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(54) **Title:** DEVICE SYSTEM AND METHOD FOR MONITORING AND CONTROLLING BLOOD ANALYTE LEVELS

(57) **Abstract:** A device and system for monitoring an analyte in a subject and for controlling blood analyte levels are provided. The device and system include a sensor element which is designed and configured for detecting the analyte in blood flowing through the bone of the subject.

DEVICE SYSTEM AND METHOD FOR MONITORING AND CONTROLLING BLOOD ANALYTE LEVELS

FIELD AND BACKGROUND OF THE INVENTION

The present invention relates to an analyte monitoring device having a bone implanted analyte sensor and, more particularly, to a continuous glucose monitoring system having a bone implanted glucose sensor and infusion pump.

Although diabetes is a chronic condition, it can usually be managed by diet, medications and proper glucose control. The main goal of treatment is to keep blood glucose levels in the normal range. Monitoring blood glucose levels is the best way of managing diabetes. A healthcare provider will periodically order laboratory blood tests to determine the average blood glucose levels via tests such as hemoglobin A1C measurements. While The results of these tests gives an overall sense of how blood glucose levels are controlled daily functional control of blood glucose levels and treatment requires that patients monitor their own blood glucose levels frequently between six and ten times a day.

Numerous devices for home monitoring of glucose levels are known in the art. The most popular devices currently in use employ a lancet for pricking skin to draw a drop of blood and test strips which are read by an optical reader. Although such devices are accurate, they necessitate periodic skin pricking which may produce discomfort to the tested individual. In addition, such devices cannot provide continuous blood glucose monitoring which is important to diabetic individuals and are necessary for real time medicinal and dietetic adjustments to glucose levels

To overcome these problems, non-invasive monitoring devices or implantable continuous monitoring devices have been proposed.

Non-invasive glucose sensing is the ultimate goal of glucose monitoring, but the most investigated non-invasive approach utilizing near-infrared (NIR) spectroscopy, is presently too imprecise for clinical application (there is not even one single non invasive techniques in clinical use). Thus, non-invasive glucose monitors (e.g. GlucoWatch G2 Biographer, manufactured by Cygnus Inc.) require daily invasive measurements in order to be maintain calibration. In addition, since such devices tend to be less accurate than invasive glucose measurements, doctors recommend that periodic conventional blood glucose monitoring be used along with such devices.

To traverse the limitations of NIR glucose monitoring, interstitial fluids monitoring devices have been developed.

Percutaneous monitoring devices utilize iontophoresis to sample the interstitial fluid without breaking the skin surface. The accuracy of such devices is influenced by skin temperature and perspiration and as such use thereof for continuous glucose monitoring is limited.

Implanted monitoring devices typically employ a sensor which is implanted subcutaneously. Implantable glucose sensors typically utilize an amperometric enzyme probe or an optical probe which measure the level of glucose in the interstitial fluid surrounding the tissue every several seconds and relay the information via wires (e.g. Minimed™, Medtronics) or wirelessly (SMSI™ Glucose Sensor, Sensors for Medicine and Science) to a monitor which is carried by the user.

Continuous glucose monitoring devices provide information about the direction, magnitude, duration, frequency, and causes of fluctuations in blood glucose levels. Compared with non-implanted glucose monitors, continuous monitoring devices can provide more detail with respect to glucose trends and thus help identify and prevent unwanted periods of hypo- and hyperglycemia.

Although implanted monitors are more accurate than non-invasive monitors they suffer from several limitations. Since the body tries to isolate any implanted objects by tissue remodeling, glucose transport to the sensor can be reduced. In addition, the glucose levels in the interstitial fluid do not always accurately reflect blood glucose levels since several physiological factors might influence the interstitial glucose levels (Steil et al. Diabetes Techn and therape (5):1, 2003 and Schmidtke et al. Proc. Natl Acad Sci USA 95:294-9, 1998) and since glucose levels in the interstitial fluid can lag or lead blood glucose levels by several minutes. Such factors can severely limit the accuracy of implanted sensors and thus limit their use especially in cases where glucose monitoring is utilized for closing the loop on insulin delivery in systems for controlling glucose levels. Additionally, these devices involve the use of expensive cartridges which need to be replaced daily or every few days.

There it would be highly advantageous to have a device and system for monitoring and controlling glucose levels devoid of the above limitations.

SUMMARY OF THE INVENTION

According to one aspect of the present invention there is provided a device for monitoring a analyte in a subject comprising a sensor element being designed and configured for detecting the analyte in blood flowing through bone of the subject.

According to further features in preferred embodiments of the invention described below, the sensor element is designed and configured for implantation within bone tissue.

According to still further features in the described preferred embodiments the sensor element is designed and configured for implantation within cancellous tissue of the bone.

According to still further features in the described preferred embodiments the sensor element is designed and configured for implantation within periosteum tissue of the bone.

According to still further features in the described preferred embodiments the sensor element is designed and configured for implantation within compact bone tissue of the bone.

According to still further features in the described preferred embodiments the sensor element is designed and configured for implantation within Haversian canals (osteons).

According to still further features in the described preferred embodiments the device further comprises a power source for powering the sensor element.

According to still further features in the described preferred embodiments the device further comprises circuitry for remotely powering the sensor element.

According to still further features in the described preferred embodiments the analyte is selected from the group consisting of urea, ammonia, hydrogen ions, minerals, enzymes, and drugs.

According to still further features in the described preferred embodiments the analyte is glucose.

According to still further features in the described preferred embodiments the sensor element is an electrochemical or an optical sensor element.

According to still further features in the described preferred embodiments the sensor element includes a membrane selective for the analyte.

According to still further features in the described preferred embodiments the cage housing the sensor element includes non- osteoconductive material.

According to another aspect of the present invention there is provided a system for monitoring a analyte in a subject comprising a device including a sensor element being designed and configured for detecting the analyte in blood flowing through a bone of the subject and a control unit for controlling the device.

According to still further features in the described preferred embodiments the sensor element is designed and configured for implantation within bone tissue.

According to still further features in the described preferred embodiments the sensor element is designed and configured for implantation within cancellous tissue of the bone.

According to still further features in the described preferred embodiments the sensor element is designed and configured for implantation within periosteum tissue of the bone.

According to still further features in the described preferred embodiments the sensor element is designed and configured for implantation within compact bone tissue of the bone.

According to still further features in the described preferred embodiments the sensor element is designed and configured for implantation within Haversian canals.

According to still further features in the described preferred embodiments the device and the control unit are designed for wireless communication.

According to still further features in the described preferred embodiments the wireless communication is mediated via magnetic, electromagnetic or acoustic energy.

According to still further features in the described preferred embodiments the device is wired to the control unit.

According to still further features in the described preferred embodiments the device includes a power supply.

According to still further features in the described preferred embodiments the device includes an induction coil.

According to still further features in the described preferred embodiments the analyte is selected from the group consisting of urea, ammonia, hydrogen ions, minerals, enzymes, and drugs.

According to still further features in the described preferred embodiments the analyte is glucose.

According to still further features in the described preferred embodiments the sensor element is an electrochemical or an optical sensor element.

According to still further features in the described preferred embodiments the sensor element includes a membrane selective for the analyte.

According to still further features in the described preferred embodiments the sensor element includes non-osteoconductive material.

According to yet another aspect of the present invention there is provided a method of monitoring a analyte in a subject comprising detecting the analyte in blood flowing through bone tissue of the subject thereby monitoring the analyte in the subject.

According to still further features in the described preferred embodiments detecting is effected by implanting an analyte sensor in a bone of the subject.

According to yet another aspect of the present invention there is provided a system for controlling blood glucose levels in a subject comprising: (a) a sensor element being designed and configured for detecting the analyte in blood flowing through a bone of the subject; and (b) a reservoir for providing to the blood flowing through the bone of the subject at least one composition capable of modifying a level of glucose.

According to still further features in the described preferred embodiments the sensor element is designed and configured for implantation within bone tissue.

According to still further features in the described preferred embodiments the reservoir is in fluid communication with a port/catheter attached to tissue of the bone.

According to still further features in the described preferred embodiments the system further comprises a mechanism for pumping the composition from the reservoir to the blood flowing through the bone.

According to still further features in the described preferred embodiments the system further comprises a power source for powering the sensor element and the mechanism.

According to still further features in the described preferred embodiments the mechanism utilizes peristalsis, a propellant, osmotic pressure, a piezoelectric element or an oscillating piston/rotating turbine.

According to still further features in the described preferred embodiments the sensor element is an electrochemical or an optical sensor element.

According to still further features in the described preferred embodiments the reservoir further includes a filling port.

According to still further features in the described preferred embodiments the reservoir is intracorporeal or extracorporeal.

According to still further features in the described preferred embodiments the at least one composition is insulin and/or glucagon.

