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Physics and new technologies in the treatment of diabetes mellitus – Could Nanotechnology help fight diabetes?

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Abstract

Diabetes technology has gained a relevant position in diabetes therapy in the last decades. In the past, some 20 years ago, diabetes technology dealt primarily with blood glucose meters, insulin pens and insulin pumps; however, in recent years the range of topics has broadened considerably. Today continuous glucose monitoring (CGM) and the combination thereof with insulin pumps for sensor augmented pump therapy and more recently towards Artificial Pancreas (AP) are hot topics. Most probably, we will see more visionary developments, such as the automated estimation of the carbohydrate content of a given meal by use of a smart phone. After a brief consideration of relevant advances in diabetes technology we provide an overview and highlight the prospects of this area of research for the future of diabetes therapy. An important question is whether such innovative ideas and products will become available for patients with diabetes, but this is closely linked to the issue of cost reimbursement.

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Abstract

Diabetes technology has gained a relevant position in diabetes therapy in the last decades. In the past, some 20 years ago, diabetes technology dealt primarily with blood glucose meters, insulin pens and insulin pumps; however, in recent years the range of topics has broadened considerably. Today continuous glucose monitoring (CGM) and the combination thereof with insulin pumps for sensor augmented pump therapy and more recently towards Artificial Pancreas (AP) are hot topics. Most probably, we will see more visionary developments, such as the automated estimation of the carbohydrate content of a given meal by use of a smart phone. After a brief consideration of relevant advances in diabetes technology we provide an overview and highlight the prospects of this area of research for the future of diabetes therapy. An important question is whether such innovative ideas and products will become available for patients with diabetes, but this is closely linked to the issue of cost reimbursement.

Key terms

Diabetes Technology is a wide range of methods and devices for diagnostic and especially as an aid for diabetes therapy under daily life conditions.

An artificial pancreas is the biggest goal for development of diabetes technology. The system consists of a glucose sensor for measurement of glucose concentration, a device for continuous insulin delivery and software algorithms for calculation of insulin dose on the basis of measured glucose concentration.

Continuous glucose monitoring is the use of subcutaneous glucose sensors worn by the user which convert glucose from the subject's interstitial fluid into an electronic signal, the strength of which is proportional to the amount of glucose present in the fluid.

Insulin pumps: A device that delivers only short-acting insulin over an infusion set: continuous small dose for compensation of glucose release from the liver (basal rate) and discontinuous boluses for compensation of the carbohydrates absorbed from nutrition or also for correction of elevated blood glucose levels. The therapy this insulin pumps is the continuous subcutaneous insulin infusion (CSII) or insulin pump therapy. Worldwide more than 500.000 patients with diabetes are treated with this form of insulin therapy.

Sensor augmented pump therapy (SaP): connection between insulin pump and CGM system. This is the first therapy which a glucose sensor can intervene directly in therapy. Therefore SaP is the first step to an automated insulin pump system.

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1. Diabetes mellitus – a growing disease that requires treatment with methods of modern technology

The number of people with diabetes worldwide has increased dramatically. Today, on the earth there are 382 million people living with diabetes [1]. This chronic disease occurs when the body becomes unable to produce insulin (Type 1 diabetes) or cannot use insulin effectively (Type 2 diabetes). Especially the Type 2 diabetes is a problem of actual "way of life" in Europe and USA: the permanent availability of food, lack of exercise and growing obesity. Further, people grow older because of insights of modern medicine.

But not only the incidence of Type 2 diabetes increased, also the incidence of Type 1 diabetes has been steadily growing worldwide since the middle of the 20th century [1].

Since the organism of patients with Type 1 diabetes produces no insulin, in any case an insulin therapy is necessary in order to maintain life quality. Thus, it is necessary to supply the body with insulin, but this requires technical assistance [2]. Given that the insulin is ideally adapted to the physiological insulin requirements, the glucose measurement is required, either selectively at the time of adjustment or continuously. Glucose measurement requires technical solutions. It is an actual goal to develop this technology so that it is quick and easy to handle in every day's life of the patient and his therapy. The range of possible technical supports culminates in the development of an artificial pancreas, which automatically adjusts insulin delivery to the patient's insulin requirements. This is one of the biggest challenges for the development of new methods and technologies.

