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Preventive Systems for the Late Complications of Diabetes

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Aim of this work is to review and characterize methods and systems that are used to prevent onset and to slow down the progression of the late complications of diabetes. Two groups of methods and systems that might be used to prevent or to slow down the progression of the late complications of diabetes are characterized in this paper. Each of these two groups serves a different purpose. The first group is composed of the systems that facilitate a maintenance of strict metabolic control in diabetic patients, i.e. the systems which are used for monitoring and treatment of diabetes. The second group contains systems that are aimed at screening/monitoring or treatment of the risk factors or the early signs of the late complications. Obesity increases risk of diabetes and its complications. Thus, body mass monitoring and control systems are examples of the tools that belong to this group. Other examples include the diabetic retinopathy telescreening systems and the systems for monitoring of the diabetic foot syndrome.

Keywords: diabetes mellitus, diabetes late complications, telemedicine, glucose monitoring, diabetic retinopathy, diabetic foot syndrome, telecare, telemonitoring

1. Introduction

According to the WHO the main chronic diseases including diabetes are related to some non-modifiable risk factors such as age and heredity but also to some common modifiable risk factors such as unhealthy diet or physical inactivity. Common interaction of these factors together with some underlying socioeconomic, cultural, political and environmental determinants, e.g. population aging leads to intermediate risk factors such as overweight / obesity, glucose intolerance, insulin resistance, which in turn leads to diabetes [1].

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Diabetes mellitus is listed among the most serious and dangerous chronic diseases. The International Diabetes Federation and the WHO describe the dramatic increase of the number of cases of diabetes that is occurring throughout the world today as "the most challenging health problem of the 21st century" [2]. Diabetes is characterized by high blood glucose level (hyperglycemia) leading to a number of late complications related to the microangiopathy, the macroangiopathy and the neuropathy that impair vital functions of the body. The most serious complications include: the diabetic retinopathy (DR), the diabetic foot syndrome (DFS), the diabetic nephropathy as well as cerebrovascular, cardiovascular and peripheral vascular diseases, which means that diabetes is not only one of the main chronic diseases but it is also a risk factor for some other chronic diseases. Because of this in the course of diabetes the risk of kidney failure, heart attack or stroke is 2–4 times higher than in the healthy population. Moreover, the prevalence of blindness is 10 times higher and the lower limb amputations have to be conducted 20 times more often among diabetic patients. In fact, DR is the primary cause of blindness in the developed countries and the diabetic foot syndrome is the primary cause of no traumatic lower limb amputations [2].

The most obvious way for preventing the late complication of diabetes is to prevent diabetes itself. This has not been possible for type 1 diabetes yet. However, in case of type 2 diabetes all the life-style related factors, such as diet, physical activity, alcohol consumption, etc. might be controlled and modified in a way lowering the risk of onset of the disease. An appropriate control of the life-style related factors, especially diet and physical activity, is also necessary during treatment of diabetes. In this respect, similar or virtually the same methods and systems can be used to facilitate such a control preventing from both diabetes in case of a healthy person and the late complications of diabetes in case of a diabetic patient.

There can be distinguished two groups of methods and systems that might be used to prevent or at least to slow-down the progression of the late complications of diabetes when diabetes has been already diagnosed. Each of these two groups serves a different purpose.

The first group is composed of the systems that facilitate a maintenance of strict metabolic control, i.e. long-term stabilization of the glycemia course in the normal range in diabetic patients, that is the systems which are used for monitoring and treatment of diabetes. The glucose concentration meters (for sparse or continuous; invasive or non-invasive measurements), the electronic logbooks, the home and mobile telecare systems, the data analysis and decision support systems and the insulin dosage devices such as injectors and pumps are the major components of such a system. Currently, these elements are usually interconnected in the open-loop systems but close-loop systems have been under development for the last 30 years, too.

The second group contains systems that are aimed at screening/monitoring or treatment of the risk factors or the early signs of the late complications development. Obesity increases the risk of the micro- and macroangiopathy or the foot ulceration in the course of the diabetic foot syndrome. Thus, body mass monitoring and control systems are one of a few examples of the tools that belong to this group. Other example, concerning early diagnosis of DR (that has not manifested to the patient in form of a deterioration of his/her visual acuity yet), includes tele-screening systems that make use of digital fundus cameras. In case of the diabetic foot syndrome, increased risk of the ulceration is accompanied, among others, by altered foot temperature, plantar pressure and foot volume, skin conductance and oxygenation. Although, sensors that can be used to measure these quantities are available, a complete, integrated, smart, wearable system is still missing.

The aim of this work is to review and characterize methods and systems that are used to prevent onset and to slow down the progression of the late complications of diabetes that belong to the above-mentioned two groups of the preventive systems. A special attention will be paid to the solutions that have been designed and developed in the Nałęcz Institute of Biocybernetics and Biomedical Engineering PAS.