The present invention successfully addresses the shortcomings of the presently known configurations by providing a system which enables real-time accurate monitoring and controlling of glucose levels.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. In case of conflict, the patent specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention is herein described, by way of example only, with reference to the accompanying drawings. With specific reference now to the drawings in detail, it is stressed that the particulars shown are by way of example and for purposes of illustrative discussion of the preferred embodiments of the present invention only, and are presented in the cause of providing what is believed to be the most useful and readily understood description of the principles and conceptual aspects of the invention. In this regard, no attempt is made to show structural details of the invention in more detail than is necessary for a fundamental understanding of the invention, the description taken with the drawings making apparent to those skilled in the art how the several forms of the invention may be embodied in practice.

In the drawings:

FIG. 1a is a drawing illustrating bone anatomy.

FIG. 1b illustrates the iliac crest bone.

FIG. 2a-b illustrate a system for continuous glucose monitoring constructed in accordance with the teachings of the present invention and implanted in an axial skeleton bone.

FIGs. 3a-b illustrate several embodiments of a system for controlling the level of glucose in a blood of a subject.

FIGs. 4a-c are graphs illustrating glucose levels in blood drawn from a vein or bone marrow of rabbits following administration of dextrose or insulin; Red line – vein blood, Blue line – bone derived blood.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention is of an analyte monitoring device and system which can be used to continuously monitor blood analyte levels and thus provide a monitored subject with data relating to real-time analyte levels, trends in analyte levels and the like.

The principles and operation of the present invention may be better understood with reference to the drawings and accompanying descriptions.

Before explaining at least one embodiment of the invention in detail, it is to be understood that the invention is not limited in its application to the details of construction and the arrangement of the components set forth in the following description and example or illustrated in the drawings. The invention is capable of other embodiments or of being practiced or carried out in various ways. Also, it is to be understood that the phraseology and terminology employed herein is for the purpose of description and should not be regarded as limiting.

Monitoring of glucose levels is the main goal of continuous analyte monitoring technologies. Although numerous attempts have been made to produce a reliable continuous glucose monitoring device, the reality is that at present day no implanted continuous monitoring device is commercially marketed as stand-alone solution.

Prior art implanted glucose monitors suffer from several limitations which result from the site of implantation. Subcutaneous implantation of glucose monitors can lead to implant encapsulation while accuracy of such devices is limited by the fact that ISF glucose levels sampled by such devices do not mirror those of blood. On the otherhand, while blood vessel coupled glucose monitors are more accurate, attachment thereof to blood vessels such as veins can lead to systemic infections, blood flow perturbations, clotting, generation of emboli, and tissue reactions to the implant.

While reducing the present invention to practice, the present inventors have devised an analyte sensor which directly monitors blood analyte levels and yet does not suffer from the limitations of blood vessel-coupled analyte sensors.

As is further detailed herein, the present device is designed and configured for detecting analytes within blood flowing through a bone tissue. Blood flow through bone marrow has been shown to be an accurate real time mirror of systemic blood measurements [Hurren JS, Burns. 2000 Dec;26(8):727-30; Ummenhofer et al Resuscitation. 1994 Mar;27(2):123-8) and Example 2 hereinbelow]. Bone-attachment of an analyte sensor minimizes the possibility of infection, migration or movement of the analyte sensor, tissue

reaction to the implant (encapsulation) and generation of emboli while enabling sampling of blood fluids with minimal flow perturbations.

Thus, according to one aspect of the present invention there is provided a device for monitoring an analyte in a subject.

The device of the present invention includes a sensor element(s) which is designed and configured for detecting the analyte in blood flowing through a bone of the subject.

The term "analyte," as used herein, refers to a substance or chemical constituent which is present in a biological fluid (e.g. blood) and can be monitored (e.g. quantified and/or qualified). Analytes can include naturally occurring substances, artificial substances, metabolites, and/or reaction products. Preferably, the analyte for monitoring by the device of the present invention is glucose. However, other analytes are contemplated as well, including but not limited to, PH, electrolytes, CO_2 and O^2, ammonia, acetone and beta-hydroxy-butyrate, acetoacetate, lactate, ascorbic acid, uric acid, dopamine, noradrenaline, 3-methoxytyramine (3MT), 3,4-Dihydroxyphenylacetic acid (DOPAC), Homovanillic acid (HVA), 5-Hydroxytryptamine (5HT), and 5-Hydroxyindoleacetic acid (FHIAA), acarboxyprothrombin; acylcamitine; adenine phosphoribosyl transferase; adenosine deaminase; albumin; alpha-fetoprotein; amino acid profiles (arginine (Krebs cycle), histidine/urocanic acid, homocysteine, phenylalanine/tyrosine, tryptophan); andrenostenedione; antipyrine; arabinitol enantiomers; arginase; benzoylecgonine (cocaine); biotinidase; biopterin; c-reactive protein; carbon dioxide; carnitine; camosinase; CD4; ceruloplasmin; chenodeoxycholic acid; chloroquine; cholesterol; cholinesterase; conjugated 1-.beta. hydroxy-cholic acid; cortisol; creatine kinase; creatine kinase MM isoenzyme; cyclosporin A; d-penicillamine; de-ethylchloroquine; dehydroepiandrosterone sulfate; DNA (acetylator polymorphism, alcohol dehydrogenase, alpha 1-antitrypsin, cystic fibrosis, Duchenne/Becker muscular dystrophy, glucose-6-phosphate dehydrogenase, hemoglobinopathies, A,S,C,E, D-Punjab, beta-thalassemia, hepatitis B virus, HCMV, HIV-1, HTLV-1, Leber hereditary optic neuropathy, MCAD, RNA, PKU, Plasmodium vivax, sexual differentiation, 21-deoxycortisol); desbutylhalofantrine; dihydropteridine reductase; diptheria/tetanus antitoxin; erythrocyte arginase; erythrocyte protoporphyrin; esterase D; fatty acids/acylglycines; free .beta.-human chorionic gonadotropin; free erythrocyte porphyrin; free thyroxine (FT4); free tri-iodothyronine (FT3); fumarylacetoacetase; galactose/gal-1-phosphate; galactose-1-phosphate uridyltransferase; gentamicin; glucose-6-phosphate dehydrogenase; glutathione; glutathione perioxidase; glycocholic acid; glycosylated hemoglobin; halofantrine; hemoglobin variants; hexosaminidase A; human

erythrocyte carbonic anhydrase I; 17 alpha-hydroxyprogesterone; hypoxanthine phosphoribosyl transferase; immunoreactive trypsin; lactate; lead; lipoproteins ((a), B/A-1, .beta.); lysozyme; mefloquine; netilmicin; oxygen; phenobarbitone; phenyloin; phytanic/pristanic acid; progesterone; prolactin; prolidase; purine nucleoside phosphorylase; quinine; reverse tri-iodothyronine (rT3); selenium; serum pancreatic lipase; sissomicin; somatomedin C; specific antibodies (adenovirus, anti-nuclear antibody, anti-zeta antibody, arbovirus, Aujeszky's disease virus, dengue virus, Dracunculus medinensis, Echinococcus granulosus, Entamoeba histolytica, enterovirus, Giardia duodenalisa, Helicobacter pylori, hepatitis B virus, herpes virus, HIV-1, IgE (atopic disease), influenza virus, Leishmania donovani, leptospira, measles/mumps/rubella, Mycobacterium leprae, Mycoplasma pneumoniae, Myoglobin, Onchocerca volvulus, parainfluenza virus, Plasmodium falciparum, poliovirus, Pseudomonas aeruginosa, pH, respiratory syncytial virus, rickettsia (scrub typhus), Schistosoma mansoni, Toxoplasma gondii, Trepenoma pallidium, Trypanosoma cruzi/rangeli, vesicular stomatis virus, Wuchereria bancrofti, yellow fever virus); specific antigens (hepatitis B virus, HIV-1); succinylacetone; sulfadoxine; theophylline; thyrotropin (TSH); thyroxine (T4); thyroxine-binding globulin; trace elements; transferrin; UDP-galactose-4-epimerase; urea; uroporphyrinogen I synthase; vitamin A; white blood cells; and zinc protoporphyrin. Salts, sugar, protein, fat, vitamins and hormones naturally occurring in blood or interstitial fluids may also constitute analytes in certain embodiments. The analyte may be naturally present in the biological fluid, for example, a metabolic product, a hormone, an antigen, an antibody, and the like. Alternatively, the analyte may be introduced into the body, for example, a contrast agent for imaging, a radioisotope, a chemical agent, a fluorocarbon-based synthetic blood, or a drug or pharmaceutical composition, including but not limited to insulin; ethanol; cannabis (marijuana, tetrahydrocannabinol, hashish); inhalants (nitrous oxide, amyl nitrite, butyl nitrite, chlorohydrocarbons, hydrocarbons); cocaine (crack cocaine); stimulants (amphetamines, methamphetamines, Ritalin, Cylert, Preludin, Didrex, PreState, Voranil, Sandrex, Plegine); depressants (barbituates, methaqualone, tranquilizers such as Valium, Librium, Miltown, Serax, Equanil, Tranxene); hallucinogens (phencyclidine, lysergic acid, mescaline, peyote, psilocybin); narcotics (heroin, codeine, morphine, opium, meperidine, Percocet, Percodan, Tussionex, Fentanyl, Darvon, Talwin, Lomotil); designer drugs (analogs of fentanyl, meperidine, amphetamines, methamphetamines, and phencyclidine, for example, Ecstasy); anabolic steroids; and nicotine.