Nanotechnology could help fight diabetes [3], as e.g. injectable nanogel could monitor blood-sugar levels, and discharge insulin when needed. This may someday eliminate the need for patients with Type 1 diabetes to constantly monitor their blood-sugar levels and inject themselves with insulin.

2. Diabetes Technology for diagnosis and therapy – an overview

Physical effects lead to a number of technological applications in various fields. Particularly useful are those in medicine, because the treatment of diseases, especially of chronic diseases also comprehends a high ethical standard. In what follows, this is shown on the example of diabetes mellitus, a chronic disease that holds people captive on a day's basis within the meaning of its self-management. Diabetes technology includes a wide range of devices and procedures. In principle, such products are classified in diagnostic techniques and therapeutic procedures. Therapeutic procedures are aids and give directly support for treatment of diabetes under daily-life conditions. The following list gives an overview on several, albeit not all methods and devices. As an example for the application of modern diabetes technology, the development of an artificial pancreas should be described. This includes two important methods, which are listed in table 2: insulin delivery via an insulin pump and the continuous measurement of glucose with glucose sensor.

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Diabetes diagnostic tools	Method
Routinely applied methods in everyday life to the assessment of metabolic and vital status and of the therapeutic success of diabetes patients	Point by point glucose measurement (self-monitoring of blood glucose with electrochemical test strips (SMBG))
	Continuous Glucose Monitoring (CGM)
	Measurement of HbA_{1c}, a important biochemical parameter of diabetes therapy for diabetes control (show the mean blood glucose value over 8-12 weeks)
Measurement of other relevant parameters for diabetes therapy	Ketones in blood
	blood pressure
	Lipids in blood
	Parameter of blood coagulation (Quick value/INR, von Willebrand factor, PAI-1, plasminogen etc.)
	Electrocardiography
	bio resonance testing
Diagnosis of diabetic long term complications	Measurement of AGE's (Advanced Glycation Endproducts)show the concentration of glycol proteins, responsible for development of long term diabetic complications in blood vessels
	- ophthalmoscopy/fundus copy/ fundus drawing - fluorescence angiography - methods for measurement of neurological parameter - parameter of diabetic nephropathy (albuminuria) - determination of vascular status (angiography, magnetic resonance topography (MRT), Doppler investigation, ultrasound, etc.)

Table 1: Overview about processes and systems for the diagnosis of the metabolic situation and diabetes-related complications

3. Development of an artificial pancreas

The development of an artificial pancreas, or closed loop system, remains one of the visions of insulin pump manufacturers and the dreams of diabetes patients. Contemplations about this inevitably arose from the technical understanding of a closed circulation of glucose measurement, insulin delivery and the metabolic situation arising from this.

The hardware for a closed loop system consists of a glucose sensor for continuous glucose monitoring (CGM) and an insulin pump. Unfortunately, the very attractive possibility of the use of an implantable insulin pump and an implantable glucose sensor is currently not realistic because of the unfavorable risk-benefit and cost-effectiveness ratio, although there have been successful experiments on this [4]. A realistic configuration of a closed loop system consists of the external insulin pump, connected with the glucose sensor over a wireless interface. This system is commercially available with the Paradigm®VEO™ system (Medtronic Inc.). It represents the simplest and safest version for a possible closed loop system. The missing but decisive link is the software containing the algorithms for controlled insulin delivery on the basis of the measured glucose levels. Different algorithms are in development in diverse scientific groups [5,8].