2. Methods and Systems Facilitating Strict Metabolic Control

Several long-term clinical trials have been conducted so far indicating clearly that diabetes intensive treatment aimed at maintenance of strict metabolic control (i.e. lowering blood glucose) effectively delayed the onset and slowed down the progression of the late complications of diabetes such as retinopathy, nephropathy and neuropathy. In the biggest study concerning type 1 diabetes and involving 1441 patients, called Diabetes Control and Complication Trial (DCCT), risk reductions for various outcomes ranged from 35 to 75% [3]. For newly diagnosed type 2 diabetes it was demonstrated in The United Kingdom Prospective Diabetes Study (UKPDS) based on 5102 patients that the overall microvascular reduction rate decreased by 25%. Moreover, an epidemiological analysis showed a continuous association between the risk of cardiovascular complications and glycemia [4]. The study indicated also that lowering blood pressure significantly reduced strokes, diabetes-related deaths, heart failure, microvascular complications, and visual loss.

Based on the above-mentioned results it is clear that regardless of the treatment method applied, blood glucose monitoring and regular control of other physiological parameters such as the arterial blood pressure or body weight is required to prevent or to slow down the progression of the late complications of diabetes.

2.1. Glucose Monitoring

Currently, there is a lot of miniature, accurate, precise, affordable and easy to use glucometers available on the market that are used by diabetic patients for self-monitoring of capillary blood glucose (SMBG). The principle of operation of these devices is based on enzymatic reaction of glucose with water and oxygen leading to creation of gluconic acid and hydrogen peroxide. Glucose concentration is measured indirectly using disposable test strips either in a form of a Clark type electrode or in a form of a dry chemical test. In the first case a glucometer works as a microamperometer and in the later case – as a reflectometer. Some glucometers use internal memory to store the measured blood glucose values. Others allow also to input and store some other data related to size of the meals, intensity of physical activity, etc. and may serve as electronic logbooks. The stored data can be transmitted to PCs, PDAs or mobile phones using built-in communication ports utilizing RS-232C (e.g. Optium Xido from Abbott), USB (e.g. Contour USB from Bayer), IrDA (e.g. Accu-Chek from Roche) or BlueTooth (e.g. GlucoTel from BodyTel) protocol.

Invasiveness and painfulness of the blood sampling is the main disadvantage associated with the SMBG application. Few different approaches have been used during last decade or so to reduce these disadvantages either aiming at decrease of the blood sample volume that allows for sampling from body regions less pain-sensitive than fingertips or aiming at development of minimally invasive/noninvasive methods of intermittent glucose testing.

In the first group of solutions, an introduction of coulometric sensor that measures electrical charge instead of the current was the most important achievement. This sensor was developed by Therasense company and implemented in a FreeStyle glucometer in year 2000. This device has required blood sample of one third of micro-liter, the smallest drop of blood used by any glucometer on the market till now. For the last decade there have been also introduced some other amperometric and reflectometric glucometers which have been able to use submicro-liter samples (e.g. Accu-Chek Go from Roche and Contour TS from Bayer). Thanks to decrease of the sample volume, blood can be withdrawn from the palm of a hand, the forearm, the arm, the calf or the thigh, what is less painful for the patients. It must be stressed, however, that the alternative sampling sites should be avoided in case of rapid glycemia changes because of a delayed reaction related to lower density of capillaries in these body regions [5].

In the second group, few approaches aimed at painlessly collecting of a sample of the interstitial fluid (ISF) onto the surface of the skin in the minimally invasive blood glucose meters have been tried. For example, in a SpectRx system few tiny micropores are created with a laser in the outer, dead layer of skin. Then a small chamber used for collecting of the interstitial fluid with a flow rate of about 1 μl/min is placed over these micropores. Finally, the collected ISF is used to measure glucose concentration with an amperometric sensor.

Most non-invasive systems for intermittent glucose concentration testing that have been reported so far, used the near or medium range infrared spectroscopy to sense glycemia changes in capillaries under the skin of: the finger (e.g. Dream Beam system from Futrex), the forearm (e.g. Diasensor system from Biocontrol Technology Inc.), the lip, the oral mucosa or, recently, the eardrum (Infratec system from Infratec

Inc.). Till now, none of these systems has reached the accuracy and precision of the standard glucometers sufficient to become a real noninvasive alternative for blood glucose testing. Recently, OrSense company from Israel has presented NBM-200G glucose monitor that uses occlusion spectroscopy to overcome key obstacles that hinder the performance of the mentioned above straight-forward approaches. However, at the current stage of development this system is utilized for investigation and market awareness purpose only, as OrSense claims on the company's web page [6].