The device of the present invention can be implanted within any bone of the subject. Preferred bones are pelvis and sternum, vertebral bodies and long bones.

Figure 1a schematically illustrates anatomy of a bone showing the various bone tissue regions. Figure 1b illustrates an iliac crest with cortex removed, exposing bone marrow comprised of cancellous bone. Bone marrow is a naturally occurring arterio-venus shunt and thus is highly suitable for placement of an analyte sensor, in particular a continuous, real time glucose sensor.

The present device can be partially or fully implanted within any tissue region of a bone including cancellous tissue, periosteum tissue and compact bone tissue.

Implantation can be effected via any one of numerous approaches used to access bone tissue, including for example, various drilling or cutting approaches. Such approaches are well known to the ordinarily skilled artisan and as such no further description of such approaches is provided herein.

The present device is designed such that when it is implanted to bone tissue, the sensor element(s) resides within the intra-medullary/intra-bone marrow blood sinus present within bone tissue. This enables the sensor element(s) to sample blood flowing through the bone tissue and to provide accurate and real-time analyte monitoring.

The present device can be of any shape and size suitable for bone attachment. The shape and size of the present device will largely depend on whether the device is partially or fully implanted within the bone, the site of implantation and the type of communication between the device and a controller unit (further described hereinbelow). In general, the device can be spherical, cylindrical, rectangular or in shape having a diameter/width of 1 mm -2.5 cm and a length of 5 mm-5 cm. Figure 2a which is described in greater detail Examples section which follows illustrates one preferred device configuration.

In a configuration in which the device is partially implanted within bone, the sensor element(s) component of the device is configured such that it extends into the bone tissue and contacts the blood flowing within intra-medullary/intra-bone marrow blood sinus, while the device body which houses additional components such as power source, circuitry, communications devices (e.g. coils, antennas) and the like can be placed within soft tissues surrounding the bone or it can be attached to the bone surface via attachment anchors suitable for bone anchoring. Bone anchor configurations suitable for use with the present device include bone screws/plates and the like. Soft tissue anchoring can be effected via sutures staples or anchors using approaches well known in the art.

In the partially implanted configuration of the present device, the sensor element(s) can be fitted into a small hole/slit which is drilled or cut into the bone. Such a hole or slit is long enough to extend through the cortex and into cancellous bone. For example, in a device configured for use in long bones, a hole 5 mm-5 cm mm long and 1 mm-2.5 cm in diameter can be drilled into the bone and used to accommodate the sensor element(s) of the present device.

Since a partially implanted configuration requires minimal bone drilling/cutting, such a configuration is highly suitable for smaller bones which cannot accommodate the entire device. Examples of such bones include vertebral bodies, sternum, and the like.

A fully implanted configuration in which the entire device is implanted within the bone is also contemplated herein. In such a configuration, the device body is implanted into the bone tissue and the sensor element(s) is exposed to the blood flowing therein. As is well known in the art, implantation of foreign objects (e.g. orthopedic implants) within bone is well tolerated by the body and produces minimal body reactions as compared to implantation within soft tissues. Thus, a fully implanted configuration is advantageous in that the device body is fully encapsulated by bone tissue and less exposed to possible tissue reactions that could lead to encapsulation, biofilm formation. erosion and the like.

As is mentioned herein, the device of the present invention includes a sensor element(s) which is designed for detecting an analyte of interest.

Such a sensor is preferably chemical or optical in nature. Chemical sensors used for analyte detection are typically amperometric enzymatic sensors.

A typical amperometric enzymatic sensor element(s) includes a non-conductive housing, a working electrode (anode), a reference electrode, and a counter electrode (cathode) passing through and secured within the housing thus forming an electrochemically reactive surface at one location on the housing and an electronic connective means at another location on the housing. The sensor element(s) also includes a membrane affixed to the housing and covering the electrochemically reactive surface. The counter electrode generally has a greater electrochemically reactive surface area than the working electrode. During operation of the sensor, a blood sample or a portion thereof contacts (directly or after passage through the membranes) an enzyme (for example, glucose oxidase in the case of glucose monitoring). The reaction of the analyte and the enzyme results in the formation of reaction products that allow a determination of the analyte (e.g., glucose) level in the blood sample.

The sensor element(s) can be shaped as a cylinder or a thin film, typical thin film electrochemical sensors are described in U.S. Pat. Nos. 5,390,671; 5,391,250; 5,482,473; and 5,586,553.

Three general strategies are used for the electrochemical sensing of an analyte, all of which use an immobilized form of an enzyme that catalyzes the oxidation of the analyte. For example, in the case of glucose, glucose oxidase is used to convert glucose to gluconic acid with the production of hydrogen peroxide. The first detection scheme measures oxygen consumption; the second measures the hydrogen peroxide produced by the enzyme reaction; and a third uses a diffusable or immobilized mediator to transfer the electrons from the glucose oxidase to the electrode.

In the case of glucose monitoring, the present device can utilize a sensor which allows glucose and oxygen to diffuse into the enzyme region of the sensor from one direction, but only oxygen diffuses from the other direction. This design helps eliminate the "oxygen deficit", the low ratio of oxygen to glucose that exists in the body. The modulation of oxygen transport to an oxygen electrode by oxygen participation in the enzyme reaction provides the means for glucose determination. The enzyme catalase is immobilized with the glucose oxidase to remove the hydrogen peroxide, which can shorten the active lifetime of glucose oxidase. This sensing method requires an additional oxygen electrode setup to indicate the background concentration of oxygen.

Hydrogen peroxide sensors measure the product of the enzymatic reaction on an anodically polarized electrode. One of the advantages of hydrogen peroxide sensors is that the signal increases with increasing glucose concentrations. However, the oxidation of hydrogen peroxide requires an applied potential at which many other species commonly found in the body are electro-oxidizable, creating the possibility of interference. The most problematic species are urea, ascorbate (vitamin C), urate, and acetaminophen. Interferences are minimized with semipermeable membranes that restrict their passage. The enzyme reaction still requires oxygen, which is usually assumed to be adequate.

Glucose sensors that use nonleachable electrochemical mediators circumvent the oxygen deficit described above by using a species other than oxygen to transfer the electrons from the glucose oxidase to the electrode. Because oxygen remains in the system, the mediator must compete effectively with the oxygen for the electrons. In the past, ferrocene has been used as a mediator but it is diffusable and toxic. A more recent version of the mediator sensors is the "wired" glucose oxidase electrode designed by Adam Heller and his group in the Department of Chemical Engineering at the University of Texas at

Austin. The mediator does not leach because it is bound to a polymer, which is cross-linked. The glucose oxidase is tethered to the electrode with a hydrogel formed of a redox polymer with electrochemically active and chemically bound complexed osmium redox centers.

To ensure long term operation of an electrochemical enzymatic sensor, the present device can be configured capable of "recharging" the sensor with fresh enzyme solution. Such a solution can be pumped into a thin channel between a membrane contacting the bone tissue and the electrode surface. The spent enzyme suspension can be flushed from the system, and fresh enzyme can be injected through a skin port which is in fluid communication with the device.

Electrochemical interferences which can affect the accuracy of the analyte readings can be minimized in two ways. The applied potential can be set low enough that few species other than the detected reaction product are oxidized, or a layer that restricts the diffusion of interferences to the electrode can be utilized. In the oxygen-based enzyme sensors, electrochemical interference is much less of a problem because of a pore-free hydrophobic layer between the enzyme and electrode surface that permits oxygen transport but stops polar molecules.

In the case of glucose monitoring, a high-performance glucose sensor, pyrrolo-quinoline quinone dependent glucose dehydrogenase (PQQ-GDH) can be used in the sensor element(s) (U.S. Pat. No. US Pat No. 7,005,048) in order to increase sensor accuracy.

Optical sensors which can be used by the present device include a fluorescent chemical complex immobilized in a thin-film (e.g. thin film hydrogel). The film is a biocompatible polymer which is permeable to the analyte. The sensing system has two components: a fluorescent dye and a "quencher" that is responsive to the analyte. In the absence of the analyte, the quencher binds to the dye and prevents fluorescence, while the interaction of the analyte with the quencher leads to dissociation of the complex and an increase in fluorescence. In such sensors, fluorescence is typically translated into current which is relayed to the monitoring unit.

Optical monitoring of glucose can utilize artificial glucose receptors molecules that are fluorescent, such as the compound produced by the coupling of the fluorescent dye, anthracene, to boronic acid, which covalently but reversibly binds to two of the hydoxyl groups on glucose (James TD, Sananayake KRAS, Shinkai S. A glucose-selective molecular fluorescence sensor. Angewandte Chemie International Edition in English. 1994;33:2207–2209) With this receptor, a change in fluorescence intensity occurs on

glucose binding. It also can utilize a NIR light source (Diode/ laser etc.) and suitable detectors that measures color changes associated with Glucose fluctuation rates.

