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Porous TiNi-based material and infrared radiation in needle-free treatment of diabetic patients

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ABSTRACT

Despite the prescribed benefits of insulin widely used in treating diabetes, patients still feel the inconvenience and perceived pain related to multiple daily administrations by needle insulin injections. Approved inhaled insulin of the second generation has not so far achieved expectations. Design of needle-free delivery systems for insulin is an active area of research and this paper reports on the development of a new needle-free approach to deliver insulin treating diabetes. Porous TiNi-based alloys serve as high-density materials being capable of holding insulin solutions within the structure of the material, and infrared radiation promotes the directional diffusion of insulin from the TiNi porous structure into the skin. Taking these two facts into account, the needle-free device (NFD) for delivering insulin uses a new porous-permeable TiNi-based material and a novel infrared radiation mediated delivery system. The NFD described causes no skin irritation or lesions and is safe to use in practice. Its efficiency in delivering insulin was clinically assessed on 42 diabetic patients. The results show promising prospects as a new technology for delivering insulin and other liquid drugs. Copyright © 2016 VBRI Press.

Keywords: Diabetes; porous TiNi-based material; infrared radiation; insulin.

Introduction

Numerous studies have demonstrated a large prevalence and a steady increase in the incidence of diabetes mellitus, regardless of age, gender, and ethnicity.

The primary goal in the treatment of diabetes mellitus is to reduce the high blood glucose level to near normal, wherein intensive insulin regimens help achieve this goal. In healthy people diurnal insulin secretion has a discrete pattern that occurs in response to elevated blood glucose levels and adds to the basal insulin release from the pancreas. Administering long-acting insulin simulates basal insulin secretion, and the administration of short-acting insulin 30 min before a meal leads to an additional peak in blood insulin levels that coincides with the hyperglycaemia seen after a meal. Currently, a common method of treatment involves percutaneous injection of insulin which is associated with mechanical trauma, pain, aseptic problems, and psychological discomfort. Besides, allergic reactions occur both at the injection site due to high concentration of the drug and there is an ever present risk of hypoglycaemia [**1–4**].

At present, there is a great interest in the development of new methods of insulin delivery that can provide a sustained effect. This will relieve the patients from frequent injections of short-acting insulin (up to 3–4 times a day), which are associated with a negative emotional response to pain and problems in complying with necessary aseptic and antiseptic conditions. The development of non-injection methods of insulin delivery in humans is one of the solutions to this problem. Presently, new methods of oral and inhalation insulin delivery and even pancreas transplantation are being actively developed, but these are not effective enough and are not widely used [**5**].

There are methods and devices that permit needle-free mechanical administration of insulin, for example, an insulin solution jet injected subcutaneously at a high rate allows the liquid flow to diffuse (punch) through the skin. However, this method not only requires expensive and complicated equipment, but is also, in principle, not very different from the conventional method of injection with a needle [**5–7**].

As exclusion the need during insulin administration will significantly increase the comfort of the procedure, new transdermal (percutaneous) therapeutic systems, based on the diffusion of insulin solution through the skin, are being considered as promising alternatives. Diffusion of liquids can occur through a large surface area of contact, typically tens of square centimetres of skin, without any mechanical damage. The main obstacle is the stratum corneum, which has a low-permeability for large molecules, including insulin which contains more than 6000 atoms. Thus, to create channels or micropores in the stratum corneum, various physical methods like ultrasound treatment, laser radiation, and electric and radiofrequency treatment have been applied. To facilitate diffusion, insulin molecules are packed into liposomal capsules with enhanced penetration ability.

A method of needle-free administration of insulin utilising a new generation of porous alloys based on TiNi and infrared

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(IR) radiation is considered to be most promising [**8–10**]. The development of powder metallurgy technology and self-propagating high-temperature synthesis (SHS) in the combustion mode has enabled the creation of a new class of structurally complex, highly-permeable, porous TiNi-based biomaterials for cell tissue engineering and clinical practice (**Fig. 1**) [**11, 12, 13**]. The SHS has been successful in producing porous specimens with porosity counts as high as 65%. The SHS TiNi-based materials can hold liquid media in their porous space, including an insulin solution. A combination of both capillary action and diffusion, and the use of IR-radiation, facilitate a targeted release of the liquid from the pores into the tissue.

