, is improved with CIIS therapy.

Oscillations in glycaemia are reduced due to the use of fast-acting insulin analogues whose absorption variability is much lower than other insulins, and with which there is the possibility of programming different rhythms of infusion (Bruttomesso et al., 2008; Pickup et al., 2006).

The accumulated experience of CIIS use in children and adolescents is very promising. This modality of treatment reduces the incidence of acute complications, not only hypoglycaemias but also ketoacidosis, together with improved metabolic control, increased adherence to the treatment and promotion of family involvement. Treatment with CIIS in the paediatric population is safe and efficacious and represents a valid option in selected patients of whatever age provided that there is always appropriate family and health-care professional support (Boland et al., 1999; Danne et al., 2008; DiMeglio et al., 2004). The results of the use of CIIS in pregestational diabetes have not been quite conclusive. Although some trials had observed benefits in metabolic control (Lapolla et al., 2003), more studies are needed to confirm their advantages in achieving maternal and foetal objectives, and regards their safety during the gestation (Cummins et al., 2010; Mukhopadhyay et al., 2007; Volpe et al., 2010).

There are several studies that have found that the CIIS improves the quality-of-life of the patients because it allows better flexibility in relation to food intake and towards the conduct of various planned or unplanned activities. The considerable acceptance of this modality among users is due to the individual not being obliged to link food intake and social activities to insulin administration since several hours can elapse between the activities; as occurs when multiple dose insulin is used. The intake can be delayed or omitted and the content varied. Also, the intensity of the exercise can be modified as can the timing of the activity without compromising the glycaemia control target (EQuality1 Study Group, 2008; Radermecker & Scheen, 2004; Torres et al., 2009). The advantages of CIIS are summarised in Table 3.

Improvement in metabolic control
Correction of the dawn phenomenon
Decrease in hypoglycaemias
Improvement in brittle diabetes
Effective in adults, adolescents and children
Flexibility and improvement in quality-of-life

Table 3. Advantages of CIIS

Interruption of insulin delivery by mechanical failure in the system of infusion leads quickly to hypoglycaemia and ketoacidosis due to the absence of a subcutaneous deposit of insulin (Krzentowski et al., 1983). This and other similar circumstances are preventable by training the individual to identify a potential episode, to warn and to treat the elevated levels of glycaemia (Guilhem et al., 2006). At the site of insertion of the cannular there may appear atrophy, hypertrophy, pruritus, erythema and infection. In the majority of cases the clinical picture is slight and related to inadequate hygiene in the techniques used. Systematic rotation and changing the catheter a maximum of every 3 days would decrease, or pre-empt, these complications (Guilhem et al., 2006). The better strategy to prevent these complications is to instruct the patients using specific educative programs that highlight frequent monitoring of the glycaemia, objectives of glycaemia control, calculation of dietary carbohydrates and the adaptation of daily fluctuations in glycaemia induced by intake,

physical exercise and situations of stress or illness. Further, family help and social environment are important for outcomes (Jeandidier et al., 2008; Tamborlane et al., 2003).
The indications for CSII treatment are not universally established. Appropriate patient selection is fundamental in minimising the risks that these devices can involve. The best results are obtained in psychologically stable patients, with sufficient intellectual capacity, highly motivated and supervised by a multi-disciplinary team. CIIS therapy requires a specifically formed team of healthcare professionals with sufficient time dedication to their patients not only for the training but also for clinical follow-up. The circumstances for CIIS treatment apply to any age in achieving good metabolic outcomes (Bruttomesso et al., 2009; Cummins et al., 2010). The indications more widely accepted are collected in Table 4

HbA1c >7% despite good adherence to therapy with multi-injection systems
Severe hypoglycaemias, recurrent, nocturnal or inadvertent
Significant dawn phenomenon
Brittle diabetes. Wide glycaemia variation, independent of HbA1c
Planned pregnancy if no good control with multi-injection
Need for flexible life-style
Low insulin requirements (<20 UI/day)

Table 4. Indications for CIIS

4.3 CIIS monitoring

Frequent monitoring of glycaemia is a highly positive factor in obtaining good results with CIIS therapy (Shalitin et al., 2010). The information provided by CGMS enables better adaptation not only to the rhythm of basal infusion but also to the bolus. If it is accepted that if the patients treated with CIIS are more motivated, the outcomes resulting from the application of CGMS in this group could be greater (Leinung et al., 2010; Raccah et al., 2009). Currently, better practical advantages are to be gained in the *in situ* subcutaneous sensors with continuous reading in real time which integrate the CGMS in a continuous infusion of insulin using wireless communication; the technique termed continuous interactive monitoring. In this mode, the users of CIIS can adapt the insulin infusion and diet to the real metabolic status. This is possible because the information generated by CGMS allows for the detection of inadvertent hypoglycaemias, information on trends and speed-of-change of glucose, and provides help in planning the bolus to reduce the duration of the hyperglycaemic episode (Hirsch, 2009). A recent innovation has consisted of semi-automatic models that, apart from integrating the insulin infusion and the CGMS, automatically incorporates the delay in infusion over 2 hours in case of having produced an alarm for hypoglycaemia but had not obtained a response from the user (Hirsch et al., 2008a).
Real time information is an important advance in self-care by the patients but, as well, implies a challenge in applying this technology with safety and rigor. In the past 10 years the precision of these systems has improved and the durability of the sensor has increased up to 6-7 days. However, one important limitation is that none of the sensors currently available have the precision of the standard glucometers. This is because they do not measure the blood sugar directly but, rather, evaluate glucose in the subcutaneous interstitial fluid. The defects in precision are related to the low concentration of glucose in the interstitial fluid, the specific dynamics of the glucose in the capillary and interstitial fluids and the delays inherent in the measurement (Torres et al., 2010).