Another example of a useful fluorescence technique is "fluorescence resonance energy transfer" (FRET), which relies on the transfer of excitation energy from one fluorescent molecule (the donor) to another nearby molecule (the acceptor) that has overlapping spectral properties. Changes in fluorescence intensity or lifetime are reporters of the changing distance between the donor and acceptor. Model FRET schemes have been described for glucose sensing in vitro with the glucose binding lectin concanavalin A coupled to near infrared fluorescent molecules (olosa L, Szmacinski H, Rao G, Lakowicz JR. Lifetime-based sensing of glucose using energy transfer with a long-lifetime donor. Anal Biochem. 1997;250:102–108; and Rolinski OJ, Birch DJS, McCartney LJ, Pickup JC. Near-infrared assay for glucose determination. Soc Photo-optical Instrumentation Engineers Proc. 1999;3602:6–14)

Conformation change in a protein upon binding of an analyte can also be sensed via a conformation-sensitive fluorophore which is attached to the protein. Molecular engineering techniques are being used in this respect for the rational adaptation of proteins to produce new molecules with modified functions more suited to sensing. For example, conformation sensitive fluorescent groups have been incorporated into allosteric proteins such as the glucose binding protein from *Escherichia coli* (Marvin JS, Hellinga HW. Engineering biosensors by introducing fluorescent allosteric signal transducers: construction of a novel glucose sensor. J Am Chem Soc. 1998;120:7–11). This protein undergoes a large conformational change on glucose binding that can be transduced into a change in fluorescence in the engineered protein. Molecular (e.g. nanotube) sensors which react strongly with a chemical such a glucose to change conformation and thus a fluorescent response can also be utilized by the present invention.

Other sensor element(s) configurations which include other sensing mechanisms, including but not limited to biochemical sensors, cell-based sensors (e.g. US 20020038083), electrocatalytic sensors, optical sensors, piezoelectric sensors, thermoelectric sensors, and acoustic sensors can also be used in the present device.

For example, a chemical sensor which permits selective recognition of an analyte using an expandable biocompatible sensor, such as a polymer, that undergoes a dimensional change in the presence of the analyte (see for example, U.S. Pat. No. 6,480,730) can also be used by the present device.

Artificial receptor molecules can also be utilized for analyte monitoring. One of the most promising techniques for creating artificial receptors is called "molecular imprinting" or "plastic antibodies" (Haupt K, Mosbach K. Plastic antibodies: developments and applications. Trends Biotechnol. 1998;16:468–475.) Monomers that have chemical groups that interact with a template molecule related to the analyte are polymerized around the template, the template is then removed, leaving a polymer that is specific in shape and binding capacity for the analyte. An example for glucose monitoring uses the interaction at alkaline pH between a metal ion complex and glucose, which releases hydrogen ions on glucose binding (Chen G, Guan Z, Chen C-T, Fu L, Sundaresan V, Arnold F. A glucose sensing polymer. Nature Biotechnol. 1997;15:354–357.) A porous polymer specific for glucose has been made whereby glucose concentration can be measured by titratable release of protons.

Regardless of the sensor type, sensors readings are typically interpreted using circuits such as L-C circuits which are housed within the device of the present invention. For example, the sensor can be coupled to a frequency tuned L-C circuit, where the sensor translates the changes in the physiological condition to the inductor or capacitor of the tuned L-C circuit. Thus, changes in the sensor whether chemical, optical or physical result in changes in the L-C circuit which can be quantified and used to asses analyte concentration.

The present device may include one sensing region, or multiple sensing regions. Each sensing region can be employed to determine the same or different analyte. Different sensing mechanisms may be employed by different sensor regions on the same device.

Although sensor configuration for detection of glucose is exemplified herein, it will be appreciated that any analyte can be detected by the device of the present invention by fitting the system with a sensor (e.g. electrode) designed capable of detecting such an analyte. For example, hydrogen ions (pH) can be detected using an electrode whose output voltage changes as the hydrogen ion concentration changes; hormones can be detected via antibody-based electrodes such as those described by Cook and Devine (Electroanalysis Volume 10, Issue 16 , Pages 1108 - 1111; Feb 1999) while nitric oxide can be detected by the electrode describe by Mizutani et al. (Chemistry Letters Vol. 29, No. 7 p.802 2000).

The present device is configured capable of communicating with a remote unit which can be used for controlling the functions of the implanted device, powering it and obtaining readings therefrom. Thus, the present device forms a part of a system for analyte

monitoring that further includes a control unit for controlling the operation of the implantable device.

Communication between the implanted device and the control unit can be through wires extending from the device to the control unit; in such cases, the control unit can be implanted under the skin or worn on the body. Communication can also be effected wirelessly, as is further described below.

Powering of the present device can be effected through an implanted power source (which can be integrated into the device) or through remote powering via a remote control unit; remote powering and control of the implanted device is presently preferred.

Several configurations for remote powering and controlling of the present device can be used by the present invention, for a general review of telemetry please see, U.S. Pat. No. 6,201,980.

Inductive coupling of the device and the control unit can be effected through radiofrequency (RF) signals. The implanted device can utilize a first coil which can inductively couple to a second coil provided on the control unit.

During use of the system, the second coil is positioned adjacent the first coil and a high frequency carrier signal is applied to the second coil. The signal is coupled to the first coil, even though there is no direct connection between the two coils, in much the same manner as an AC signal applied to a primary winding of a transformer is coupled to a secondary winding of the transformer. Once received by the first coil, circuitry within the present device rectifies the signal and converts it to a DC signal which is used as the operating power for the implant device. Moreover, modulation applied to the carrier signal provides a means for sending control signals to the implanted device from the control unit. Further description of RF telemetry systems is provided in U.S. Pat. Nos. 6,667,725 and 5,755,748.

Thus, in the case of an electrochemical sensor element(s) and tuned L-C circuitry, a signal transmitted to the coil in the implanted device is converted into a DC current which powers an LC circuit having a frequency which is modulated by the current produced in the sensor electrodes. Such a current is proportional to the amount of analyte present in the environment of the electrodes. Once powered by the signal the LC circuit transmits back to the control unit a frequency modulated signal. The frequency of this signal is interpreted by the control unit to derive an analyte concentration.

Induction coupling for the purpose of powering and controlling the implanted device of the present invention can also be achieved through magnetic (see, for example,

U.S. Pat. No. 6,963,779), acoustic (see, for example, U.S. Pat. Nos. 6,764,446 and 7,024,248) or optical telemetry (see, for example, U.S. Pat. No. 6,243,608 and 6,349,234) in the case of optical telemetry, a subcutaneous receiver can be wired to the implanted device and serve as a conduit between the device and the extracorporeal control unit. Such a receiver can be a near-infrared light sensor/emitter which converts received light into electrical energy and vise versa.

In any case, telemetry can be used for both controlling and powering of the implanted device.

The control unit can include a user interface for displaying to the user the information relayed by the sensor element(s) of the implanted device. Such information can include the level of the analyte in the blood, trends over a predetermined time period as well as alarms for indicating high or low levels of the analyte. The control unit can store information relating to the subject including analyte level history, personal profile, medications being taken and the like. The control unit can also include an input device such a keypad for inputting information which can be used to set up the system or calibrate it.

The control unit can be in the form of a dedicated wearable device such as a wrist watch, or be integrated into an existing user device such as an MP3 player, a cell phone or the like. Use of a cell phone or other communications-capable device (e.g. computer, PDA) is particularly advantageous since it enables further transmission of the analyte information to a third party over a communications network such as a cellular communication network or a computer network.

The present system can also include an implanted device configuration which includes ports for delivery of medication or alternatively the control unit of the present system can communicate with implanted drug delivery pump or reservoir. Such communication can be though wires or through the telemetry configurations outlined above.

The above described sensor can be integrated into a closed (feedback) loop system which can be used, for example, in controlling blood glucose levels of diabetics. To achieve a closed feedback loop for blood glucose control, a clinically applicable system requires coordination of three components: an implantable insulin pump, an implantable blood glucose sensor, and a control unit which can be implanted or not.

The goal of a fully automatic glucose control system includes prevention or delay of chronic complications of diabetes, lowered risk of hypoglycemia, and less patient

inconvenience and discomfort than with multiple daily glucose self-tests and insulin injection.

Implantable insulin pumps which deliver insulin to subcutaneous tissue or a blood vessel such as a vein are feasible for satisfactory control of diabetes for extended time periods. However, closed loop systems employing such implantable pumps are limited by the glucose sensors utilized which provide glucose level readings that are different from real-time blood glucose levels. In addition, subcutaneously implanted insulin pumps are also limited by complications which arise from obstructions in the insulin infusion catheter.

The present inventors postulate that a system which utilizes a bone implanted glucose sensor, such as that described above, in combination with a reservoir having a bone implanted port/catheter would overcome these limitations of prior art systems. Such a system can be a closed loop system in which a signal from the sensor controls an infusion pump, or it can be an open loop system which includes an extracorporeal control unit which receives signals from the sensor and is used (by the subject/physician) to operate the pump accordingly.