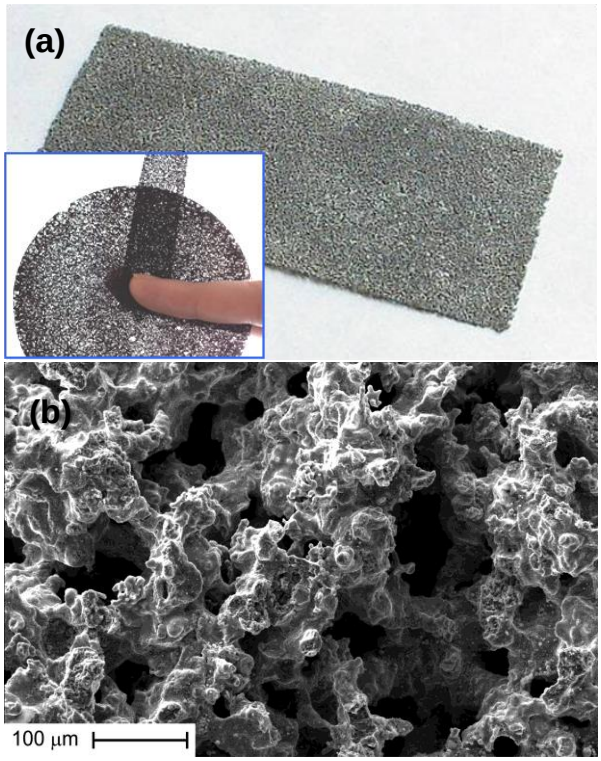

Fig. 1. High permeable porous TiNi-based SHS material: (a) porous plate and disc; (b) SEM image of the structure.

The objective of the work is to present the developed NFD comprising porous TiNi plate for needle-free administration of insulin, and to carry out clinical study how the device was successfully tested in 42 diabetic patients. The obtained data are believed to be used in the following diabetic treating studies.

Experimental

The SHS causes the solids to dissolve by introducing a liquid phase to promote the kinetics of mass transfer. Due to the exothermic reaction of Ni with Ti, the process was initiated by a thermal explosion ignited at one end of the charge, which then propagates through the charge in a self-sustaining manner [**14, 15, 16**]. In the study, body of porous TiNi-based alloy was fabricated by SHS method using the following powders: Ti – PTM or PTOM and Ni – PNK-10T2 or PNK–1L5 (Russian brand/classification), in a purified argon atmosphere at the initial SHS temperature varying within 400-500 °C. The effect of processing variables such as the kind of starting powders, ignition temperature and preheating schedule on the behavior of combustion wave propagation, the formation of phases and pore structure was taken into consideration. Since the success of SHS is greatly dependent on the shape of the canister for a thorough reaction to occur, we used a quartz cylinder sleeve (55 mm inner diameter) having the dead end, as prescribed in [**16**]. Depending on the mentioned factors, the produced porous body can have different min and max pore size, pore size distribution as well as, most importantly, different surface condition of pore space surface – topography of pore walls, phase and chemical structure.

Macrostructure of the produced porous TiNi body represents the 3D pore cluster, which morphologically is typical to highly porous materials obtained through the eutectic reaction. It has a large specific surface due to open and interconnected pores. The porosity was 75%, disordered porous structure with pore size distribution – within 40–900 μm, and the mean pore size – 150 μm see **Fig. 1(b)**. The plate (45×30×0.7 mm) of porous TiNi-based body for the IR NFD was prepared by electric-discharge wire-cut.

The scheme of the NFD designed for insulin delivery is shown (**Fig. 2**). The essence of the original NFD is to convert electrical energy into the heat flow what occurs in the porous TiNi plate, also serving as the insulin depot, by means of the IR radiation providing thermal effect.

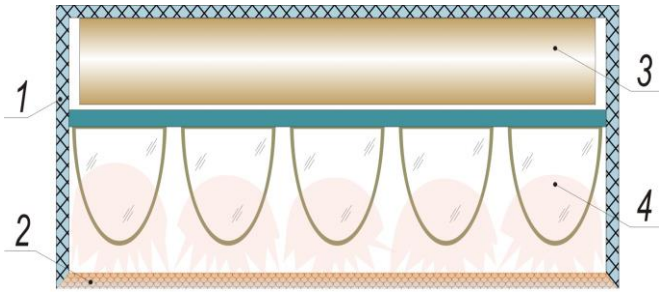

Fig. 2. Outline of the NFD: *1* – body, *2* – detachable porous TiNi plate, *3* – emitting IR LEDs; *4* – rechargable battery and controller.

