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ADVANCED MEDICAL TECHNOLOGIES USED IN MONITORING AND THERAPY FOR DIABETES - REVIEW WORK

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Abstract
Throughout the years monitoring and therapy of diabetes has been significantly changing. Undoubtedly, a definite improvement of applied technologies not only increased the average life expectancy of diabetic patients but also influenced their quality of life. The purpose of the review was to present the history of diagnostic methods and treatment of diabetes. Additionally, promising modern medical technologies were reviewed. Nanotechnology, modern robots and transplants of pancreatic islets are currently being evaluated showing satisfactory results. These technologies enable monitoring of glucose level, prevent hypoglycemia and sustain normoglycemia. Moreover, surgical attempt involving transplantation gives a chance to counter the complications that follow diabetes development.
Key words: diabetes, nanomedicine, medical technologies

Introduction
A development of 21st century medicine seems to be inextricably linked to advances in technology. Genomics, medical robotics, nanomedicine, telemedicine and many other areas may be listed in which these two disciplines, cannot exist without each other. Moving away from treatment developed on the basis of a lock and key mechanism, as in the case of antibiotic therapy or any other pharmacotherapy designed for specific site of action, is a visible trend[1]. Scientists around the world compete against each other in creating new diagnostic and therapeutic methods that provide the highest possible comfort for the patient and improve both - diagnosis and treatment of civilization diseases.

What is diabetes?
Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from impaired insulin secretion or activity. Chronically occurring hyperglycemia causes damage, malfunction and failure of various organs. In recent decades, the number of people with diabetes has significantly increased. In 1980 the patients number was estimated to be 108 million, while in 2014 this amount was already about four times higher. Considering the data presented by

1 S. Mukherjee - 03.2015 [video talk] „Soon we'll treat diseases with a cell not a pill", https://www.ted.com/talks/siddhartha_mukherjee_soon_we_ll_cure_diseases_with_a_cell_not_a_pill.

International Diabetes Federation, the global incidence of diabetes in 2017, reached 425 million of cases (20-79 years). Predictions indicate that this number will rise to 629 million by 2045[2].

Diabetes type 1 is the most common form of the disease (90%) in case of children and adolescents in many Western populations. Additionally, white race is more commonly affected. In general, type 1 diabetes affects 5-10% of diabetic patients from all age groups. It is statistically estimated that around 80,000 children up to the age of 15 are diagnosed with type 1 diabetes every year[3]. Over past decades, a global increase in the incidence of type 1 diabetes has been observed due to the growth of the world population and increase in average life-span of the population. Such pattern is correlated with the increased percentage of people with HLA genotype at risk of developing the disease. This may suggest an increasing impact of environmental factors on the disease emergence[45]. The incidence of type 1 diabetes varies widely across countries and between ethnically different populations. Statistically, the highest values were observed in Northern Europe[6] and Canada[7]. Considering the latest recommendations of the Polish Diabetes Association (PDA), the overall goal of glycemic control expressed as HbA1c should be <6.5% (53 mmol/mol). The purpose of the article is to present the modern blood glucose control methods that aim to achieve this value.

How was it in the past?

Last century was undoubtedly a breakthrough time in the field of diabetes and inventing modern methods of glucose control. Until 1950, the Benedict test was the only possible way to measure blood glucose levels[8]. In 1953 the urine tablets appeared and few years later stripes were introduced to assess the glucose values in urine. In 1955 the first sulfonylurea derivatives appeared whereas in 1959 the method of determining insulin level in the body of patients was developed. It was then discovered that some patients were still producing their own insulin. That is how the concepts of insulin-dependent diabetes mellitus (type 1) and insulin-independent diabetes mellitus (type 2) arose. The first glucometer appeared in 1970, manufactured by the Ames Company. In 1958, a new parameter, glycated - glycosylated hemoglobin (HbA1C), was discovered and introduced as a standard method for measuring long-term diabetes control.

The need of monitoring of blood glucose level forces diabetic patients to collect small blood samples, often several times a day. Considering the long-term course of the disease, the standard monitoring methods available to date have caused a great deal of discomfort to patients, due to the need to frequent interruption of skin continuity. The development of medical technology has

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5 Gillespie KM, Bain SC, Barnett AH, The rising incidence of childhood type 1 diabetes and reduced contribution of high-risk HLA haplotypes. Lancet (2004), 364: 1699–1700.