Thus, according to another aspect of the present invention there is provided a system for controlling blood glucose levels of a subject.

The system includes the above described bone implanted sensor unit (which in this case is configured for glucose sensing as described above) and a reservoir which receives control signals from the glucose sensor (closed loop) or communicates therewith through an extracorporeal control unit (open loop) and is configured for providing a blood glucose-level modifying composition such as insulin, glucagons, as well as combinations thereof to bone tissue of the subject.

As is further described herein, both the glucose sensor and reservoir are implanted in communication with a bone (preferably skeletal bone) of the subject as is described herein with respect to the analyte sensor described above. The glucose sensor and reservoir are preferably implanted such that each is in communication with a different bone region or a different bone since sensing and infusion in the same bone/bone region can lead to aberrations in blood glucose levels. For example, the glucose sensor can be implanted on one iliac crest and the reservoir on another.

The implanted reservoir can be any implantable reservoir which is capable of delivering insulin and/or other compositions (e.g. glucagons) through a bone infusion port/catheter. Thus, the reservoir can be implanted subcutaneously with a catheter leading to bone tissue, or it can be implanted against bone tissue and anchored thereto with a port

leading directly into the bone tissue as is further illustrated in Example 2 of the Examples section which follows.

In any case, the basic configuration of the reservoir includes one or more chambers (each containing a composition), an infusion port/catheter connected thereto and a controllable valve and optionally a pumping mechanism for controlling flow from the reservoir to the port/catheter.

The infusion port/catheter can be anchored into bone tissue as described above for the analyte sensor. To prevent bone ingrowth or local clotting/tissue reactions, the infusion port/catheter can be coated with an anti-clotting composition or bone growth suppressors as described above.

To deliver the composition from the reservoir and through the infusion port/catheter, the pumping mechanism can utilize peristalsis, a propellant, osmotic pressure (e.g. U.S. Pat. No. 6,632,217), a piezoelectric element (e.g. U.S. Pat. Nos. 3,963,380 and 4,344,743), a combination of osmotic pressure and an oscillating piston/rotating turbine and the like.

The pumping mechanism can be utilized to facilitate controlled chamber collapse for delivering the composition contained therein to the bone tissue.

Chamber collapse can be actuated by a mechanical mechanism, an electrically powered mechanism or by using a two-phase fluid, or propellant, that is contained within the housing of the pump in a fluid-tight space adjacent to the composition chamber. Such a propellant is both a liquid and a vapor at patient physiological temperatures, and theoretically exerts a positive, constant pressure over a volume change of the chamber/reservoir, thus effecting the delivery of a constant flow of the composition. When the reservoir is expanded upon being refilled, the propellant is compressed, where a portion of such vapor reverts to its liquid phase and thereby recharges the vapor pressure power source of the pump. Other pump configurations can include a plunger pump mechanism (e.g. Minimed. Medtronic)

Provision of the composition can be as a bolus or a slow infusion. In any case, control of infusion is preferably effected through the valve which is positioned between the reservoir and port/catheter. One configuration of a valve mechanism which can be used by the system of the present invention in variable rate delivery of the composition is described in U.S. 20050054988. Infusion rate is preprogrammed according to the signal received from the sensor and parameters associated with the subject as determined via an examination prior to implantation of the system.

The reservoir can be configured for storing a liquid or a dry preparation of the composition (e.g. insulin).

Since insulin and glucagons have a short half life as liquid preparations, a reservoir which is configured for storage of a dry (e.g. lyophilized) preparation is presently preferred. A reservoir having such a configuration can include a mechanism for suspending the stored composition in a liquid prior to provision. Such liquefying can be effected by the addition of saline (from a second chamber) or by collection of interstitial fluid (ISF) from the environment surrounding the pump. Alternatively, the reservoir can be configured for direct delivery of a dry composition into the bone in the form of microparticles, such as PLA/PGA microparticles.

Since the system of the present invention is utilized for long term provision of blood glucose level modifying agents, a reservoir utilized thereby might require periodic replenishing. Thus, the reservoir can also include a filling port which can be implanted within the skin. The reservoir may be refilled as needed by an external needle injection through a self-sealing septum provided in a skin port.

As is mentioned hereinabove, the present system can be configured as either a closed loop system or as an open loop system (or a combination of both). In the closed loop configuration, the implanted glucose sensor monitors blood glucose levels and periodically relays glucose readings (e.g. every hour) to the implanted insulin reservoir. The sensor or reservoir can include a processing unit for converting blood glucose level signals to a pump activation signal. Such a processing unit can be accessible from outside the body through a communications port or a wireless communication mode similar to that described above for the implantable analyte sensor and control unit. The processing unit is first calibrated by a physician based on glucose readings and insulin effect as measured by standard tests. The processing unit can be calibrated prior to or following implantation and be recalibrated periodically (e.g. once or several times a year) if need be.

In any case, the signal provided by the glucose sensor is processed and an appropriate infusion-activation signal (amount of insulin, flow rate etc) is provided.

Implantation and operation of closed loop configurations of the present system is illustrated in Example 2 of the Examples section which follows.

The open loop configuration requires operator control over provision of the composition from the reservoir. As such, the open loop configuration further includes a user operated extracorporeal control unit which is similar in function to the control unit of

the analyte sensor described hereinabove. Such a control unit can be used to monitor blood glucose levels and modify infusion rates/composition type periodically.

Control and powering of the pumping mechanism can be as described above for the sensor. A single control and powering unit can be co-implanted with the sensor and reservoir assemblies and provide power and communication for both, as well as processing of sensor and activation signals.

As used herein the term "about" refers to ± 10 %.

Additional objects, advantages, and novel features of the present invention will become apparent to one ordinarily skilled in the art upon examination of the following examples, which are not intended to be limiting. Additionally, each of the various embodiments and aspects of the present invention as delineated hereinabove and as claimed in the claims section below finds experimental support in the following examples.

EXAMPLES

Reference is now made to the following examples, which together with the above descriptions, illustrate the invention in a non limiting fashion.

EXAMPLE 1

Implantation of a bone-implanted electrochemical glucose sensor

Figure 2a illustrates a device 10 which is constructed in accordance with the teachings of the present invention and positioned with bone tissue of a subject. Device 10 includes a housing 20 which houses a sensor element(s) 12 which is connected via circuitry 14 to a power source and telemetry unit 16. Housing 20 can be fabricated from any biocompatible material including polymers, ceramics, alloys and the like. Sensor element(s) 12 is a membrane encapsulated glucose enzyme electrode. Device 10 is positioned such that sensor element(s) 12 extends into bone marrow 24 and as such is exposed to blood flowing therein.

Device 10 is positioned in the bone (e.g. iliac crest) by making an incision in the skin, striping the muscle off the bone. A drill bit is then utilized to drill a hole 26 through the periosteum, cortical bone and cancellous bone layers. Hole 26 is slightly larger in diameter than housing 20 at sensor element(s) 12. Sensor element(s) 12 portion of device 10 is then inserted into hole 26 and positioned such that sensor element(s) 12 is exposed to

bone marrow tissue. Housing 20 is then secured against cortical bone 22 via bone screws 18 and the unit is powered tested and calibrated against blood glucose analysis performed using standard laboratory tests. Following calibration, muscle and skin tissue are replaced into position covering device 10 and are sutured or stapled.

EXAMPLE 2

System For Controlling Blood Glucose Levels

Figures 3a-b illustrate two configurations of a system for controlling glucose levels constructed in accordance with the teachings of the present invention.

Figure 3a illustrates a system 50 which includes drug delivery device 52 mounted against the skin of the subject with cannula 54 extending through skin 56 and bone tissue 58 and into bone marrow 60. Cannula 54 conducts fluid from reservoirs 62 and 64 into bone marrow 60 under the driving force of pump 66.

System 50 also includes detector 68 which includes glucose monitor 70 and cannula 72 for conducting blood from bone marrow 60 and into glucose monitor 70 for glucose level assessment. Sensor assembly further includes a reservoir 74 for delivering heparin into bone marrow 60 through cannula 72 under the driving force of pump 76.

Drug delivery device 52 and detector 68 can communicate through a hard wire connection (which can be implanted under the skin of the subject) or through wireless communication through transceivers 80. System 50 is powered in this configuration by a battery 82 (e.g. a Li-ion battery) although other forms of powering including capacitors and coils are also envisaged.

System 50 is positioned as follows: an incision is made above the bone with access obtained to cortical bone. Based on the size of the portion of the device to be inserted into the bone marrow a space is cut through the cortex and into the bone marrow with standard drills and osteotomy tools. The device is then secured with the sensor elements implanted within the bone marrow and the external housing attached to cortical bone by screws.