Dimensions of the current NFD sample (45×30×16 mm) were empirically determined by both the mean wrist' size and the installed Li-ion rechargeable battery (840 mA, 5V). The NFD can be used repeatedly, and in order to provide charging when using, the mini-USB cable is included that connects to the PC USB port or the wall/travel charger. On the side, there is the power button with the LED indicator and mini-USB port. The NFD uses a "Kingbrig" type L-53SF6C LEDs (6 pcs) as the IR-radiation source (wavelength λ = 920 nm, power consumption – 120 mW). A total weight of the NFD is 51 gr and it looks like a wrist watch attached by a leather strap.

For the next procedure, one needs to impregnate and administrate the insulin solution. Such a kind of action can be in outpatient care that greatly simplifies the use of the NFD. The following steps are to be implemented to operate the device. The battery should be fully charged and the porous operating element should be saturated with insulin solution, and then this plate is set in the housing groove such that it forms one of the surfaces of the NFD. The device is then applied such that the porous plate rests on the skin, and is fastened in this position. The power button is switched on.

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The time dependence of the NDF' heating dynamics during operation was drawn (**Fig. 3**). As seen, in 5 min after start the temperature reaches saturation not exceeding 45 °C and from the moment, the therapeutic effect takes place.

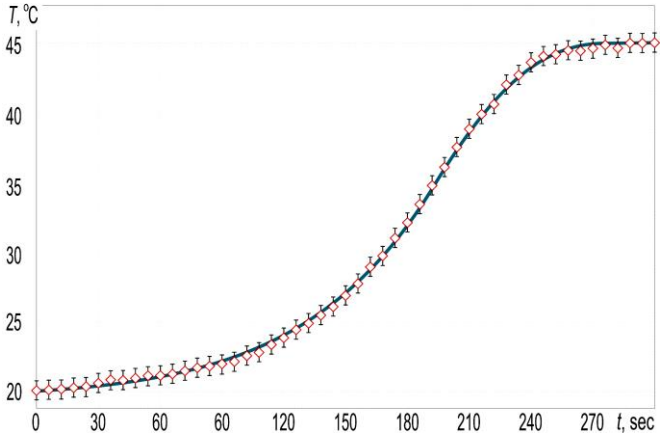

Fig. 3. Timeline measured temperature change and saturation of the interface during the NFD operation.

The NFD is applied in the thinnest skin area with easy access, such as in the elbow or the wrist (see **Fig. 4**). The duration of NFD' application is 30–120 min, that was determined based on the changes observed in blood glucose levels upon using the device.

Fig. 4. Original NDF appearance: (a) general view and modifications; (b) practical use.

In order to test the efficacy of the NFD, a study was evaluated on 42 diabetic patients. The study was fully conducted in accordance with the Declaration of Helsinki, its protocol was approved by the Ethical Committee of the Siberian State Medical University, and informed consent was obtained from all patients before the inclusion in the study. At this point, a group of patients with varied initial high blood glucose level have participated in this study on the use of the NFD.

Inclusion criteria were:

- Age between 18 and 80
- Type 1 or 2 diabetes
- LDL-cholesterol level between 130 and 190 mg/dl
- Body mass index value between 25 and 30 kg/m^2
- Triglycerides level between 150 and 400 mg/dl
- Fasting plasma glucose level under 125 mg/dl.

Exclusion criteria were:

- concomitant cancer pathology
- inconstant or not-stabilized assumption of drugs which may interfere with lipid or glucose metabolism
- chronic gastrointestinal diseases and assumption of drugs for their treatment
- known thyroid, liver, renal or muscle diseases
- known allergy or intolerance to insulin
- any medical or surgical condition which could lead to an inconstant adhesion to the protocol.

