

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 was significantly changing. Undoubtedly, a definite improvement of applied technologies not only increased the average life expectancy of diabetic patients but also influenced their comfort. The purpose of the study was to present the history of methods diagnosis and treatment of diabetes. Additionally, promising modern medical technologies were reviewed. Nanotechnology, modern robots and transplants of pancreatic islets are currently under experiments showing satisfactory results. These technologies enable monitoring of glucose level, prevent hypoglycemia and sustain normoglycemia. Moreover, surgical attempt involving transplantation give a chance to counter the complications followed by diabetes development.

Key words: diabetes, nanomedicine, medical technologies

Introduction

A development of 21st century medicine seems to be inextricably linked to improvement of technology. Genomics, medical robotics, nanomedicine, telemedicine and many other areas may be mentioned in which these two disciplines cannot exist without each other. A visible trend is 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 acting on a specific point of grip. Beginning of current century was an initiative point of intensive development of immunology and highly advanced medical technologies¹. 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 108 million, while in 2014 this amount was already about four times higher. Considering the data presented by WHO, the global incidence of diabetes in 2014 among people over 18 was 422 million cases reported.

Diabetes type 1 is the most common form of the disease (90%) especially in case of children and adolescents in many Western populations. Additionally, white race is more commonly affected. However, considering all age groups - type 1 diabetes emerges in 5-10% of diabetics. It is statistically estimated that around 80,000 children up to the age of 15 are diagnosed with type 1 diabetes every year². Over past decades, a global increase in the incidence of type 1 diabetes has been observed due to the escalation of the world population and elongated average age 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 emergence³⁴. The incidence of type 1 diabetes varies widely across countries, between them and between ethnically different populations. Statistically, the highest values were denoted in Finland, Northern Europe⁵ and Canada⁶. 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 levels⁷. 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. It was then discovered that

¹S. 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.

² Craig ME, Jefferies C, Dabelea D, Balde N, Seth A, Donaghue KC.

Definition, epidemiology, and classification of diabetes in children and adolescents. *Pediatric Diabetes*, (2014), 15 (20): 4–17.

³ Hermann R, Knip M, Veijola R, Temporal changes in the frequencies of HLA genotypes in patients with type 1 diabetes – indication of an increased environmental pressure? *Diabetologia* (2003), 46: 420–425.

⁴ 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.

⁵ Berhan Y, Waernbaum I, Lind T, Mollsten A, Dahlquist G, Swedish Childhood Diabetes Study Group: Thirty years of prospective nationwide incidence of childhood type 1 diabetes: the accelerating increase by time tends to level off in Sweden. *Diabetes* (2011), 60: 577–581.

⁶Newhook 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.

⁷ Benedict SR. A Reagent For the Detection of Reducing Sugars. *J. Biol. Chem.* (2005), 5: 485–487, 1909.

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 enabled the use of continuous blood glucose monitoring using nanorobots⁸. 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 properties⁹. 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^{10,11}. This enables the highest possible level of biocompatibility to avoid the immune system reaction against foreign body¹². The construction of nanorobots has the appropriate properties to ensure the identification of devices by the transponder system using radio frequencies. That results in determination of their correct location and data reading - most often using customized applications¹³.

Proper monitoring of blood glucose level by nanorobot is possible due to presence of chemosensor. This device uses the modulated human protein carrier SGLT3 and serves as a transmitter that identifies glucose¹⁴. 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 chip¹⁵.

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, tattoos and ear pads.

⁸ Cavalcanti A, Shirinzadeh B, Kretly LC, Medical nanorobotics for diabetes control. *Nanomedicine: NBM* (2008), 4:127-138.

⁹ Narayan RJ. Pulsed laser deposition of functionally gradient diamond- like carbon-metal nanocomposites. *Diam Relat Mat* (2005), 14:1319-1330.

¹⁰ Freitas Jr RA. Nanotechnology, nanomedicine and nanosurgery. *Int J Surg* (2005), 3:1-4.

¹¹ Marchant RE, Zhang T, Qiu Y, Ruegsegger MA. Surfactants that mimic the glycocalyx. United States patent US 6759388; 1999.

¹² Grieninger G, Fu Y, Cao Y, Ahadi MZ, Kudryk B. Monospecific antibodies against a subunit of fibrinogen. United States patent US 6025148; 2000.

¹³ Ahuja SP, Myers JR. A survey on wireless grid computing. *J Supercomput* (2006), 37:3-21.

¹⁴ Wright EM, Sampedro AD, Hirayama BA, Koepsell H, Gorboulev V, Osswald C. Novel glucose sensor. United States patent US 0267154; 2005.