Other non-invasive systems that use different frequency ranges, like terahertz radiation produced with a nano-engineered gallium arsenide lasers (Spire Corp.) and/or different principles of operation, like Raman spectroscopy (Light Touch Medical Inc.) have been in the early stages of development.

The continuous glucose monitoring systems (CGMS) have been developed in parallel with the intermittent glucose measurement systems for the last 30 years. The first commercially available CGMS was introduced by MiniMed Inc. in 1999. MiniMed's CGMS measured glucose concentration every 10 seconds with a needle-type electroenzymatic sensor implanted into the abdominal subcutaneous adipose tissue for up to 3 days. The average concentration was stored in an internal memory of the system every 5 minutes. The sensor had to be calibrated at least 4 times a day using the plasma glucose concentration data as a reference [7]. Today, three systems using similar principle of operation are manufactured by Medtronic (Fig. 1), Abbott and DexCom companies. Over the last decade, the sensor's lifetime increased up to 7 days (STS Seven Plus from DexCom) and the calibration frequency dropped to one calibration per 30 hours (FreeStyle Navigator from Abbott). A limited precision is the main disadvantage of all of these systems. The mean absolute relative difference (MARD) is in the range of 10.3%–21.2% [8].

There are also two systems available that use microdialysis probes, i.e. GlucoDay from Menarini (Italy) and Accu-Chek SCGMS from Roche (Switzerland). These systems measure concentration of glucose diffusing from ISF to the dialysate through the semi-permeable wall of the probe inserted under the skin. They can achieve

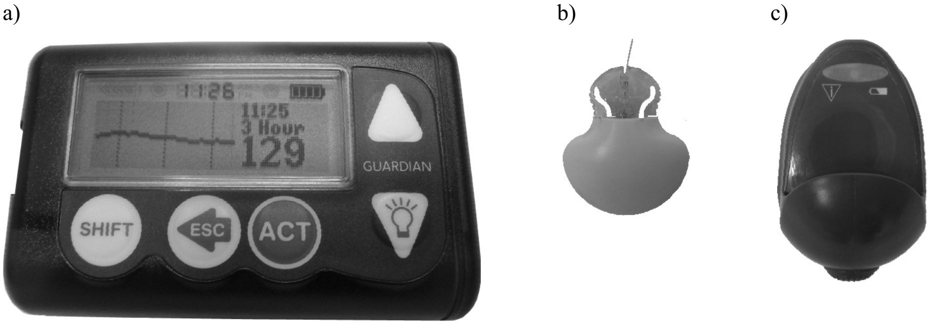

Fig. 1. Exemplary continuous glucose monitoring systems (Guardian RT, Medtronic Inc., Minneapolis, MN, USA): a) monitor, b) glucose sensor and transmitter, c) charger

similar or slightly better precision to the systems utilizing the needle-type sensors (MARD = 13.6%–15.6%) with comparable calibration and measurement frequencies [8, 9]. On the other hand, the microdialysis-based systems are technically more complicated, heavier, more expensive, consume more energy and may introduce additional time delay necessary to collect the sample in case of low flow rates of the microdialysate.

Skin irritation, noted in as much as 50% of users and sensitivity to sweating and the temperature fluctuations that lead to removal of about 20% of all measurements are the main problems of a GlucoWatch Biographer from Cygnus (CA, USA) [10]. This wrist-watch like semi-continuous system uses the reversed iontophoresis to withdraw ISF through the skin, measures glucose concentration up to 6 times per hour, and requires calibration once every 12 hours. Precision of this device is similar to that of the needle-type sensor systems or the microdialysis systems (MARD = 15.6%) [11].

With the exception of the above-mentioned systems more than a hundred other glucose measuring devices which tried to use various phenomena, like the radio waves impedance spectroscopy, the fluorescence or the photo-acoustic phenomenon, to name just a few examples have been under development [12]. Till today, however, a dominant position of the standard glucometer as a basic SMBG tool has not been endangered.

2.2. Telecare of Diabetes

Glucose concentration measurements start the monitoring phase of the diabetes treatment. SMBG data are collected together with other variables describing the patient's metabolic state (e.g. symptoms of hypoglycemia), the life-style (e.g. size and content of meals, intensity of the physical activity, exposition to stress) and the course of the treatment (e.g. insulin dosage). All these data are passed to the physician (or the medical care team) for evaluation. Routinely, paper logbook have been used for this purpose. Such logbooks are affordable, widely accepted and easy to use. However, the frequency of the data reporting to the physician is in general limited to the frequency of the control visits in the physician's office, the data storage and analysis is troublesome and reliability of the data might be a problem in case of this traditional data gathering method [13]. These drawbacks might be overcome, at least partially, with an application of the electronic logbooks and telemedicine techniques. First systems of this kind were successfully tested in the beginning of 1990s. Most of the systems that has been applied so far operated through the PSTNs using standard modems [14]. Two types of electronic logbooks have been used, i.e. either glucometers with an internal memory and a communication port that were mentioned earlier in this review or palmtops, PDAs or laptops equipped with specialized software systems. In some systems, e.g. IDEATel, which was the largest telemedicine state-financed project at the beginning of the 21st century, a desktop