Personal data, history and pharmaceutical anamnesis of each patient were inquired at the beginning of the trial. Anthropometrical parameters were collected at the beginning together with hemodynamic and biochemical parameters. Hemodynamic parameters were collected measuring orthostatic and clinostatic systolic and diastolic blood pressure. Also orthostatic and clinostatic wrist blood pressure and cardiac frequency were collected. Blood glucose level was determined using an Accu-Chek Active glucose meter with test strips 393 and 436. The device was calibrated in accordance with the user manual. In parallel, at each measurement, blood glucose level was verified on a visual glycaemic scale presented on the package of the test strips.

Glucose measurements were made at baseline, and at 30, 60 min after the device was attached to the wrist (**Fig. 5**). Normal food load and motor activity of the patients were continued and the patients were asked to discontinue the previous glucose-lowering therapy (insulin or drugs).

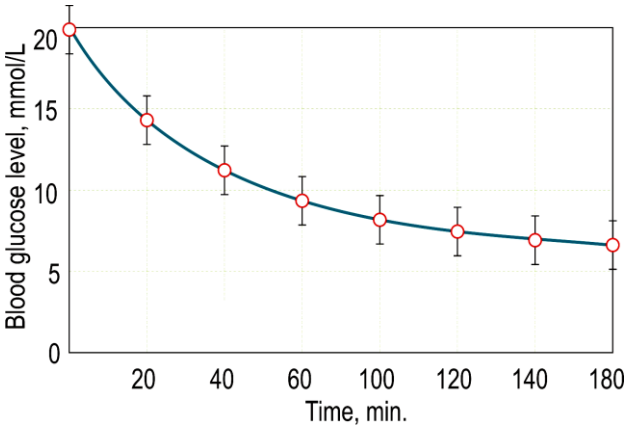

Fig. 5. Typical timeline dependence of the blood glucose level during the NFD operation.

10 units of short-acting insulin (2 types of insulin – Actrapid® HM and Rinosulin® NPH) were applied to the surface of the device such that it was evenly distributed over the porous plate. Data have been analysed by mean of the Statistical 5.0 for Windows.

Results and discussion

Studies on the interaction of TiNi-based alloys with various body fluids have shown that these alloys are effective and capacitive medical materials [**15**]. Conducive physical and mechanical properties of TiNi-based alloys, the possibility of producing porous construction elements based on them along

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with high intensity of heat transfer and low thermal conductivity make it possible to create effective high-capacity devices for needle-free delivery of insulin into the body using these alloys. The development of such devices also depends on the source of IR-radiation to control diffusion of the solution.

Given that these elements have a porosity of 60-70 %, more than half of the volume of the capacitive construction element can be filled with an insulin solution. The process of diffusion from the porous TiNi matrix depends on many factors such as viscosity, specific gravity, density, TiNi permeability, pore size, pore length, surface area in contact with the external environment, and temperature of the porous body, among others. The dependence between the rate of change of fluid volume in the TiNi porous structure and the basic parameters of solution diffusion is presented by the following equation [**15, 17, 18**]:

$$\Delta Q = k \cdot \frac{V_0 \cdot \rho \cdot g \cdot \Delta h \cdot S \cdot P \cdot \Delta T}{\mu \cdot L} \qquad (1)$$

where, ΔQ – the rate of fluid diffusion from porous TiNi; k – diffusion coefficient; ΔT – the temperature gradient of the porous material; μ – liquid viscosity; p – liquid density; V_0 – the initial volume of the liquid in the porous material; S – the area of the contact between the surface pores of the sample and the tissues; Δh – the level of the liquid in the porous material; L – the average length of the sample pores; P – porosity; g – acceleration of gravity.

The temperature parameter, ΔT (temperature gradient), in the equation can be changed using infrared radiation, and depending on the power, wavelength, and its duration of action adjustments can be made to the rate of diffusion of the solution [**5**].

IR-radiation of wavelength in the range of 880-1200 nm has a strong thermal effect that leads to the release of thermal receptors in the skin, mucous membranes, cornea; and in the hypothalamus and the spinal cord of the central nervous system. These rays penetrate body tissue to a depth of 2-4 cm. The depth of penetration depends not only on wavelength, but also on moisture of the skin, its blood supply, degree of pigmentation and other individual factors.