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7 Newhook LA, Penney S, Fiander J, Dowden J. Recent incidence of type 1 diabetes mellitus in children 0–14 years in Newfoundland and Labrador, Canada climbs to over 45/100,000: a retrospective time trend study. BMC Res. Notes, (2012), 5: 628.

8 Benedict SR. A Reagent For the Detection of Reducing Sugars. J. Biol. Chem. (2005), 5: 485–487, 1909.

enabled the use of continuous blood glucose monitoring using nanorobots[9]. The application of nanotechnology not only improves the quality of life of patients and free them from the obligation of regular glucose levels checks or frequent laboratory tests. In addition, it ensures ongoing control of the patient's parameters by a doctor who receives current data on the patient's condition from the device.

Modern technologies in diabetes monitoring

Nanotechnology is a powerful tool that enables the development of devices for monitoring blood glucose, in particular using nanorobots. They are the basic means used in modern devices used for measuring glucose. An example of the external structure of a nanorobot includes a thin coating, reminiscent of diamond in structure and physical properties[10]. It is covered with an artificially created layer of glycocalyx, which ensures a reduction in adsorption and bioactivity in relation to fibrinogen and other proteins found in the blood[1112]. This enables the highest possible level of biocompatibility to avoid the immune system reaction against foreign body[13]. The construction of nanorobots has the appropriate properties to ensure the identification of devices by the transponder system using radio frequencies. That results in confirmation of their correct location and data reading - most often using customized applications[14].

Proper monitoring of blood glucose level by nanorobot is possible due to presence of chemosensor. This device uses the modulated human protein SGLT3 and serves as a transmitter that identifies glucose[15]. The medical nanorobot should adapt its structure and functionality to ensure compatibility with typical medical applications. Such approach enables synchronous operation of the antenna, reader and nano processor and maintains compactness, putting all necessary elements in one chip[16].

Currently, many research groups are working on introducing all kinds of new technologies to the market in order to improve patient comfort during daily, mandatory glucose measurements. These are easy-to-use devices such as: contact lenses, eMosquito, saliva analyzers, ear pads and even tattoos.

For example, several research groups are currently working on introducing contact lenses with built-in biosensors for continuous and non-invasive monitoring of glucose levels in the secretion in tears. In biosensors boronic acid is used, which bind groups containing diols, such as carbohydrates, thus forming boronates[17]. These sensors built into the device can diffract light, so that any change in blood glucose will change the color of the light. Then, the patient can determine the glucose result

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by checking the color of the contact lens sensor using a device containing a white light source, mirror and color card. In a similar manner, boric acid derivatives can be designed to detect glucose by fluorescence. Boronic acid fluorophores induce spectral changes in the presence of carbohydrates. These fluorophores can be introduced into disposable commercial contact lenses by incubating for 24 hours and then washing with water to remove excess dye. Another aspect in favor of this method, in economic terms, is the low production costs gel from boronic acid[18].

Scientists from the University of Calgary have developed eMosquito, which in action is supposed to resemble a mosquito bite[19]. The goal is to measure blood glucose levels in the least invasive way. The device comes in the form of bracelets that include six small needles which puncture the skin in a way that does not threaten nerve irritation nor causes pain. Punctures are sequential and occur at pre-programmed intervals. Due to the sensors connected with the needles it is possible to control the level of glucose in the blood several times a day. Recorded data can be sent automatically to a telephone or computer. This device is still being tested[20].

GlucoTrack is another device available on the market for non-invasive blood glucose measurement. This device monitors changes in glucose concentration in the capillaries earlobe using three technologies: ultrasonic, thermal and electromagnetic. These parameters change due to shifts in compressibility and hydration of cellular and extracellular tissue of the earlobe that are associated with changes in glucose concentration[21]. The earlobe tissue consists of three layers: epidermis, dermis and subcutaneous tissue. These layers differ in the volume of blood plasma that may affect the delay of glucose dispersion dynamics between these layers[22]. This delay depends mainly on blood perfusion, which affects vascular permeability[23] according to the studies conducted by Tamar Lin, Yulia Mayzel, Karnit Baharta, the influence of factors that may cause microvascular complications on the occurrence of glucose dynamics delay[24]. The results showed that factors such as diabetes duration, smoking history and HbA1c levels do not significantly affect device accuracy. Demographic factors such as age, gender, body weight, and ear piercing affect GlucoTrack performance, which further supports the usefulness for people with type 2 diabetes. In these studies, the accuracy of the device was comparable for people with different clinical characteristics[25].