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Technology in support of diabetes therapy	Method
Insulin delivery	Conventional delivery tools • pens and syringes for insulin application, • Insulin Patches • transdermal insulin delivery by using of high pressure
	Insulin pumps • conventional insulin pumps (insulin delivery in the skin by using of external infusion set) • Insulin pump systems (optional in connection with glucose sensors (CGM)) for Sensor augmented pump therapy (SaP) and for artificial pancreas (Closed-Loop system) • „Patch pumps (waste device for one times using)
	Disposables aids for Insulin delivery • very fine cannulas (micro fine cannulas) • micro needles/micro needles patches • infusion sets with very fine cannulas, Teflon cannula's, inserter
	Systems for the manipulation of skin surface for the purpose of faster insulin intake and - action • Ultrasound • heating up of skin surface (small area)
Glucose measurement to therapy support	Point by point glucose measurement (self-monitoring of blood glucose (SMBG) with test strips (electrochemical method)
	Continuous Glucose Monitoring (CGM)
	Lancets for blood sampling (SMBG) • micro lancets (polished thin section) • Laser lancets
	Non-invasive or minimally invasive glucose measurement with physical methods (light absorption, light scattering, Raman spectroscopy, fluorescence spectroscopy etc.)
Technologies for the "biological healing of diabetes"	• extraction and separation of islet cells • encapsulation of islet cells (biological insulin producing cells) • implantation of islet cells (individually cells or cell complexes) • procedures of gene therapy
Information technology for therapy support	• software for better overview and the faster assessment of glucose measurement (including apps for medical care) • software to optimize the diabetes therapy based on the analysis of glucose values - or CGM profiles • software with recommendations for diabetes therapy adjustment • telemedicine
Technologies for the treatment of diabetic complications	• treatment and healing of diabetic foot ulcers: vacuum-assisted closure technology (V.A.C. technology) • vacuum pumps in case of erectile dysfunction • Polyneuropathy: electro stimulation, transcutaneous electrical nerve stimulation (TENS) • Devices for dialysis (dialyzer and different tools for hemodialysis and peritoneal dialysis etc.) • cardiac pacemakers , heart defibrillator • Stents
Technology for treatment adiposity (Bariatric surgery)	• gastric bypass • intragastric balloon • duodenal-jejunal bypass sleeve (DJBS) • gastric banding • Gastric pacemaker

Table 2: Overview of tools and methods to support therapy and for the treatment of diabetes-related complications

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4. Component of a Closed-loop system: Continuous Glucose Measurement

One important device for a closed-loop system is the glucose sensor for continuous glucose measurement. There are two different processes for glucose measurement, independent on the fact whether one has to measure continuously or discontinuously:

- Physical processes which use the interaction of glucose with administered energy (radiation, heat, electromagnetic fields, etc.) for measurement of glucose concentration,
- Chemical processes in which the glucose concentration is measured via reaction products arising in a chemical reaction.

For physical processes, no sample material needs to be obtained. In principle, the measurement of glucose concentration is possible without having to injure the skin (non-invasive measurement). Different possibilities are shown in Fig. 1. Unfortunately, many investigations with different physical methods, like light absorption, light scattering, Raman spectroscopy, fluorescence spectroscopy etc. were not successful in the past. One reason is the insufficient accuracy and reproducibility of non-invasive physical methods for glucose monitoring under daily life conditions. Good results were obtained only in technological laboratories.