The use of this device leads to a steady decrease in blood glucose levels in the first 30 min followed by gradual deceleration in the next 30 min. A steady-state level is at the mean reached in 120 min (**Fig. 5**).

Our observations also suggested that a significant effect does not occur before the first 30 min, and that the maximum effect is reached at not later than 120 min. Thus, the duration of exposure was set as between 30 and 120 min.

Thermophoresis is the main physical factor that stimulates the diffusion of insulin solution into the subcutaneous layer. The heating of the skin that is in contact with the heated and moisturised surface of the porous plate (heated by IR-radiation and saturated with insulin solution) causes swelling of the skin which then promotes diffusion of the insulin solution into the tissue. Experimental studies have shown that effective diffusion requires three factors: a temperature gradient in the area of contact between insulin and the skin, heating of the adjacent skin, and the direct effect of IR radiation on the inner skin layer(s). The presence of these factors leads to the targeted percutaneous diffusion of insulin, allowing a good therapeutic effect.

A temperature gradient is established in the liquid insulin solution contained within the porous plate, activated by IR-radiation on pore walls/intersections, and, actually, also on the liquid insulin solution in the pores. A partial absorption of the IR radiation by the plate surface creates the necessary temperature gradient, as heat transfer from the opposite surface that is in contact with the skin is regulated by the body itself by controlling blood flow to the area. This temperature gradient creates a driving force for insulin transfer from an area of higher temperature to an area of lower temperature. Under the driving force of the temperature gradient, targeted transfer of molecules into the skin occurs and is characterised by the presence of an excess pressure distributed over the surface area of contact between the porous plate and the skin. Importantly, even a “slight increase” in the temperature of the porous TiNi containing insulin is sufficient to activate diffusion and the release of insulin from the surface of the material into the tissue in contact. The time dependence of heating dynamics during the NFD operation obviously shows and explains more detailed the term “slight increase”, so far as the term concerns the difference between the current NFD’ temperature compared to the wrist’ one.

The second factor, heating of the surface layer of the skin, is provided by the warm layer of the metal porous plate (heated by IR-radiation) adjacent to the skin. An increase in the temperature of the skin in the area in contact with the plate saturated with insulin solution occurs due to contact with the liquid, leading to swelling of the skin and an increase in tissue permeability. Insulin that diffuses from the surface of the porous TiNi into the tissue is continuously replenished from the internal pores by wetting and capillary action. The rate of insulin removal is determined by the liquid concentration gradient at the interface and ability of the skin to absorption. Moreover, we took into consideration some studies, which suggested that heating the insulin may accelerate insulin absorption by locally warming the infusion [**19**]. The third factor, i.e. the direct effect of IR-radiation on tissues, is the ability of an optical spectrum (with LED wavelength λ = 920 nm) to penetrate through the skin and into the tissues to a depth of 3-4 mm. A plate thickness of 0.2–1 mm and a pore size of 10–500 μm provide partial transparency to the direct effect of infrared radiation on the skin and the inner layer of the tissue.

Signals from activated thermal receptors enter the thermoregulatory centres located in the hypothalamus and the spinal cord, and resultant thermoregulatory reactions lead to vasodilatation of the skin, a localised increase in blood volume, and an increase in sweating. Neuro-reflex reactions also occur as a result of infrared radiation on the reflective zones of skin segments that are directly associated with the internal organs. All of these result in the production of bioactive substances such as bradykinin and kallidin that play an important role in the humoral regulation of local and systemic circulation. For instance, bradykinin has a strong vasodilating effect, which can be observed locally and systemically.

Irradiation with small and medium doses of infrared rays enhances metabolism, cell proliferation and enzymatic reactions, apart from stimulating regenerative processes. IR-

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radiation sharply accelerates the process of liquid transfer from the porous TiNi to the tissue surface, as, firstly, on a wet surface, heat flow leads to the formation of a temperature gradient at the boundary layer, and, secondly, because tissue vasodilatation occurs as IR-radiation passing through the interporous cavities of the porous TiNi plate lead to accelerated diffusion of insulin into the adjacent tissue.

LEDs for IR-radiation are small in size and provide a high degree of light output. A set of IR LEDs enable easy to control over the flow of radiation (by selecting the level of current required for LED' power supply). The level of radiation obtained is far below the threshold for thermomechanical damage to the stratum corneum of the skin, and it is possible to adjust and evaluate the heating mode to ensure the efficient power supply.