Following positioning, glucose sensor assembly of system 50 is first calibrated against a standard blood glucose test, following which, reservoirs 62, 64 and 74 are filled via syringes 84 and the system activated. Flow rate of insulin from reservoir 62 of drug delivery device 52 can be determined/adjusted by the subject according to the blood glucose levels determined by glucose monitor 70 and displayed on display 86 or such levels can be automatically determined/adjusted by running system 50 in a closed loop mode, in which case, system 50 will self adjust insulin flow rates according to glucose monitor 76

readings. Typical insulin delivery rates are in the range of 0.1 unit/hr in young children to 2-6 units/hr in adults. System 50 also preferably employs shutoff and warning mechanisms to prevent flow rates exceeding optimal levels depending on the body weight, age and typical insulin usage range of the subject.

Drug delivery device 52 can periodically deliver a hormone such as glucagons (10-20 microgram/kg/24hr) or somatostatin analogues (3-4 mg/kg/day) from reservoir 64 if blood glucose levels drop rapidly towards hypoglycemic levels, as detected by glucose monitor 70. In addition, in order to prevent clogging of cannula 72, a blood thinner/clot dissolver such as heparin can be periodically delivered from reservoir 74 through cannula 72.

In order to maintain glucose control accuracy, system 50 would preferably be calibrated periodically against blood glucose tests.

Figure 3b illustrates a second configuration of system 50 in which drug delivery device 52 and detector 68 are implanted under skin 56 and anchored against or within bone tissue 58. In this configuration system 50 includes an extracorporeal unit 100 which includes a charger 102 which provides the power to pump and sensors (or to a rechargeable battery connected thereto) and a display 86 for displaying information (e.g. glucose levels) to the subject.

Unit 100 can further provide communication functions to drug delivery device 52 and detector 68 (e.g. coordinating communications therebetween), as well as provide processing of sensor information and relaying of commands to drug delivery device 52. Unit 100 can further include an interface (e.g. keypad) for enabling input of information (e.g. subject information such as weight, operational commands etc).

An alternative embodiment of system 50 can include the implantable configuration described in Figure 3b and a pager-like device. Both the detector and the drug delivery device are positioned under the skin and attached to the bone marrow as described above. Each includes a separate internal rechargeable battery thus extending operational time of the system. The pager is placed outside the body and provides data processing and controls insulin/glucagon infusion rates etc. Operation of this configuration of system 50 is similar to that described in Figure 3a.

EXAMPLE 3

Monitoring glucose levels in blood drawn from a vein or bone marrow of rabbits

Although tight glycemic control in patients with diabetes has been founded to reduce the risk of micro vascular and macro vascular complications, it is also associated with an increased risk of episodes of severe hypoglycemia. Thus, the ultimate goal in diabetes treatment is to develop an autonomous system (artificial pancreas) capable of continuous glucose sensing and maintaining normal blood glucose levels, thereby mimicking the physiologic function of the islet beta cells and freeing the patient from the need for constant calculations of daily insulin and carbohydrates.

A study was performed in order to compare bone-marrow glucose to blood glucose in healthy and diabetic animals at base line and following insulin or dextrose treatment.

The blood glucose levels of eight adult female rabbits (2 kg each) were manipulated via i.v. infusion of 50% dextrose and 2IU insulin, the Glucose levels of these rabbits were then measured in vein (IV) and bone (IO) blood (Figure 4a).

All eight rabbits were subjected to the following phases:

(i) First phase - measurement of steady state glucose level for about 10- 30 minutes (sampling every 5-10 min)

(ii) Second phase – Infusion of 50% dextrose

(iii) Third phase – Infusion of 2IU of insulin (over 3-5 hours)

Samples were obtained from both vein and bone marrow access at the same time in order to correlate glucose levels in blood obtained form both sites

As is clearly shown in Figure 4a, glucose levels measured in blood drawn from bone marrow track well with glucose levels present in vein blood with a very high correlation level (+-4% error).

The glucose levels in vein and bone marrow derived blood were compared in two rabbits tested with bone marrow insulin infusion (Figure 4b) and vein insulin infusion (Figure 4c). Glucose level response to bone marrow delivery of insulin was comparable to that of vein insulin delivery (both reduced glucose levels within 5-10 minutes).

These results clearly illustrate that a system that includes glucose sensing in blood derived from bone as well as insulin delivery into bone blood can be effective in maintaining normal glucose levels and thus can be used in a closed or open loop configuration to treat diabetics.

It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable subcombination.

Although the invention has been described in conjunction with specific embodiments thereof, it is evident that many alternatives, modifications and variations will be apparent to those skilled in the art. Accordingly, it is intended to embrace all such alternatives, modifications and variations that fall within the spirit and broad scope of the appended claims. All publications, patents and patent applications mentioned in this specification are herein incorporated in their entirety by reference into the specification, to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated herein by reference. In addition, citation or identification of any reference in this application shall not be construed as an admission that such reference is available as prior art to the present invention.

WHAT IS CLAIMED IS:

1. A device for monitoring an analyte in a subject comprising a sensor element being designed and configured for detecting the analyte in blood flowing through a bone of the subject.

2. The device of claim 1, wherein said sensor element is designed and configured for implantation within bone tissue.

3. The device of claim 2, wherein said sensor element is designed and configured for implantation within cancellous tissue of said bone.

4. The device of claim 1, further comprising a power source for powering said sensor element.

5. The device of claim 1, further comprising circuitry for remotely powering said sensor element.

6. The device of claim 1, wherein said analyte is selected from the group consisting of urea, ammonia, hydrogen ions, minerals, enzymes, and drugs.

7. The device of claim 1, wherein said analyte is glucose.

8. The device of claim 1, wherein said sensor element is an electrochemical, biological or an optical sensor element.

9. The device of claim 1, wherein said sensor element includes a membrane selective for said analyte.

10. A system for monitoring an analyte in a subject comprising a device including a sensor element being designed and configured for detecting the analyte in blood flowing through a bone of the subject and a control unit for controlling said device.

11. The system of claim 10, wherein said sensor element is designed and configured for implantation within bone tissue.

12. The system of claim 11, wherein said sensor element is designed and configured for implantation within cancellous tissue of said bone.

13. The system of claim 10, wherein said device and said control unit are designed for wireless communication.

14. The system of claim 13, wherein said wireless communication is mediated via magnetic, electromagnetic or acoustic energy.

15. The system of claim 10, wherein said device is wired to said control unit.

16. The system of claim 10, wherein said device includes a power supply.

17. The system of claim 10, wherein said device includes an induction coil.

18. The system of claim 16, wherein said device includes a battery.

19. The system of claim 10, wherein said analyte is selected from the group consisting of urea, ammonia, hydrogen ions, minerals, enzymes, and drugs.

20. The system of claim 10, wherein said analyte is glucose.

21. The system of claim 10, wherein said sensor element is an electrochemical, biological or an optical sensor element.

22. The system of claim 10, wherein said sensor element includes a membrane selective for said analyte.

23. A method of monitoring an analyte in a subject comprising detecting the analyte in blood flowing through bone tissue of the subject thereby monitoring the analyte in the subject.

24. The method of claim 23, wherein said detecting is effected by implanting a sensor of said analyte in a bone of the subject.

25. The method of claim 23, wherein the analyte is glucose and said sensor is a glucose sensor.

26. The method of claim 23, wherein said sensor is implanted in contact with blood flowing through said bone.

27. The method of claim 23, wherein said bone is selected from the group consisting of iliac crest bone, axial skeleton bone and rib cage bone.

28. A system for controlling blood glucose levels in a subject comprising:

(a) a sensor element being designed and configured for detecting the analyte in blood flowing through a bone of the subject; and

(b) a reservoir for providing to said blood flowing through said bone of the subject at least one composition capable of modifying a level of glucose.

29. The system of claim 28, wherein said sensor element is designed and configured for implantation within bone tissue.

30. The system of claim 29, wherein said reservoir is in fluid communication with a port/catheter attached to tissue of said bone.

31. The system of claim 28, further comprising a mechanism for pumping said composition from said reservoir to said blood flowing through said bone.

32. The system of claim 31, further comprising a power source for powering said sensor element and said mechanism.

33. The system of claim 32, wherein said mechanism utilizes peristalsis, a propellant, osmotic pressure, a piezoelectric element or an oscillating piston/rotating turbine.