The field of high technology can bring a breakthrough in the future. One possibility is nano-technology. For example is the glucose detection possible by using nanotube-based optical sensors [9]. Optical properties of commonly used organic and nanoparticle fluorescent probes are depending on quantum yield, human tissue penetration, and photobleaching stability. Single-walled carbon nanotubes are cylindrical molecules based on graphene where the nanometre scale radius serves to quantum confine electrons, imparting the material with new and unique properties [10]. A select number of carbon nanotubes fluoresce in the near infrared where human tissue penetration is maximum and biological auto-fluorescence is minimal.
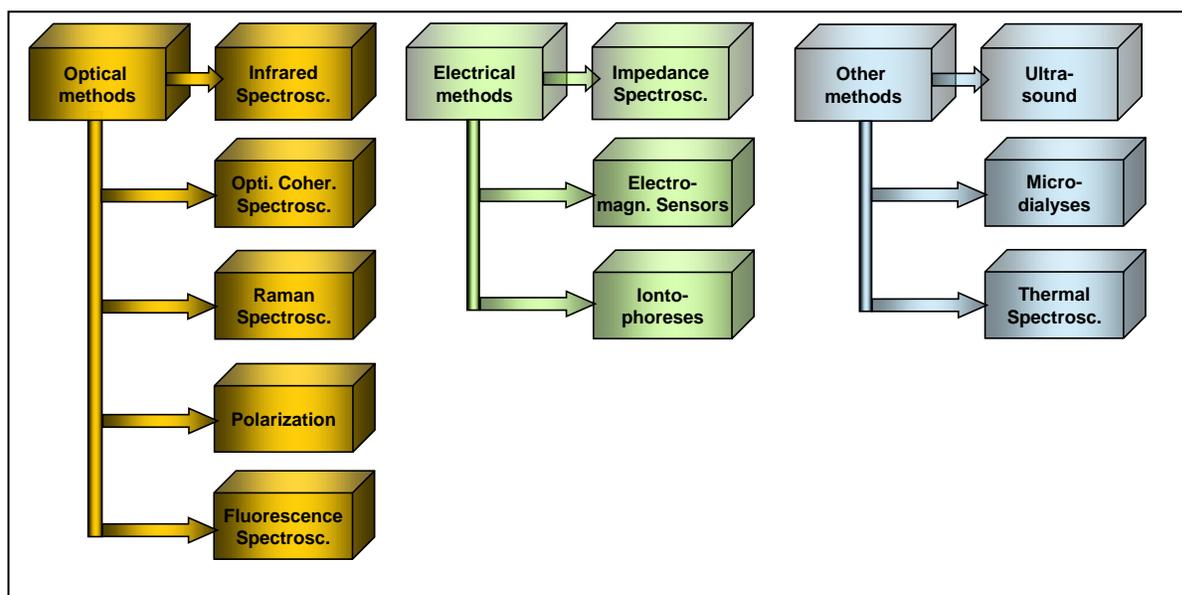

Fig. 1: Several physical methods for non-invasive glucose monitoring

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They are also infinitely photo-stable and are therefore one of very few fluorphores that are viable as long-term optical biosensors.

The chemical process for a measurement of glucose is the technology for self-monitoring of blood glucose (SMBG) with test strips. This method is used by diabetic patients under insulin therapy for their therapy adjustment under daily life conditions. For electrochemical measurements of glucose usually sample material is taken, i.e. blood or interstitial fluid. However, it is also possible to place an electrochemical sensor inside the tissue.
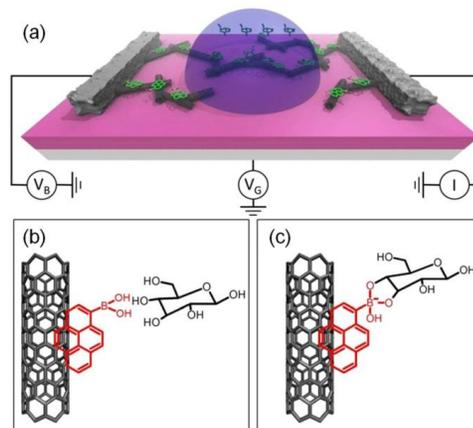

Fig. 2: Nano-tube based sensor for the measurement of glucose level in patients with diabetes. This technology is in development [9].

Of the various continuous glucose monitoring (CGM) technologies available, which are based on chemical principles, only minimally invasive approaches have been proven to be practicable in everyday situations [11]. These approaches are all based on electrochemical conversion of glucose using biocatalysts [12, 13]. Accordingly, the glucose sensor of these CGM systems must have direct access to a compartment with a fluid containing glucose. This means that the sensor, in the form of a membrane-clad, needle-shaped enzyme electrode, must be inserted through the skin into the subcutaneous fatty tissue to have access to interstitial fluid. A complete CGM system comprises the glucose sensor itself, which is inserted through the skin, a small electronic unit that is fixed onto the skin, and a separate display/storage device. The electronic unit contains the current source of the sensor, the amplifier of the sensor signal, and the data transmitter. The data are transferred to a pager-like display device via radio frequency; the range supported is up to 3 meters.