PC computer has been used as a base for the patient's module, that facilitated not only the data transfer but also life tele-video-consultations and tele-education [15]. Some other approaches have been tested, too. For example, in Billiard's et al. system from 1991, French MiniTel terminals were used [16], in the Humalink system from 1996, an automatic answering machine was applied for the data transfers [17] and in the M^{2}DM system (1999–2002), a multi-access approach was adopted enabling the patients to feed the system with the date in variety of ways (e.g. through web pages or using WAP, SMS, e-mail, modem transmission, etc.) [18].

Frequency of the data transfers from the patient to the physician was, with just few exceptions, comparable to the frequency of the routine check-ups in the physician's office, i.e. weekly or once every few weeks [14]. The mentioned above exceptions might be exemplified by the Tele-DiaPreT system that has been designed and developed in IBBE PAS and evaluated during long-term randomized trial on the group of 30 type 1 pregnant diabetic women in the Clinic of Gastroenterology and Metabolic Diseases, Medical University of Warsaw [19]. In this case, the patient-collected data were transmitted to the physician on daily basis throughout the whole study period lasting for 6 months in average [20]. As a result, the average metabolic control was significantly improved during application of the system and variation of the glycemic control among the patients in the study group was significantly lower in comparison with the control group patients, in which control visits in the physician's office were scheduled once every 3 weeks in average [19–21]. In general, taking into account these results and the results of other studies and meta-analysis of the home telecare of diabetes, it can be stated that this technique is feasible and is accepted by the patients and the physicians. The telematic support of the diabetes treatment facilitates long-term maintenance of the strict metabolic control. In some groups of patients, the home telecare makes it possible to achieve better metabolic control in more repeatable way than in case of application of the routine model of care [19, 22]. The average difference of hemoglobin A1c (HbA1c) concentration improvement was in the range of 0.11% to 0.59% in favor of the telematically supported treatment [14, 23, 24]. Today, home telecare of diabetes can be realized using many different commercially available devices, systems and networks, e.g. series of the Viterion TeleHealth monitors or the Health Buddy network [25, 26].

In the recent years, the home telecare started to evolve into the mobile telecare facilitating the patient's state monitoring and the diabetes control during her or his normal daily activities by applying of mobile information and telecommunication technologies. This switch to the mobile solutions is driven mainly by a widespread use of the mobile phones (in some countries the number of cell phones in use surpasses the population of these countries).

The very first randomized study claiming to be "a real-time telemedicine support on glycemic control" was reported by A. F. Farmer et al. in 2005 [27]. This study showed difference in change in HbA1c at the level of 0.25% between two groups of young adults with type 1 diabetes treated with (study group) or without (control group) telematic support over a period of 9 months. However, in this study the patient-collected data in the study group were transmitted to a hospital multiple times a day but they were analyzed by a diabetological nurse only once every few weeks. In 2006, Ładyżyński et al. reported results of the first short-term application of TeleMed – a mobile telecare system for intensive insulin treatment and patient education (Fig. 2) [28].

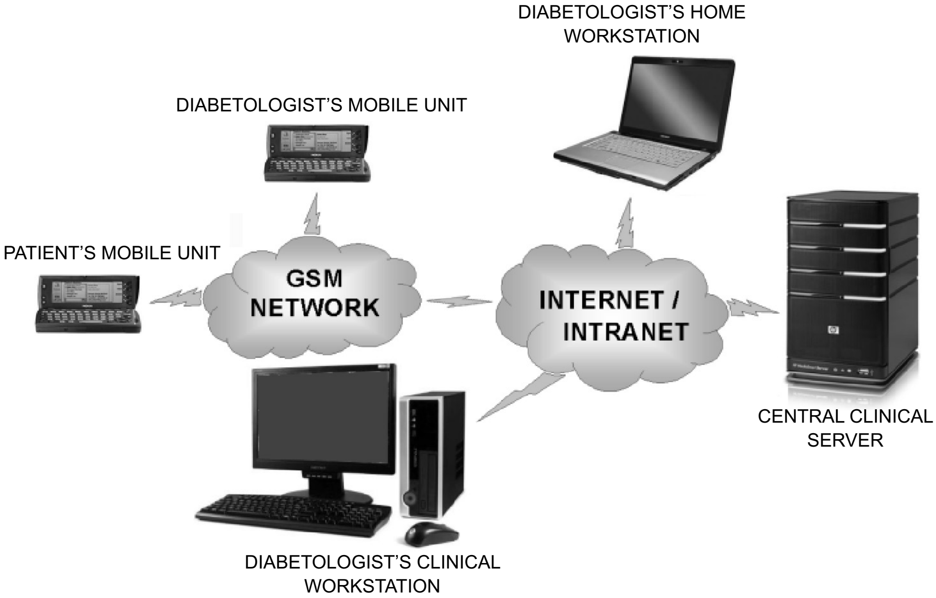

Fig. 2. Scheme of the TeleMed system for the mobile telecare of diabetic patients