The working part of the NFD, the porous TiNi plate, can be used repeatedly, and reuse only requires ordinary sanitation and re-impregnation with a solution of insulin. As this can be carried out in outpatient care or at home, it facilitates the use of the NFD.

Table 1. Change of blood glucose level in experimental group, mmol/l

Case#	Baseline	In 30 min	In 60 min	Case#	Baseline	In 30 min	In 60 min
1	17.3	12.8	9.9	22	14.7	10.9	7.7
2	19.6	11.7	9.2	23	15.6	11.0	7.4
3	16.7	12.6	9.1	24	18.2	13.2	8.5
4	18.6	11.2	8.8	25	17.9	12.6	7.6
5	16.1	10.6	7.9	22	14.7	10.9	7.7
6	16.3	11.0	8.7	27	17.5	12.5	8.4
7	17.4	10.8	8.6	28	14.8	8.4	6.6
8	15.2	9.5	7.2	29	18.1	13.2	8.9
9	16.2	11.9	8.0	30	16.0	11.1	7.3
10	19.4	13.9	9.5	31	17.7	12.5	7.8
11	15.2	10.5	6.9	32	15.9	9.4	6.5
12	18.1	12.3	7.6	33	18.4	12.9	8.7
13	16.4	11.6	7.4	34	20.8	14.7	9.9
14	15.5	10.2	6.3	35	18.3	12.2	7.3
15	17.7	12.0	8.8	36	14.9	9.8	6.8
16	19.8	14.9	10.4	37	19.1	14.1	10.2
17	14.7	8.6	6.7	38	17.5	12.0	7.4
18	17.5	13.1	8.4	39	15.7	11.5	7.1
19	14.3	10.7	7.9	40	18.3	13.4	8.4
20	18.0	14.6	9.5	41	15.8	10.2	6.5
21	16.4	12.8	8.6	42	17.2	12.8	7.9

All 42 patients were included in the study to evaluate the efficiency of the NFD (Table 1). Average blood glucose in the experimental group was 17.11 mmol/L at baseline, 11.92 mmol/L in 30 min, and 8.16 mmol/L in 60 min. The average reduction in blood glucose level from baseline was 56% and no adverse effects were observed in any of the studied cases.

Clinical case #1. Patient M, 70-year old, case record #A1016, admitted to the Hospital of the Siberian State Medical University on 05-Mar-2014. DS: Type II diabetes requiring insulin, severe decompensation. Diabetic foot syndrome: trophic ulcer of the IV finger of the left foot. Basic treatment: Siofor 850 – b.i.d., NovoMix 20U-16U. The NFD was tested according to the proposed technique on 11-Mar-2014 at 5:00 p.m., and blood glucose levels are as follows: Baseline – 17.3 mmol/L; 30 min – 12.8 mmol/L; 60 min – 9.9 mmol/L. After normalisation of the blood glucose level (**Fig. 6**), corresponding general and local treatment was provided, the ulcer healed and the patient was discharged to outpatient treatment on 27-Mar-2012. Blood glucose level at discharge was 5.3 mmol/L.

Clinical case #2. Patient E. aged 53 years. Case record #A1263, admitted to the Hospital of the Siberian State Medical University on 24-Apr-2014. Diabetes mellitus diagnosed 6 years ago during targeted determination of blood glucose level given a history of thirst and polyuria and taking into account family history. For a long period of time, the patient was receiving various combinations of metformin and sulfonylurea before admission to the Hospital of the Siberian State Medical University.