34. The system of claim 28, wherein said sensor element is an electrochemical, biological or an optical sensor element.

35. The system of claim 28, wherein said reservoir further includes a filling port.

36. The system of claim 28, wherein said at least one composition is insulin or glucagon.

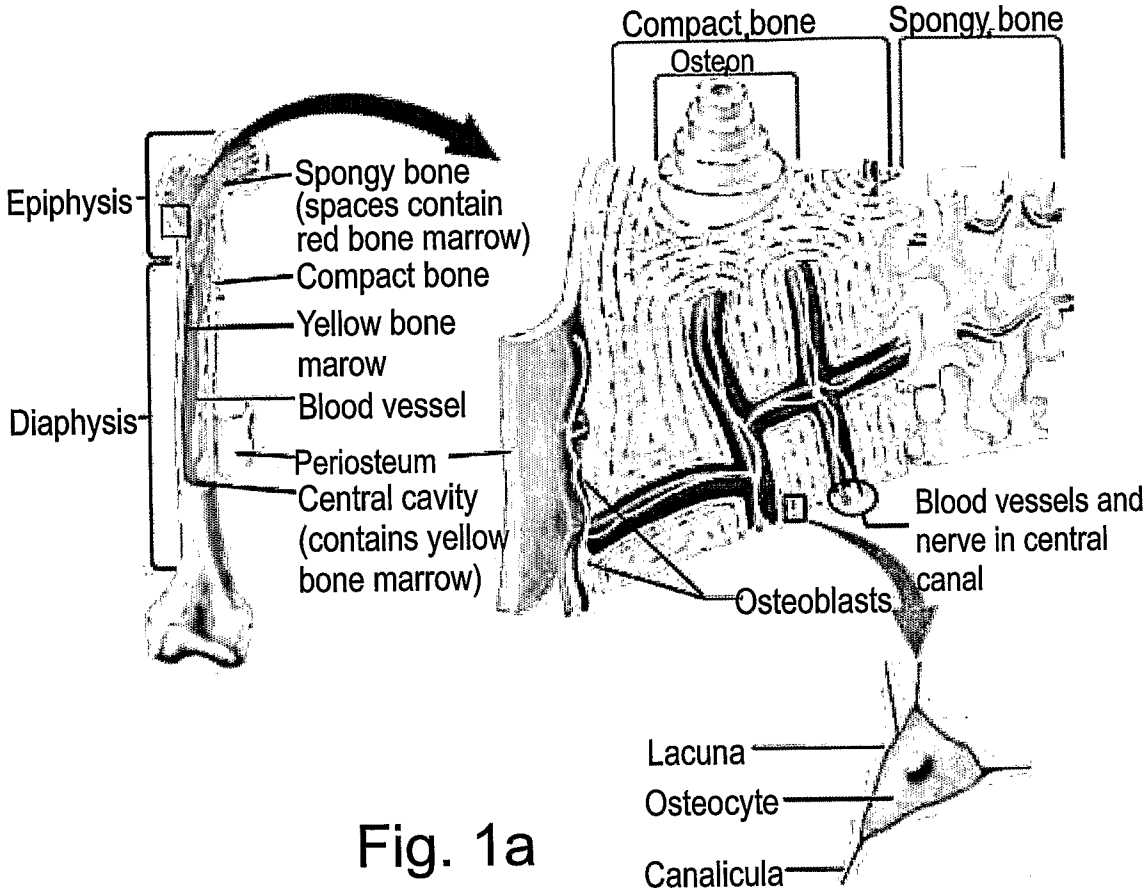

Compact bone
Spongy bone
Osteon
Epiphysis
Spongy bone (spaces contain red bone marrow)
Compact bone
Yellow bone marow
Blood vessel
Diaphysis
Periosteum
Central cavity (contains yellow bone marrow)
Blood vessels and nerve in central canal
Osteoblasts
Lacuna
Osteocyte
Canalicula