In this system, patients and their physicians can be equipped with mobile units that facilitate semi-continuous monitoring, control and education of the diabetic patients. TeleMed was applied in a group of newly diagnosed type 1 diabetic patients for 3-weeks, i.e. a period that proved to be long enough for improving the metabolic control significantly (e.g. HbA1c decreased by 27%, the number of hypoglycemia episodes decreased by 66% and the number of hyperglycemia episodes – by 47%) and for providing the patients with the knowledge necessary to maintain normoglycemia in the future [28]. Currently, more and more systems that could be used for ubiquitous, mobile telecare of diabetes have been introduced. For example, GlucoMON in the USA is an automated, long-range wireless blood glucose data transmission system that sends the data from a glucometer plugged through a cable connector into a miniature wireless computer communication module to the proprietary data management center. From there, the blood glucose alerts can be dispatched to all of the care team's mobiles, pagers, and/or e-mails anywhere in the world [29]. The HealthPia America has introduced the world's first all-in-one FDA approved glucometer cell phone and service for managing diabetes remotely [30]. Their GlucoPhone can be programmed to send text messages containing the patient's blood glucose reading to a physician or a caregiver. A few complex mobile phone-based systems enabling mobile telecare of diabetes have been also offered, e.g. eHIT [31] or BodyTel/GlucoTel systems [32].

Summing up, the home and the mobile telecare systems that help to keep glycemia under control undoubtedly constitute valuable tools preventing the late complication of diabetes.

3. Systems for Screening, Monitoring or Treatment of the Risk Factors or the Early Signs of the Late Complications of Diabetes

3.1. Body Mass Monitoring and Control

Obesity is a risk factor facilitating both, the onset of type 2 diabetes and the progression of the late complications of diabetes through development of the micro- and macroangiopathy, the body overload, etc. Thus, body mass monitoring and control systems are good examples of the tools that indirectly prevent late complications of diabetes by controlling one of the conditions that facilitates their progression.

A few problems are related to an effective body mass monitoring and control. The most important include: monitoring of the body mass itself, energy intake and energy expenditure monitoring and control, the healthy-life style promoting and the patient motivating. Obviously there is plethora of home scales available that can be used by the diabetic patients for the body mass monitoring. A few of these devices are equipped with USB or Bluetooth communication interfaces that makes it possible to include them into the home patient telecare systems that were discussed in section 2.2. There have been also a lot of meal planning software systems as well as the nutrition databases available to chose from, either commercial or free of charge, that could be used as valuable sources of information for these patients who are motivated to control their body weight, e.g. [33]. Recently an interesting application of the avatar technology was introduced and made available for these who wish to loss some weight and want to see up-front how this will influence the way they look, e.g. [34].

For the energy expenditure monitoring there have been some more or less advanced systems available on the market for the last decades. The simplest device that can be used to approximate the energy expenditure during walking or jogging is a pedometer or step counter, i.e. a portable tool that counts each step a person takes. After calibrating by the user it can estimate a distance walked in kilometers or miles. Currently, step counters are often integrated in popular portable devices such as mobile phones (e.g. Nokia 5500), MP3 players or even training shoes (Nike+iPod Sports Kit). Such step counters usually use 1, 2 or 3-axial accelerometers. The distance run or walked can be also estimated using the above-mentioned portable devices equipped with the GPS signal receivers. There are also some more sophisticated portable systems available that monitor a few parameters such as acceleration (body movement), skin surface temperature, deep body temperature, galvanic skin response, heat flux, heart rate, breathing frequency, etc. and estimate energy expenditure, duration and intensity of physical activity and/or sleep duration and sleep efficiency (e.g. SenseWear / BodyMedia from BodyMedia, Inc., PA, USA) [35]. This system can be used in "free-living" conditions, i.e. at home, at work, during physical activity and during the night [36]. Multi-parameter monitors estimating the energy expenditure during training are also integrated in some gym equipment, i.e. training machines.