The patients with CIIS who are candidates for CGMS systems need to be very motivated and to have received verbal and written information in a program of therapeutic education. The effect is to avoid false expectations and to recognise the limitations of these systems. The educative program would be orientated towards training, management of the devices, and in the interpretation of the measurements of glucose in real time; all orientated towards achieving the euglycaemia state (Gilliam & Hirsch, 2009; Hirsch et al., 2008a; Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group, 2009a). In principle, the ideal candidate would be a patient with DM type 1, with excellent motivation and optimum therapeutic education, who has not been able to achieve HbA1c levels <7%.

Several studies have demonstrated that the use of CGMS in patients with CIIS has advantages in metabolic control, with significant decreases in the levels of HbA1c (Bergenstal et al., 2010; Deiss et al., 2006; Hirsch et al., 2008b; Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group, 2008) and less glycaemia variability (Garg et al., 2006; Kordonouri et al., 2010). Some studies have, as well, demonstrated improvement in the frequency of hypoglycaemia (Garg et al., 2006; Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group, 2009b; Leinung et al., 2010). The best results have been obtained in relation of adherence to the CGMS systems; continuous use being more efficient than intermittent use (Hirsch et al., 2008b; Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group, 2008, 2009a; Raccah et al., 2009) but, in practice, can be more difficult to fulfil (O'Connell et al., 2009).

A list of possible indication for the use of CGMS is summarised in Table 5 (American Diabetes Association, 2011; Fabiato et al., 2009).

Patients with DM type 1, excellent motivation and optimum therapeutic education, but who have not been able to achieve HbA1c <7%
Severe hypoglycaemias, inadvertent hypoglycaemias or fear of hypoglycaemias that impede achieving the targets of glycaemia control
Brittle diabetes
Planned pregnancy with difficulties achieving appropriate glycaemia control
Children and adolescents with significant glucose variability or frequent hypoglycaemias, severe or inadvertent despite adjustments of the therapies. It is indispensable that they and/or the family are motivated and have appropriate training.

Table 5. Indications for interactive CGMS

5. Future research

The challenge to achieve an optimum metabolic control in type 1 DM is being progressively better addressed. New insulins and technological devices have been designed to mimic beta cell function. However, to translate these findings into the clinical practice new research and clinical trials are needed. Technological advances have enabled the development of new CIIS devices with better performance in programming and for calculating optimal dose of insulin required. Systems security alerts are getting better, and the availability of sensors that promote CIIS devices has been a promising development. A closed-loop system should include an implantable continuous glucose sensor, an insulin pump and an algorithm control leading to insulin infusion adjusted to the glucose concentrations (Kumareswaran et al., 2009). In the

future, combined use of insulin pumps and glucose sensors could become an effective and safe strategy, with minimal constraints in optimising metabolic control in diabetic patients to achieve glycaemia very close to normal (Hirsch, 2009; Keenan et al., 2010; Kowalski, 2009).
Finally, we note that both CIIS therapy and the use of CGMS are expensive. The implementation of these technologies requires public health systems that have sufficient resources to initiate treatment and to ensure appropriate monitoring by the users. Further studies are needed on cost and effectiveness of these systems (Cummins et al., 2010; Fabiato et al., 2009; Huang et al., 2010).

6. Conclusions

Several prospective studies in Type 1 DM have demonstrated the tight association existing between glycaemia and the development of micro- and macro-angiopathy complications. The most significant study (the DCCT study) demonstrated that intensive treatment was accompanied by a reduction in the appearance and progression of the micro-vascular complications. Subsequent analyses of the DCCT study population demonstrated that the beneficial effects persisted even after the intervention and that they are extended to adverse cardiovascular events, as well. To achieve this objective, treatment of DM continues to be enriched by several novel therapeutic approaches. These have increased with the incorporation of insulin analogues and the introduction and optimisation of devices for the administration of insulin (continuous infusion system, CIIS) which achieves profiles of activity closer to the physiological equivalent. Several studies have demonstrated that the treatment with CIIS improves glycaemia variation with greater decrease in the HbA1c, less hypoglycaemias, and no increase in the frequency of ketoacidosis. Methods for evaluating response to treatment have been progressively improved. Recent clinical evidence has demonstrated that the glycaemia profile of the patients with DM, especially type 1 DM, is characterised by wide fluctuations related to physical activity, diet, and the specific treatment administered. The impact and the consequences of these variations are only partially known. Hence, the possibility of having continuous information available on glucose levels is an attractive option. Glucose sensors or CGMS provide maximum information on the changes in plasma glucose levels along the course of the day, and can be used in optimising treatment in patients with DM. However, the clinical applications of the CGMS have not, as yet, been well established.

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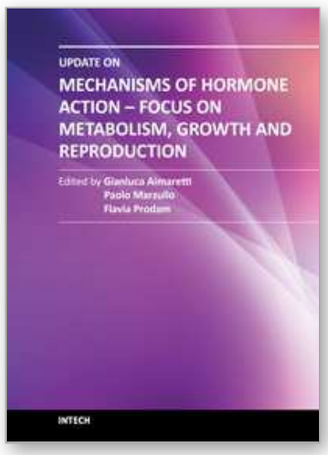

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The purpose of the present volume is to focus on more recent aspects of the complex regulation of hormonal action, in particular in 3 different hot fields: metabolism, growth and reproduction. Modern approaches to the physiology and pathology of endocrine glands are based on cellular and molecular investigation of genes, peptide, hormones, protein cascade at different levels. In all of the chapters in the book all, or at least some, of these aspects are described in order to increase the endocrine knowledge.

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