¹⁵ Cavalcanti A, Shirinzadeh B, Freitas Jr RA, Hogg T. Nanorobot architecture for medical target identification. *Nanotechnology* (2008), 19(015103): 15.

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 of tear glands. In biosensors boronic acids are used, which bind to groups containing diols, such as carbohydrates, thus forming boronates¹⁶. 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 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 sugars. 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 cost of producing gel from boronic acid¹⁷.

Scientists from the University of Calgary have developed eMosquito, which in action is supposed to resemble a mosquito bite¹⁸. The goal is to control 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 tested¹⁹.

GlucTrack is another device available on the market for non-invasive blood glucose measurement. This device monitors changes in glucose concentration in the 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 concentration²⁰. 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 dynamics between these layers²¹. This delay depends mainly on blood perfusion, which affects vascular permeability²². 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 delay²³. 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 GlucTrack performance, which further supports the usefulness of people with type 2 diabetes. In these studies, the accuracy of the device

¹⁶ Badugu R, Lakowicz JR, Geddes CD. Noninvasive continuous monitoring of physiological glucose using a monosaccharide-sensing contact lens. *Anal Chem.* (2004), 76:610–618.

¹⁷ Alexeev VL, Das S, Finegold DN, et al. Photonic crystal glucose-sensing material for noninvasive monitoring of glucose in tear fluid. *Clin Chem.* (2004), 50(12):2353-60.

¹⁸ Device makers eye better blood glucose testing experience. *Chain Drug Review* (2015), 37(5):86.

¹⁹ M Pharmaceutical Inc. [Internet]. The mosquito [2015; cited 9 Dec 2016]. Available from: <http://m-pharma.ca/mosquito>.

²⁰ Harman-Boehm I, Gal A, Raykhman AM, et al. Noninvasive glucose monitoring: a novel approach. *J Diabetes Sci Technol.* (2009), 3:253–260.

²¹ Groenendaal W, von Basum G, Schmidt KA, et al. Quantifying the composition of human skin for glucose sensor development. *J Diabetes Sci Technol.* (2010), 4:1032–1040.

²² Koschinsky T, Jungheim K, Heinemann L. Glucose sensors and the alternate site testing-like phenomenon: relationship between rapid blood glucose changes and glucose sensor signals. *Diabetes Technol Ther.* (2003), 5:829–842.

²³ Lin T, Mayzel Y, Bahartan K. The accuracy of a non-invasive glucose monitoring device does not depend on clinical characteristics of people with type 2 diabetes mellitus. *J Drug Assess* (2018), 7(1):1-7.

was comparable for people with different clinical characteristics, indicating that it is suitable for different people with type 2 diabetes²⁴.

What is more, scientists from Hong Kong Polytechnic University in China have created an accessible biosensor that measures glucose in human saliva for common use²⁵. 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 real concentrations²⁶.

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 breath²⁷. 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 diabetes²⁸. 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 into the skin²⁹. Such approach was definitely beneficial especially for young students. 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 levels³⁰.

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 measurements³¹.

²⁴ Bahartan K, Horman K, Gal A, et al. Assessing the performance of a non-invasive glucose monitor in people with type 2 diabetes with different demographic profiles. *J Diabetes Res.* (2017):4393497: 8.

²⁵ The Hong Kong Polytechnic University. "Highly sensitive biosensor for measuring glucose in saliva." *ScienceDaily.* www.sciencedaily.com/releases/2016/04/160406075341.htm (accessed August 21, 2019).

²⁶ Jia Y, Sun H, Li X, Sun D, Hu T, Xiang N, Ni Z. Paper-based graphene oxide biosensor coupled with smartphone for the quantification of glucose in oral fluid. *Biomed_Microdevices.* (2018) 12;20(4):89.

²⁷ medGadget [Internet]. Printed sensors evaluated for glucose measurement in exhaled breath [22 Jan 2016; cited 12 Dec 2016]

²⁸ Faulkner S. Handheld breathalyzer as noninvasive blood glucose monitor in development. *Drug Delivery Business* (2016), available at: <https://www.drugdeliverybusiness.com/handheld-breathalyzer-noninvasive-blood-glucose-monitor-development>.

²⁹ John C. Pickup, B.M., D.Phil., Faaizah Khan, Ph.D., Zheng-Liang Zhi, Ph.D., Jonathan Coulter, M.Chem, and David J. S. Birch, Ph.D. Fluorescence Intensity- and Lifetime-Based Glucose Sensing Using Glucose/Galactose-Binding Protein (2013) 7(1): 62-71.

³⁰ Heo YJ, Takeuhi S. Towards smart tattoos: implantable biosensors for continuous glucose monitoring. *Adv Healthc Mater.* (2013), 2(1):43-56.