A few types of sensors and measurement systems have been tried for indirect, automatic energy intake estimation, including the swallowing detectors based on microphones, laryngographs/glottographs, EMG monitors, videofluoroscopes, strain sensors, manometry pressure probes, etc. that were used separately or in different multi-sensor configurations [37–39]. Motion sensors have been applied to detect arm gestures related to food intake [40]. However, no ready-to-use solution for an effective food intake monitoring has been available so far. Therefore, diabetic patients have to rely on semi-quantitative estimation of the carbohydrates and energy content of a meal based on visual inspection of the meal size and composition.

3.2. Screening for and Monitoring of the Diabetic Retinopathy

DR is one of the most serious long-term microvascular complications of diabetes. Occurrence and severity of DR is related to duration of diabetes and level of metabolic control. Capillary occlusion, capillary leakage and new vessels' formation are three main abnormalities connected with occurrence of DR. The long-term maintenance of normoglycemia is the best preventive strategy in case of DR since in case of this disease effectiveness of pharmacotherapy is rather limited.

Presently, DR screening is used to recognize patients who have already developed the retinal lesions and who require laser photocoagulation or vitrectomy. The screening itself can not prevent DR but might save the eyesight of the patient. It is estimated that with the appropriate medical and ophthalmologic care administered at the appropriate time more than 90% of visual loss cases can be prevented. The gold standard method of the screening and monitoring of DR requires at least annual examination of the diabetic population using slit lamp biomicroscopy or stereoscopic 30º-field fundus photography with dilated pupils. However, even the most developed countries can not afford to implement such a screening and monitoring program due to high financial and organizational costs. At preset time, the retinopathy is still most often detected by a direct ophtalmoscopic examination, which suffers from low sensitivity [41]. The fundus photography is other widely used method. Even several years ago, the retinal cameras were used in connection with standard still cameras to obtain polaroid pictures or 35 mm slides of the patient's retina, which were then evaluated by a skilled grader or an ophthalmologist. Recently, this solution has been ousted by the digital fundus photography that introduced application of image processing and telematic techniques in the retinopathy screening and monitoring. One of the first region-wide DR screening programs using digital fundus photography was established in Gloucestershire County in the UK in 1998. This program used mobile digital retinal cameras, which were moved between the screening sites in vans. Two 45º-field mydriatic retinal photographs were taken for each eye and they were transferred to the single grading center on a hard drive of a laptop computer [42]. The distant screening sites were connected with the grading center using ISDN2 or ADSL telematic links in 2002. First DR telescreening systems started to emerge in the late 1990s. They were realizing a store-and-forward mode of operation. In these early systems the digital retinal images were transmitted as attachments to the e-mail messages [42, 43]. In some of them a real-time video-tele-conferencing functionality was added [43]. Over the years of development some of the DR telescreening and telemonitoring systems that started to be implemented in the 1990s have evolved into the complex health care services. For example, the Joslin Vision Network (JVN) that was designed in the Joslin Diabetes Center (Boston, MA, USA) has the Remote Imaging Workstations deployed in more than 70 locations in 20 states nationwide and also abroad. Using these workstations, which are equipped with Joslin's custom software and non-mydriatic imaging hardware a certified staff imager takes stereoscopic digital fundus images and sends them together with information regarding important risk factors that influence DR progression (e.g. HbA1c, blood pressure, etc.) to the JVN Reading and Evaluation Center. Evaluation and care summaries are returned to the remote location within two days. The accuracy of JVN as a diagnostic tool for diabetic retinopathy has been described and validated in several scientific reports, e.g. [44, 45]. It is noteworthy that within JVN an educational material may be presented to the patients emphasizing a influence of the general diabetes control on vision.

At the beginning of the 21st century the latest advancements of the web technologies enabling presentation of an interactive content within the web browsers started to be used in the DR telescreening systems. A few systems of that kind have been developed and/or implemented so far, e.g. TOSCA [46], eyePACS [47], the Spanish CESGA-CHUS [48] or the Alberta teleophthalmology program [49]. One of the first web-based systems called DRWeb has been designed, developed and preliminary tested in IBBE PAS in cooperation with the Nara Institute of Science and Technology (Nara, Japan) [50, 51]. DRWeb consisted of a set of the image acquisition stations, the database and the communication server and the image grading station interconnected through the Internet. Based on this infrastructure the system can operate in the store-and-forward mode or it can be used in the life teleconsultation mode, in which an interaction between the imager and the expert-ophthalmologist is possible. In the DRWeb system selected image processing and image analysis techniques have been implemented for an automatic assessment and enhancement of quality of the digital retinal images and for the operator-guided analysis of the retinal images, i.e. marking of the lesions (Fig. 3) [50–52].