CGM systems can be used in two different ways. On the one hand for monitoring the current "disease status," that is, glucose metabolism. These quantifying results support the treating physician to assess a patient's therapy. On the other hand, CGM can also be used as a tool to accompany therapy. In the second case, in daily situations, this information facilitates the countless therapeutic decisions, which patients with diabetes need to make in relation to food intake, exercise, and insulin delivery (although this therapeutic decision intervention requires additional performance of SMBG). Consequently, this type of monitoring actually satisfies a long-held aspiration of patients with diabetes, and the physicians who treat them. All patients applying the system will benefit due to the flexible respond to current metabolic requirements, i.e. patients with multiple daily injection therapy (MDI) or continuous subcutaneous insulin therapy (CSII). This combination leads to new therapeutic options: in case of combination of MDI and CGM to the so-called sensor-augmented therapy (SaT) and in case of combination of CSII and CGM to the so-called sensor-augmented pump (SaP) therapy. In principle, this is the first step of using a

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simple closed-loop-system. The availability of glucose sensors for continuous glucose monitoring is the most importing step in that approach.

5. Components of Closed-loop systems: Insulin pumps

Insulin pumps are the necessary device for insulin delivery in an artificial pancreas. Currently different insulin pump models are widely distributed on the market. All devices have as a standard the functions, which are characteristic for insulin pump therapy (CSII), namely [2,14]:

- The basal rate for compensation of glucose release from the liver (meal-independent insulin) It is essential that only short-acting insulin is applied in an insulin pump as this allows better control of insulin supply.
- A bolus for compensation of those carbohydrates absorbed from diet (meal-dependent insulin), but also for the correction of elevated blood glucose levels.

There are characteristic differences between pump models, becoming evident already in advanced functions (bolus manager, different basal rates, and temporary basal rate change) for a better control of insulin pump therapy, and also in the option for coupling to continuous glucose monitoring for sensor-augmented pump therapy (SaP). The last feature leads directly to the closed-loop system.

5.1. Connection between CSII and CGM for SaP therapy

In principle, SaP can initially be performed with any insulin pump. For that, a CGM system with display of current glucose levels is additionally needed. In this case, besides the insulin pump, the patient also wears the monitor for the CGM. With the Paradigm®REAL-Time and the Animas®Vibe (Johnson & Johnson), too, the glucose sensor did not, under any circumstances, immediately intervene in glycaemic regulation.

This has changed with the Paradigm®VEO system (Figure 3), in which the glucose sensor interrupts insulin delivery by the insulin pump for a maximum of two hours in the case of hypoglycaemia, if the patient does not react to the system alarm (LGS – low glucose suspend). Thereafter, the pump switches the insulin supply back on for at least another four hours. If at this point the glucose levels are still below the LGS threshold, insulin delivery is again suspended

In different prospective studies of adults, children and young adults using LGS, the number and intensity of hypoglycaemia were reduced and the diabetes control were better (degreasing mean level of glucose concentration and HbA1c, respectively [15,16]. The same result has been found in clinical randomized controlled trials in patients with hypoglycaemia unawareness, a very dangerous problem. While patients only with CSII (control group) showed still a high number of severe hypoglycemia, apparently patients

Figure 3:
SaP with the Paradigm®VEO system. On the left, the insulin pump with the infusion set, on the right, the glucose sensor with the attached transmitter which sends the data to the insulin pump.

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with SaP plus LGS decreased to zero [17]. In principle, SaP plus LGS is the first realized step of a closed-loop system.