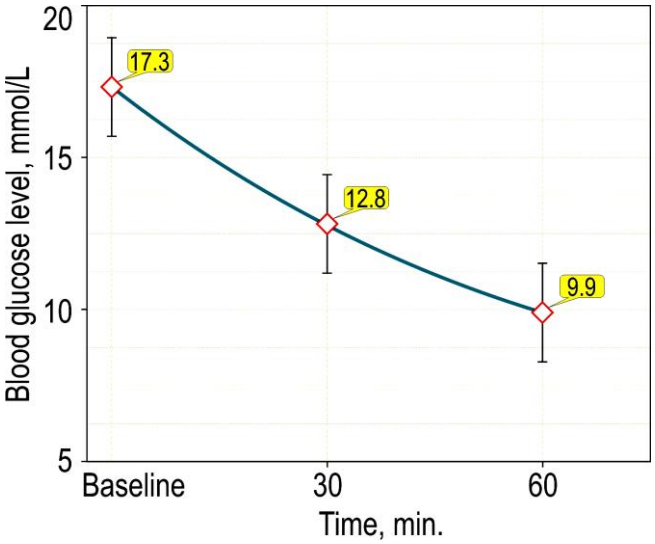

Fig. 6. Timeline blood glucose level of patient M. during the NFD operation.

Testing of the device in accordance with the proposed method was performed on 29-Apr-2014 at 5:00 p.m., and blood glucose levels were as follows: Baseline – 19.6 mmol/L; 30 min – 11.7 mmol/L; 60 min – 9.2 mmol/L. A positive result, in the form of a gradual reduction in blood glucose and associated side effects, was clearly observed upon using this device (**Fig. 7**), and it was decided to continue the use of the selected treatment for the subsequent glycaemic control.

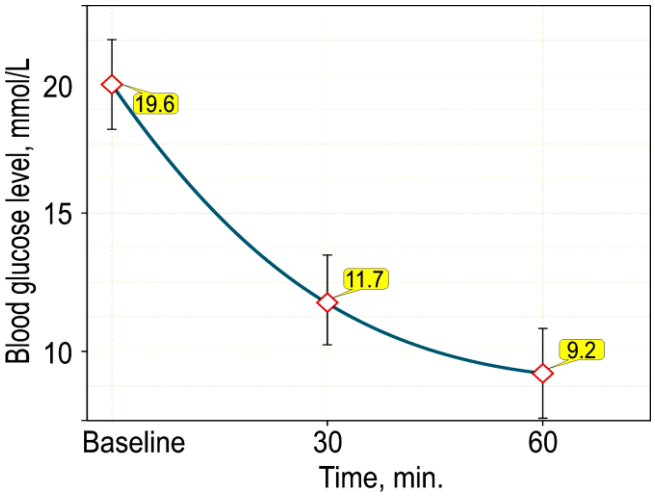

Fig. 7. Timeline blood glucose level of patient E. during the NFD operation

The blood glucose level at discharge on 05-May-2014 was 6.5 mmol/L. The said cases obviously demonstrate the efficiency of transdermal insulin administration as well as the NDF used for implementation, thus validating both a new

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method and the newly developed device. This method can be successfully used in wide medical practice with appropriate adaptation to other drugs.

Conclusion

The primary goal in the treatment of diabetes mellitus is to reduce blood glucose to near normal levels. Various modes of insulin administration that simulate the natural dynamics of insulin secretion have been used. We took into consideration, confirmed and agreed with some studies, which suggested that heating the infusion site may accelerate insulin absorption by locally warming. Administration of long-acting insulin "simulates" basal insulin secretion, while the administration of short-acting insulin 30 min before a meal results in an additional peak in insulin levels that coincide with the hyperglycaemia after the meal. This study has shown that applying local heat to skin by the NFD has a beneficial effect on insulin absorption without increasing the risk of hypoglycemia. The increase in temperature at the site had no impact on the subjects' well-being; nevertheless, it was powerful enough to enhance insulin administration. The significance and role of individual factors, such as meal composition or time of day, should be investigated in future studies. Local heating by the NFD is a step towards closing the loop, because overall insulin delivery is enhanced. This would allow patients to be less affected by the restrictions of diabetes therapy in daily life. The NFD described causes no skin irritation or lesions and is safe to use in practice. Its efficiency in delivering insulin was clinically assessed on 42 diabetic patients. The results show promising prospects as a new technology for delivering insulin and other liquid drugs. Thus, the use of IR-radiation and the porous-permeable SHS TiNi alloy, as reported here, provide an opportunity for the development of new NFDs.