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What is more, scientists from Hong Kong Polytechnic University in China have created an accessible biosensor for common use that measures glucose in human saliva[26]. It is a microfluidic analytical device which in combination with systems on smartphones is considered an effective tool for the diagnosis of biomarkers in oral fluid. Available graphene oxide coated nanomaterials are combined with smartphone colorimetric detection and used to directly quantify glucose. By means of a self-developed application, glucose levels in the physiological range can be automatically quantified. During the tests, the system was used to quantify glucose levels in artificial saliva and the results obtained using a portable system showed compliance with actual concentrations[27].

In 2016, experiments were conducted in order to introduce a glucose level sensor into a handheld breathalyzer that measures the concentration of organic components in the breath[28]. According to researchers from "Western New England University", early clinical results showed clear correlations between blood glucose and breath-induced acetone. The study using a hand-held breathalyzer involved the patient blowing air into a device. This device immediately read the level of acetone in the breath, which is closely correlated with the level of blood glucose and can be a completely non-invasive way to control glucose in people with diabetes[29]. Researchers of University of Strathclyde in Glasgow and King's College London were developing the use of nanosensors in form of intelligent tattoos that can be implanted on the skin[30]. Such approach was definitely beneficial especially for young patients. This method is permanent and the task is to monitor the changes in blood glucose levels as well as to signal a warning in the event of hypo- or hyperglycemia. These changes can be read immediately at any time, using a hand-held device, applied close to the skin. Similar experiments were conducted in Massachusetts Institute of Technology USA s regarding the creation of tattoos using a special infrared refractive ink for constant monitoring changes in blood glucose levels[31].

In addition to the above-mentioned innovative devices, CNoga Medical Ltd in Israel is also researching the use of a device that uses skin color assessment. The application of this method is not only limited to blood glucose levels monitoring but also it involves blood pressures measurements[32].

Innovative treatment for diabetes

Micro- and macroangiopathy are major complications of diabetes type 1 that pose a therapeutic problem and require a modern approach to the treatment. Despite the development of pharmacotherapy and a significant emphasis on patient education, the problem of nephropathy will develop in 9-40% of patients and retinopathy will affect 98% of them in 15 years after the onset of

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the disease[33]. These data prove that the standard approach to treatment is insufficient. Concerning the patients with unstable and complicated type 1, transplantation of the pancreas was proposed as an alternative method of therapy. Over the past 10 years, 750 such operations have been performed in over 30 international transplant centers[34]. The most common method of surgery is transplantation of the pancreas with the kidneys of the donor (simultaneous pancreas-kidney (SPK)[35]. This is the procedure recommended by American Diabetes Association (ADA), especially for patients with advanced kidney disease. The beneficial effect involves not only control of hyperglycemia, but also prevents hypoglycemia[36]. The improvement of these parameters occurs in a short period of time, which contributes to a significantly rapid improvement in the patient's quality of life. In the exemplary study, the glycated hemoglobin level of each of the 37 patients before treatment was above normal (from 5.4% to 7.4%). After transplantation, these values decreased to 6.7% after one year and 6.5% after 2 years. In addition, SPK provides protection for transplanted kidneys, which can be seen of improving renal function. A cross-sectional study of eight patients compared urinary albumin excretion and creatinine clearance. Prior to transplantation, the median excretion of albumin in patients was 103 mg per day, after 5 years - 30 mg per day, and after 10 years - 20 mg per day[37]. A decrease was also recorded for clearance - from 108 +/- 20 ml / min to 1.73 m2 to 74 +/- 14 ml / min to 1.73 m2[38] . There was also a difference in the average time of organ functioning after transplantation. after SPK it was 9 years, and after PAK (kidney transplantation after pancreas transplantation) -6, which also speaks for the effectiveness of this type of surgery.

Despite satisfactory results regarding pancreas transplantation, less invasive forms of transplantation are currently sought for the treatment of complicated type 1 diabetes. Promising solution may be the transplantation of pancreatic isles exclusively as it minimizes the extent of the operation[39]. Donor pancreas is isolated according to the Ricordi method of controlled digestion of the pancreas using a dissociative apparatus. The next step involves purifying of the islets that minimizes the amount of obtained material. Such procedure decreases the risk of potential embolism during the transplantation. Before initiation of the procedure, breeding has to be introduced for proper collection of tissues and their regeneration after completion. Isolated pancreatic islets are transplanted to the recipient under ultrasound control through the portal vein[40].