5.2. On the way to a closed-loop System

SaP showed the hardware configuration for a closed loop system. As is known from the use of CGM, the glucose sensor is situated in the interstitial tissue and undertakes its measurements in that tissue, where the levels are similar to simultaneously measured blood glucose levels in the case of stable glucose levels but in the case of increases and decreases in glucose the interstitial levels reflect these only after a time lag of between 5-25 minutes [18, 19]. As a result of the physiological differences between interstitial glucose and blood glucose, and given the pharmacodynamics of insulin, the development of insulin delivery algorithms is therefore a challenge.

The algorithms must take into account the fact that

- the glucose sensor placed in the subcutaneous fatty tissue measures in the interstitial fluid, as a result of which in the event of increases and decreases in glucose there is a time delay between the interstitial glucose and blood glucose, which depends on the metabolic situation (even in individuals with a healthy metabolism, this time lag varies depending on food intake and situation)
- insulin is infused via the subcutaneous tissue, as a result of which - unlike endocrine insulin, it is initially effective peripherally and only later effective hepatically - it has different pharmaco-kinetics and pharmaco-dynamics from endocrine insulin
- in the closed loop system the infusion of substances that raise the blood glucose (glucagon or glucose) is for complex reasons not planned (even though there have been the first successful experiments on this), and hence severe falls in blood glucose can occur without hindrance (the endogenous counter-regulation via glucagon and epinephrine only comes into play in the biological emergency of hypoglycaemia).

In the case of controlled insulin delivery on the basis of the measured subcutaneous glucose levels, not just real-time glucose regulation is involved but insulin delivery must take place in a predictive manner. That is, the algorithm has to predict how the glucose level will develop over the following 2 to 3 hours. As before, there are important deficiencies here for the implementation of a commercial closed loop system. These difficulties are also due to the too slow action of the insulin's that are available. Thus, contemporaneous regulation is possible only to a qualified degree and represents an important aspect in the development of the algorithm. For the algorithm, the glucose concentration measured by the glucose sensor is the control variable, using which of the insulin dose must be delivered and which glucose concentration can be predicted. Various influencing factors on glycaemic regulation have to be considered, such as time dependent absorption of carbohydrates and insulin, physical activity, stress, etc. The effect of insulin, still present in the body, also needs to be calculated (Figure 4, bottom right).

Various working groups have developed different algorithms, so the PID model [5], the HPS algorithm (Hypoglycaemic Predictive Algorithm [6] or the MPC (model predictive controller) algorithm [7]. The basic approach involves differential equations that calculate the insulin infusion rate depending on the time and changing glucose concentration. The initial conditions