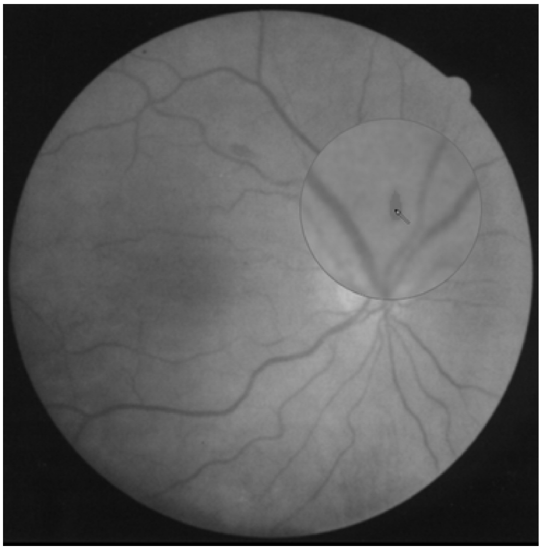

Fig. 3. Retinal image with an area of a hemorrhage marked with a user-guided region growing algorithm visible under a magnifying lens in DRWeb system

It should be stated that fully automatic detection of the lesions and fully automatic grading of the retinal images have been an ultimate goal of many researchers over last few decades. However, algorithms that have been developed so far were not reliable enough to replace the human experts evaluating retinal images.

3.3. Monitoring and Treatment of the Diabetic Foot Syndrome

DFS is a complex and evolutionary pathology with a multi-factorial pathogenesis, which involves both peripheral neuropathy and/or peripheral arterial disease (i.e. angiopathy) and infection. These factors contribute to the progression from a foot at risk to an ulcerated foot and then to an amputation. It is estimated that DSF is a direct cause of more than 50% of all lower limb amputations in the world.

Regardless of the actual phase of DFS a maintenance of the normoglycemia and an avoidance of the risk factors such as obesity are beneficial to the patient and constitute the best preventive strategy that slows down the progression of the neuropathy and angiopathy. However, there are some additional technologies, systems and devices, which might be helpful in detecting patient's in the pre-ulcerative phase and in reducing the risk of a transition of the disease from the pre-ulcerative to the acute ulcerative phase. Beside an examination of appearance of the foot some tests are performed to detect the early signs of DSF, including the reduced ability of vibration, pressure and temperature sensing on the affected foot. These tests are performed using very simple aids such like: a Rydel-Seiffer tuning fork, a 10 g Semmes-Weinstein nylon monofilament and a plastic-metal temperature sensing test, respectively. Some more sophisticated measurement methods are also available, e.g. nerve conduction measurement. Additionally, the blood pressure is measured at the ankle and in both arms and an ankle-brachial index that helps to detect pathological increase of the blood pressure in the foot is determined.

Patients at risk of DFS require an appropriate foot care and a special foot ware in the form of therapeutic shoes, depth-inlay shoes, custom-molded inserts (orthoses) or custom-molded shoes. Results of a pedobarographic examination revealing pressure distribution on the sole of the foot might help to design an appropriate foot ware.

Except the above-mentioned parameters some other physiological data like temperature, pressure, foot volume and oxygen concentration of the at-risk foot can be monitored in order to predict a risk of the foot ulceration. It has been demonstrated that all these variables are important in predicting a possible acute event in the course of DFS [53, 54]. Thus, long-term monitoring of these parameters in real time would be a great advancement either in case of the primary prevention to avoid the first lesions or in case of the secondary prevention (i.e. in the post-ulcerative phase) to reduce risk of the recurrent ulceration, infection and/or amputation. Unfortunately, despite the fact that objective instrumental measurements of all of these quantities are possible, the plantar foot pressures is the only measurement, which can be performed in dynamic conditions. So, the sensors able to measure all the above-mentioned parameters should be modified and integrated into a complete, smart, wearable system before they can be used in real life conditions.

During the acute ulcerative phase of DFS the main objective is to prevent infection and to speed-up the wound healing process and thus, to reduce the risk of amputation. In this regard, monitoring of the wound healing is one of the most important problems. In a routine way of DFS treatment the patient has to travel to a foot care clinic for regular visual inspections of the wound. Because locomotion is a big problem for the DFS patient, home telemonitoring systems have been implemented in the course of DFS treatment since the late 1990s. First systems relies on a social nurse who visited patients at home, documented the wound healing progress with a digital camera and sent this documentation by e-mail to a physician for evaluation [55, 56]. Such a nurse-based model of the DFS home telemonitoring has prevailed, with some technical modifications, till today. In Europe, the most well known system of this kind has been designed, developed and implemented in Denmark [57, 58]. In this system, the wound is documented using a mobile phone with a camera and the pictures are promptly uploaded to a web server, from which they can be retrieved by a physician using a standard web browser. The physician can communicate with the nurse to request further wound pictures or to modify the treatment. A different approach has been used in the TeleDiaFoS system that was designed and developed in the IBBE PAS [59]. In this system patients document the wound healing by themselves using the home-located patient modules that are able to make foot pictures using a built-in foot scanner (Fig 4).