³¹ Zarkogianni K, Litsa E, Mitsis K, Wu P-Y, Kaddi CD, Cheng C-W, et al. A review of emerging technologies for the management of diabetes mellitus. *IEEE Transactions on Biomedical Engineering* (2015), 62(12):2735-2749.

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 treatment. Despite the development of pharmacotherapy and a significant emphasis on patient education, the problem of nephropathy will develop in a group of 9-40% of patients, and retinopathy will cover 98% of them 15 years after the onset of the disease³². 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 centers³³. The most common method of surgery is transplantation of the pancreas with the kidneys of the donor (simultaneous pancreas-kidney (SPK))³⁴. 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 normoglycemia, but also prevents hypoglycemia³⁵. The improvement of these parameters occurs in a short period of time, which contributes to a significant 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 on the basis of improving renal parameters. 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 day³⁶. A decrease was also recorded for clearance - from 108 +/- 20 ml / min to 1.73 m² to 74 +/- 14 ml / min to 1.73 m²³⁷. 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 operation³⁸. Donor pancreas is isolated according to the Ricordi method of controlled digestion of the pancreas using a dissociative apparatus. The next step involves cleaning of the islets and that allows completing the amount of usage downloaded. Unfortunately, such procedure creates a potential risk of embolism during the transplantation. The step before the procedure is breeding, which allows the collection of tissues and their regeneration after completion. Isolated pancreatic islets are transplanted through the portal vein of the recipient under ultrasound control³⁹.

³² 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>

³³ Bruni A, Gala-Lopez B, Pepper AR, Abualhassan NS, Shapiro J. Islet cell transplantation for the treatment of type 1 diabetes: recent advances and future challenges. *Diabetes Metab Syndr Obes.* (2014), 7: 211–223.

³⁴ Chian JL, Kirkman MS, Laffel L, Peters AL. Type 1 Diabetes Through the Life Span: A Position Statement of the American Diabetes Association. *Diabetes Care* (2014), 37(7): 2034-2054.

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³⁶ Fioretto P1, Steffes MW, Sutherland DE, Goetz FC, Mauer M. Reversal of lesions of diabetic nephropathy after pancreas transplantation. *N Engl J Med.* (1998), 9; 339(2):69-75.

³⁷ Fioretto P1, Steffes MW, Sutherland DE, Goetz FC, Mauer M. Reversal of lesions of diabetic nephropathy after pancreas transplantation. *N Engl J Med.* (1998), 9; 339(2):69-75.

³⁸ Shapiro J, Lakey J, Ryan EA, Korbitt GS, Toth E, Warnock GL, Kneteman NM, Rajotte RV. Islet Transplantation in Seven Patients with Type 1 Diabetes Mellitus Using a Glucocorticoid-Free Immunosuppressive Regimen. *N Engl J Med* (2000) 343:230-238.

³⁹ Nogucchi H. Pancreatic islet transplantation. *World J Gastrointest Surg.* (2009) 30; 1(1): 16–20.

Artificial pancreas

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 automation that not only monitors blood glucose levels, but also counteracts hypoglycemia. The mechanism of 'artificial pancreas' is based on insulin injection that follows too high glucose result detection. 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 hypoglycemia⁴⁰. 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 attacks of hypoglycemia in this group⁴¹. 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 types⁴².

Patient-doctor contact

Mobile applications in the doctor-patient relationship play an increasingly important role. There are many glucose meters on the market connecting 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 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

⁴⁰ Weinzimer SA, Steil GM, Swan KL, Dziura J, Kurtz N, Tamborlane WV. Fully Automated Closed-Loop Insulin Delivery Versus Semiautomated Hybrid Control in Pediatric Patients With Type 1 Diabetes Using an Artificial Pancreas. *Diabetes Care* (2008), 31(5): 934-939.

⁴¹ Monika Reddy et al., Metabolic Control With the Bio-inspired Artificial Pancreas in Adults With Type 1 Diabetes: A 24-Hour Randomized Controlled Crossover Study. *Journal of Diabetes Science and Technology* (2016), 10(2): 405–413.

⁴² Jun Y, Kang AR, Lee JS, Jeong GS, Ju J, Lee DY, Lee S. 3D co-culturing model of primary pancreatic islets and hepatocytes in hybrid spheroid to overcome pancreatic cell shortage. *Biomaterials* (2013) 34(15): 3784-3794.

motivation for physical effort. They help in starting physical activity, as well as in maintaining regular workouts⁴³.

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 perfect device will appear. It will not require wearing an injection or insulin pump on the strap that undoubtedly will improve the comfort of people with diabetes. 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 Harari⁴⁴, 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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