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are the current glucose levels, the limiting conditions are the insulin sensitivity, insulin effect and possibly additional information about carbohydrate intake, physical activity and stress. The equations contain parameters that must be adjusted. They can only be determined from retrospective evaluation, but must be used in order to calculate the glucose profile that is to be expected. There are various ways to achieve this objective. It is not yet possible to say with certainty which algorithm is the best. It is reasonable to apply methods, such as fuzzy logic or neuronal networks [8], seeing to which of the parameters of the equations are repeatedly adjusted.
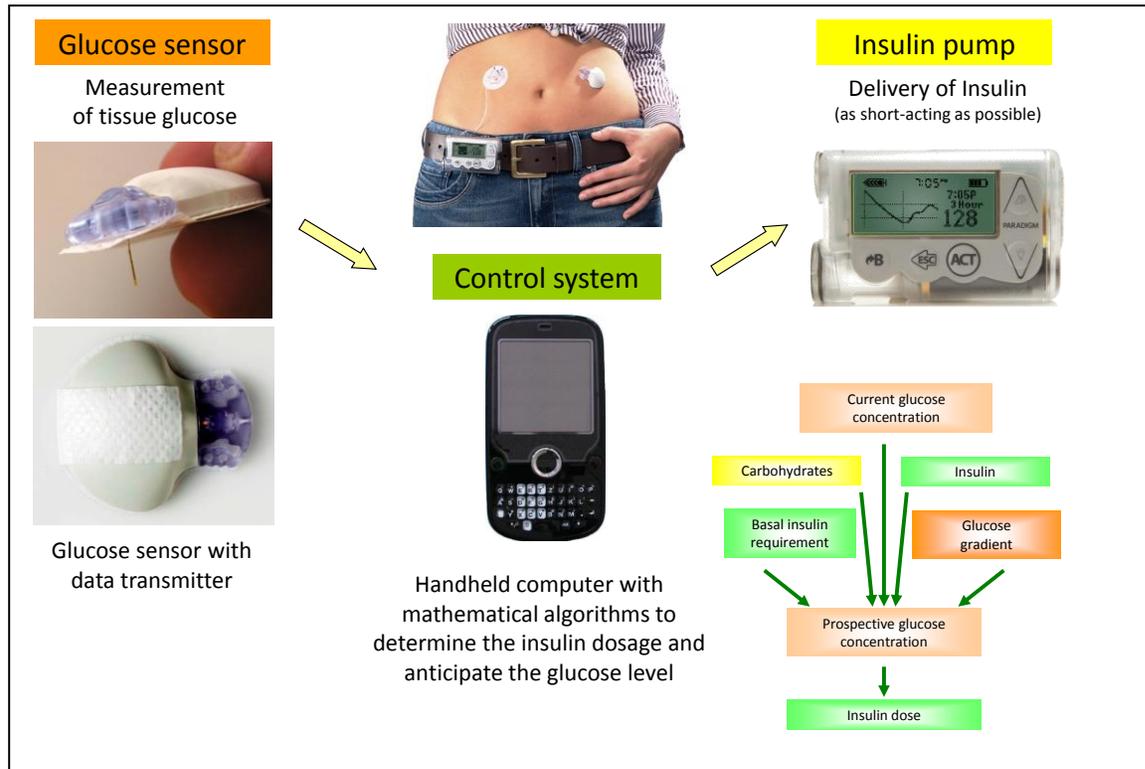

Figure 4: Components and design of a closed loop system with an external insulin pump, external glucose sensor and handheld computer that contains the algorithms for regulation of insulin delivery. The diagram on the bottom right shows the influencing factors that need to be taken into account in the calculation of the insulin dose.

The expected glucose levels can be obtained from self-learning logic, with the predictions only being reliable if the patient has the typical average day by day behavior. If there is a sudden change in circumstances (unexpected stress etc.), the patient would have to inform the system. An automatic response on the part of the system would, by contrast, mean the measurement and inclusion of parameters of vital function like heart rate or breathing being necessary.
It needs to be stated in general that calculation of the predictive course is all the more reliable the shorter the duration of action of insulin is. Regular insulin and short-acting insulin analogues limit this. In the near future, appropriate products are expected [20].

A complete closed loop system that the patient can use without any knowledge about his metabolism or without having to worry about diabetes control at all is not immediately imminent.

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What is more realistic is a stepwise progression towards this target product from a SaP system with LGS up to a semi-closed loop (utilization of information entered by the patient on meals and physical activity) and a complete closed loop. In any moment, extreme requirements will be placed on such a system in relation to its reliability.

Summary

- Diabetes technology has gained a relevant position in diabetes therapy in the last decades.

- Some 20 years ago, diabetes technology dealt primarily with blood glucose meters, insulin pens and insulin pumps; in recent years however the range of topics has broadened considerably.

- Continuous glucose monitoring (CGM) and their combination with insulin pumps for sensor augmented pump therapy (SaP), and more recently towards Artificial Pancreas (AP) (so called closed-loop system), are hot topics. Most probably, more visionary developments are in sight, such as automated estimation of the carbohydrate content of a given meal with a smart phone.

- Nanotechnology offers sensing technologies that provide more accurate and timely medical information for diagnosing disease. Research and impact of nanotechnology on biomedical sciences to cure diabetes are advancing rapidly [3,9,21-23].

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