Artificial pancreas

33 Przeszczepienie trzustki u pacjentów z cukrzycą typu 1 available at: https://www.mp.pl/cukrzyca/cukrzyca/typ1/95580,przeszczepienie-trzustki-u-pacjentow-z-cukrzyca-typu-1

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An alternative to pancreatic transplantation are modern insulin pumps cooperating with sensors. Such an enriched pump informs the patient about the hypoglycemia with a sound signal. A breaking point was the introduction of device that not only monitors blood glucose levels, but also counteracts hypoglycemia. The mechanism of ’artificial pancreas’ is based on insulin injection that follows detection of too high glucose result. Substance administration is independent of the patient, being fully controlled by appropriate device algorithms. The main advantage of the mechanism is the prevention of nocturnal hypoglycemia[41]. A study comparing "artificial pancreas" known as BiAP (Bio-Inspired Artificial Pancreas) and traditional insulin pumps with sensors indicates that for the first group, the time during which the patient was in a hypoglycemic state significantly decreased - 17.9% to 3.0% ($p<0.01$). Although the average glucose level at night was lower in the case of ordinary pumps with sensors (4.8 mmol / L vs 7.5 mmol / L), this is an imperfect assessment. Such value was caused by more frequent episodes of hypoglycemia in this group[42]. In the case of BiAP, glucose level fluctuations were smaller, but still remained at the appropriate level. That indicates the advantage of this mechanism. In addition, the number of units of insulin administered was lower in the case of "artificial pancreas" (32.2 [6.4] units, $P <.01$) than in the case of traditional pumps (38.0 [5.7] units, $P <.01$).

Biomaterials in pancreatic islets transplants

Due to the significant limitations of pancreatic islet transplantation associated with cell destruction during isolation and the small number of donors, effective methods of culturing and surgeries are still sought. Promising results were observed during co-cultivation of harvested pancreatic cells along with adipose-derived stem cells (ADSCs). The study showed that joint storage of these cells causes pancreatic islets to change their morphology. As a result, they are less susceptible to the adverse effects of external factors and also secrete more insulin in comparison to cells from individual culture. A similar relationship regarding the positive effects of co-culture was noted when hybrids were formed from pancreatic cells and hepatocytes. The functions of pancreatic cells were monitored by assessing insulin secretion and hepatic cells based on albumin, urea secretion and cytochrome P450 activity. After 4 weeks, a two-way advantage was observed in the above-mentioned parameters in relation to the individual cultures of these two cell types[43].

Patient-doctor contact

Mobile applications play an increasingly important role in the doctor-patient relationship. There are many glucose meters on the market with connection to the application on the phone. The more advanced measurement methods listed above are based entirely on the operation of the computer or telephone application. Obviously, it is easier to download automatically the results and be sure that the patients glucose measurements are real. An additional role is played by applications for monitoring physical effort. Due to various types of bands and watches, the doctor can assess not only the patient's physical activity, but also the caloric balance, heart rate and more. These can be

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parameters that objectively assess the patients physical activity translating into the degree of compliance with recommendations and the actual change in lifestyle. Research shows that such applications are a motivation for physical effort. They help in starting physical activity, as well as in maintaining regular workouts[44].

Conclusion

The article describes many methods that patients with diabetes already have access to or will use in the coming years. It applies to both diagnostic and therapeutic methods. Artificial pancreas already imitate the action of natural organs. It is possible that soon thanks to miniaturization, nanotechnology and the development of biomaterials, a more optimal device will appear. One that will not require injections or wearing insulin pump on the strap. Medical personnel should follow innovations appearing on the market to be able to provide patients with the highest comfort of therapy. Perhaps, according to the predictions of authorities such as Yuval Noah Harari[45], who extends the vision of man evolving with technology, man will become a "biological machine". It will happen that we will modify our own bodies not with implants treating disease or disability, but with implants improving the quality of life of a healthy person. In the twenty-first century, the challenge is on the side of both the doctor and patient, so that in cooperation they can maximize the potential of new technologies and contribute to the development of medicine.

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