Fig 4. Patient's module of the TeleDiaFoS system

The patients modules can also retrieve the blood glucose and the blood pressure data from internal memory of the respective meters and upload them together with the scanned images to a TeleDiaFoS server [59, 60]. The medical staff accesses the patient's data using clinical workstations, that implement an algorithm for semi-automatic wound area assessment, which is the main parameter for the effectiveness of the treatment evaluation [61].

There are also some other systems and devices that are solely aimed at measuring of the wound area or volume, e.g. the Visitrak system (Smith & Nephew, Great Britain), the SilhouetteMobile system (Aranz Medical, New Zealand), the Wound Measurement Device (Mobility Rehabilitation and Engineering Research Center, Georgia Tech Research Corporation, USA) or the Kundin gauge [61–63].

As far as the wound telemonitoring is concerned, another system that can be used by the DFS patient without assistance of a nurse is called Vincent 50 [64]. In this system a digital camera is used instead of a flat foot scanner and Vincent 50 is not able to collect any additional data except the foot pictures.

4. Conclusion

Based on the review of the technologies and systems that play an important role in the direct or indirect prevention of the late complications of diabetes it can be stated that:

- Long-term maintenance of the normoglycemia is the best known way of preventing onset or slowing down the progression of the late complications of diabetes.
- Regular and accurate blood glucose monitoring is a determinant of the effective diabetes treatment. There are many portable, accurate, precise, affordable and easy to use blood glucose meters for intermittent SMBG. Few systems for continuous glucose monitoring are also available but invasiveness, limited

precision, high cost and limited lifetime of sensors as well as calibration necessity are the most important problems hampering wider usage of these systems. The diabetic patients still wait for fully noninvasive blood glucose monitoring systems.

- The home telecare systems supporting diabetes treatment has been developing for the last 20 years. Recently they started to evolve into the mobile, ubiquitous telecare systems. The telecare application increases frequency of contacts between patients and their physician making maintenance of the metabolic control possible.
- Body weight as a major risk factor for diabetes and its complications can be easily monitored. There are systems for monitoring of the energy expenditure available too. However, systems for an automatic quantification of the energy intake are missing.
- Diabetic retinopathy can be detected early but “gold standard” methods are costly. An application of the digital fundus photography and the telescreening/telemonitoring systems might help to detect the diabetic retinopathy in early stage and to prevent blindness by implementing an appropriate treatment in time.
- Wound healing process in the diabetic foot syndrome patients can be telemonitored conveniently (preventing the infections, hopefully). On the other hand there are no integrated, wearable systems aimed at monitoring of pre-ulcerative phase of DSF, i.e. making prevention of the ulceration possible.

Most of the systems and devices presented in this review can be included into one of two main groups of technologies, i.e. either the biomeasurement/bioimaging technologies or the information and communication technologies. Each solution belonging to the first group of technologies is dedicated to measure a particular quantity or to depict a particular structure of the patient’s body. An effective diabetes treatment that slows-down the progression of all the late complications of diabetes or a prevention of the particular complication requires a group of parameters to be monitored and analyzed in parallel. ICT can be applied to facilitate collecting, transmitting, analyzing and storing of the measured data. Till now, in most cases a “selective” approach has been applied in this respect, meaning that each system utilizing ICT has been developed as a standalone application focused on a specific problem and/or group of patients. This approach was also applied in the IBBE PAS where several systems were designed and developed, i.e. the TeleDiaPreT system for home telecare of the pregnant diabetic women [19–21], the TeleMed system for mobile telecare of patients with an unstable glycemia course [28], the DRWeb system for screening and monitoring of the diabetic retinopathy [50–52] and the TeleDiaFoS system for home telemonitoring of DFS patients [59–61]. Such an approach is concordant with a way of organization of the health care system, which tends to treat each individual health problem separately. However, diabetes is a systemic disease requiring an integrated, collaborative care service to be implemented. Because of this, currently, all the systems developed in the IBBE PAS have been integrated and new subsystems have been designed to form an integrated ICT environment for a model center of diabetes treatment [65]. This center consists of: centralized patients' registration module and a set of specialized modules related to the patient's education, treatment of difficult diabetes (i.e. short-term applications of home/mobile telecare with semi-continuous connection of the patient with the care provider), treatment of diabetes before conception and during pregnancy (i.e. long-term integration of obstetrical and diabetological care), monitoring and treatment of cardiovascular complication in diabetes, monitoring and treatment of the diabetic foot syndrome and screening for and monitoring of the diabetic retinopathy.

The integrative diabetes care approach, that is exemplified in the model center of diabetes treatment would make it possible to provide high quality and low cost health care services to the diabetic patients what in turn should result in more effective prevention of the late complications of diabetes.

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