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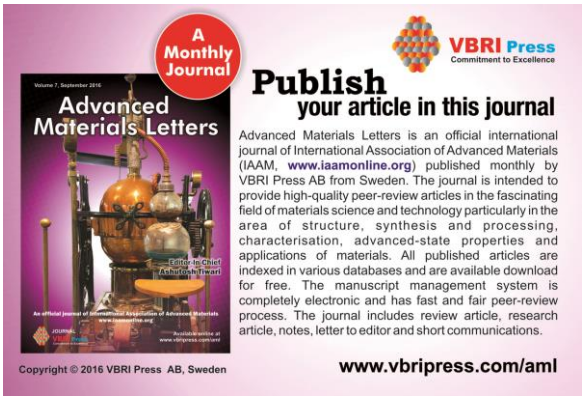
References

1. Watkins, P.J. ABC of Diabetes. 5th ed. London: Blackwell Publishing. **2003**.
ISBN: 0-7279-16939
2. Holt, T.; Kumar, S. ABC of diabetes. 6th ed. Oxford: Wiley-Blackwell. **2010**.
ISBN: 978-1-4051-7784-9
3. Owens, D.R.; *Nat Rev Drug Discov*., **2002**, 1, 529.
DOI: 10.1038/nrd836
4. Brook, C.G.; Dattani, M.T. Handbook of Clinical Pediatric Endocrinology. 2nd ed. Wiley Blackwel. **2012**.
ISBN: 978-0-4706-5788-1
5. Gunther, S.V.; Dambaev, G.Ts.; Starchenkov, D.D. *Patent RF* RU2534521. **2012**.
6. Bergenstal, R.M.; Strock, E.S.; Peremislov, D.; et al.; *Mayo Clin Proc*., **2015**, 90, 329.
DOI: 10.1016/j.mayocp.2014.12.014
7. Aronson, R.; Gibney, M.A.; Oza, K. et al. ; *Clin Ther*., **2013**, 35, 923.
DOI: 10.1016/j.clinthera.2013.05.020
8. Henkin, R.I.; *Nutrition*., **2010**, 26, 33.
DOI: 10.1016/j.nut.2009.08.001
9. Khafagy, el-S.; Morishita, M.; Onuki, Y.; Takayama, K.; *Adv Drug Deliv Rev*., **2007**, 59, 1521.
DOI: 10.1016/j.addr.2007.08.019
10. Lepore, G.; Tommaselli, L.; *Front Diabetes*., **2015**, 24, 128
DOI: 10.1159/000363486
11. Kokorev, O.V.; Hodorenko, V.N.; Chekalkin T.L.; et al.; *Artif Cells Nanomed Biotechnol*., **2016**, 44, 704.
DOI: 10.3109/21691401.2014.982799
12. Muhamedov, M.; Kulbakin, D.; Gunther, V. et al.; *J. Surg. Oncol.*, **2015**, *111*, 231.
DOI: 10.1002/jso.23779
13. Gunther, S.; Kokorev, O.; Chekalkin, T.; et al. ; *Adv. Mater. Lett.*, **2015**, 6*(9)*, 774
DOI: 10.5185/amlett.2015.5882
14. Anikeev, S.G.; Khodorenko, V.N.; Kokorev, O.V.; Chekalkin, T.L. ; *Adv Mater Res*., **2015**, 1085, 430.
DOI: 10.4028/www.scientific.net/AMR.1085.430
15. Gyunter, V.E. ; Khodorenko, V.N. ; Monogenov, A.N. ; Yasenchuk, Yu.F.; *Tech Phys Lett*., **2000**, 26, 320.
DOI: 10.1134/1.1262830
16. Kim, J.S.; Kang, J.H.; Kang, S.B.; et al. ; *Adv. Eng. Mater.*, **2004**, 6, 403.
DOI: 10.1002/adem.200405151
17. Gunther, V.E., Hodorenko, V.N., Chekalkin TL et al. Medical materials and shape memory implants: In 14 vol. / Shape memory medical materials. Tomsk: MIC; **2011**, 1.
ISBN: 978-5-9858-9044-0
18. Yasenchuk, Yu.F.; Artyukhova, N.V.; Novikov, V.A.; Gyunter, V.E.; *Tech Phys Lett*., **2014**, 40, 697.
DOI: 10.1134/S1063785014080276
19. Raz, I.; Weiss, R.; Yegorchikov, Y.; et al.; *Clin Ther*., **2009**, 31(5), 980
DOI: 10.1016/j.clinthera.2009.05.010.



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