Fig. 1a

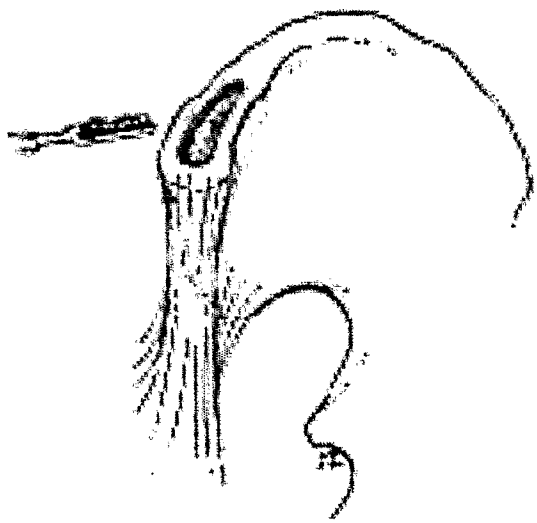


Fig. 1b

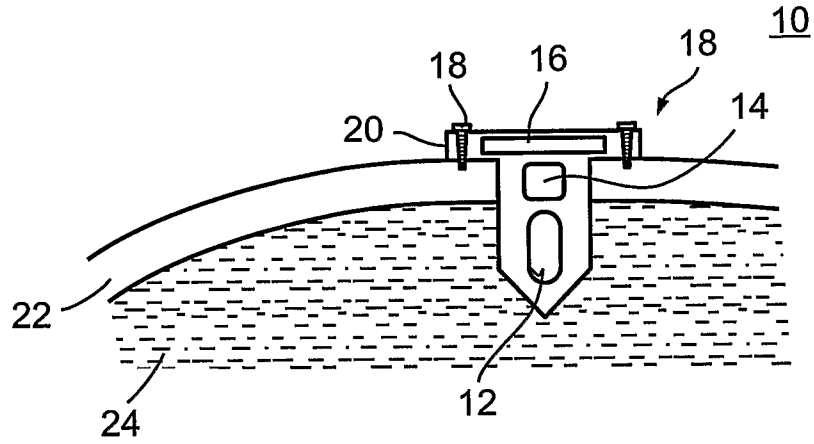


Fig. 2a

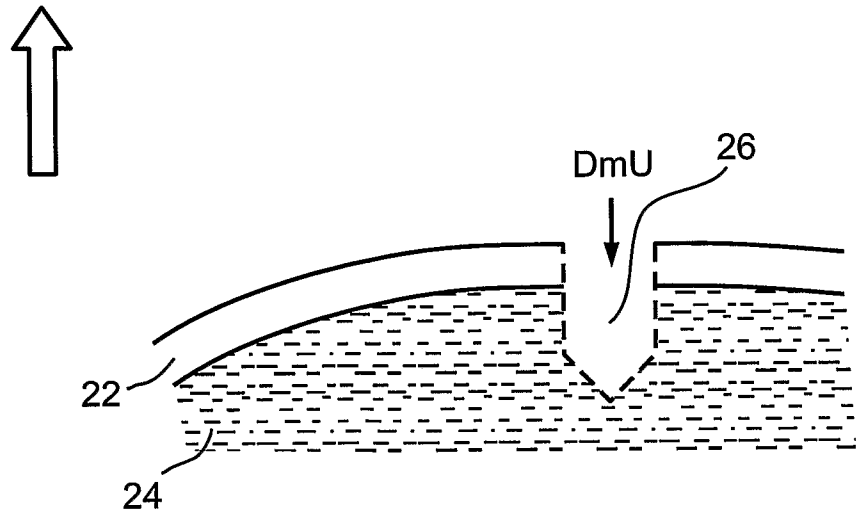


Fig. 2b

Figure 3a

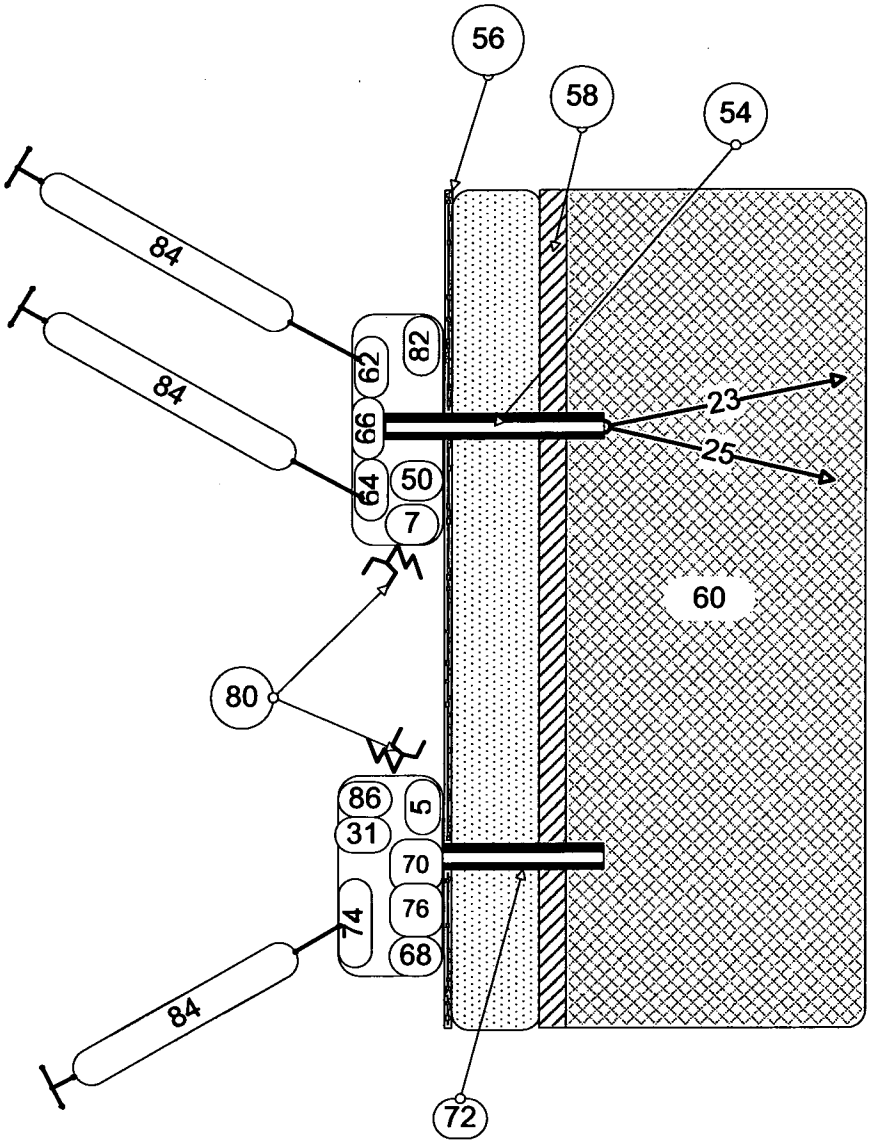
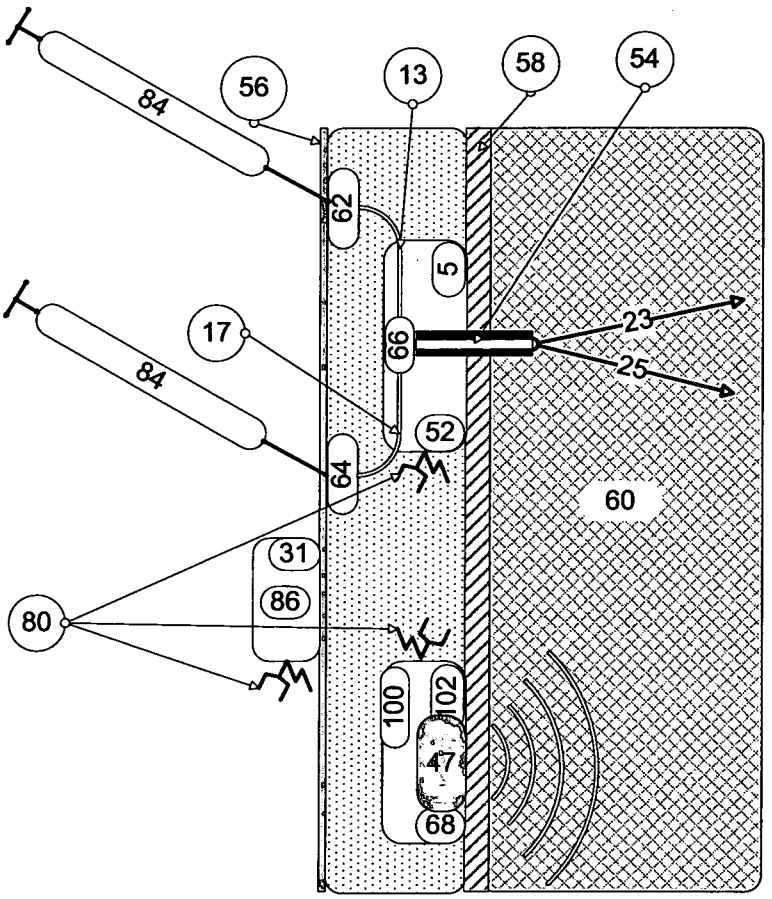


Figure 3b



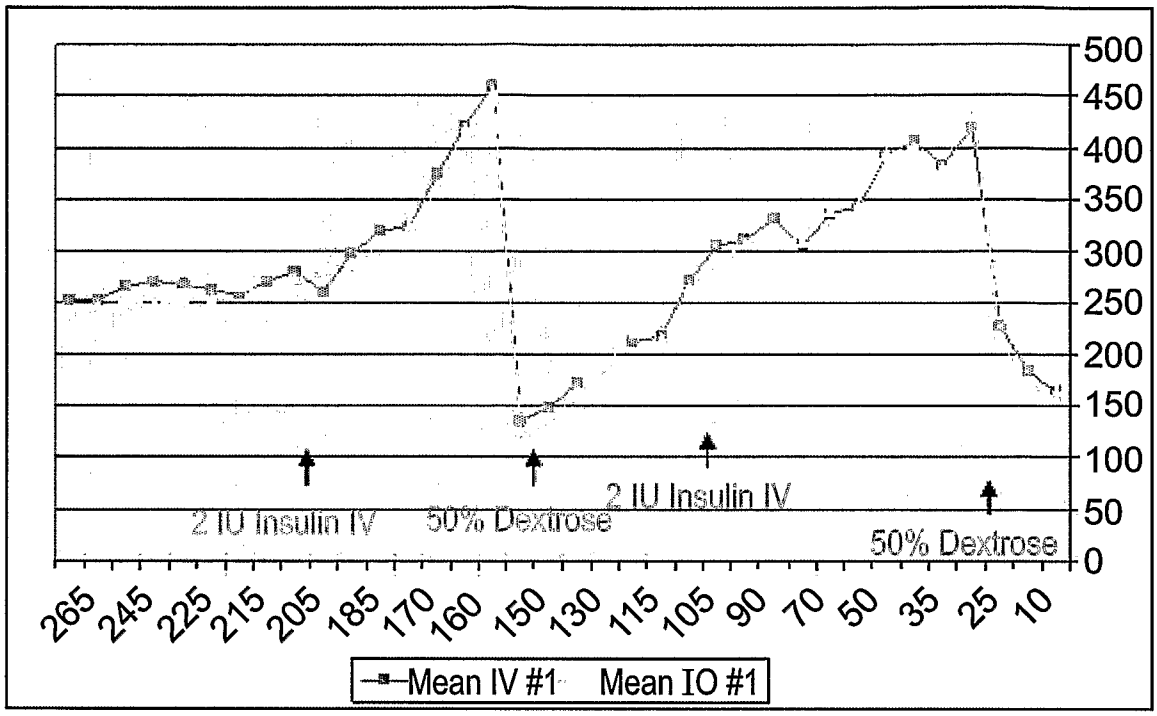

500
450
400
350
300
250
200
150
100
50
0
2 IU Insulin IV
50% Dextrose
2 IU Insulin IV
50% Dextrose
265 245 225 215 205 185 170 160 150 130 115 105 90 70 50 35 25 10
Mean IV #1
Mean IO #1

Fig. 4a

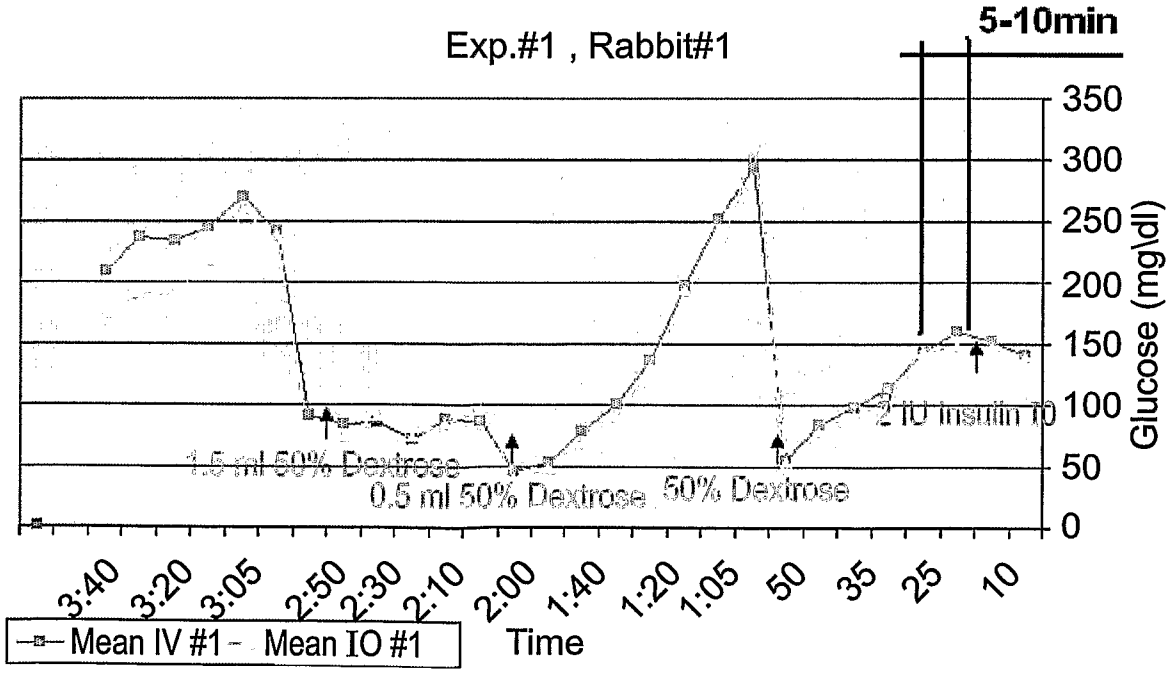

Exp.#1 , Rabbit#1
5-10min
350
300
250
200
150
100
50
0
Glucose (mg\dl)
2 IU Insulin IO
1.5 ml 50% Dextrose
0.5 ml 50% Dextrose
50% Dextrose
3:40 3:20 3:05 2:50 2:30 2:10 2:00 1:40 1:20 1:05 50 35 25 10
Time
Mean IV #1
Mean IO #1

Fig. 4b

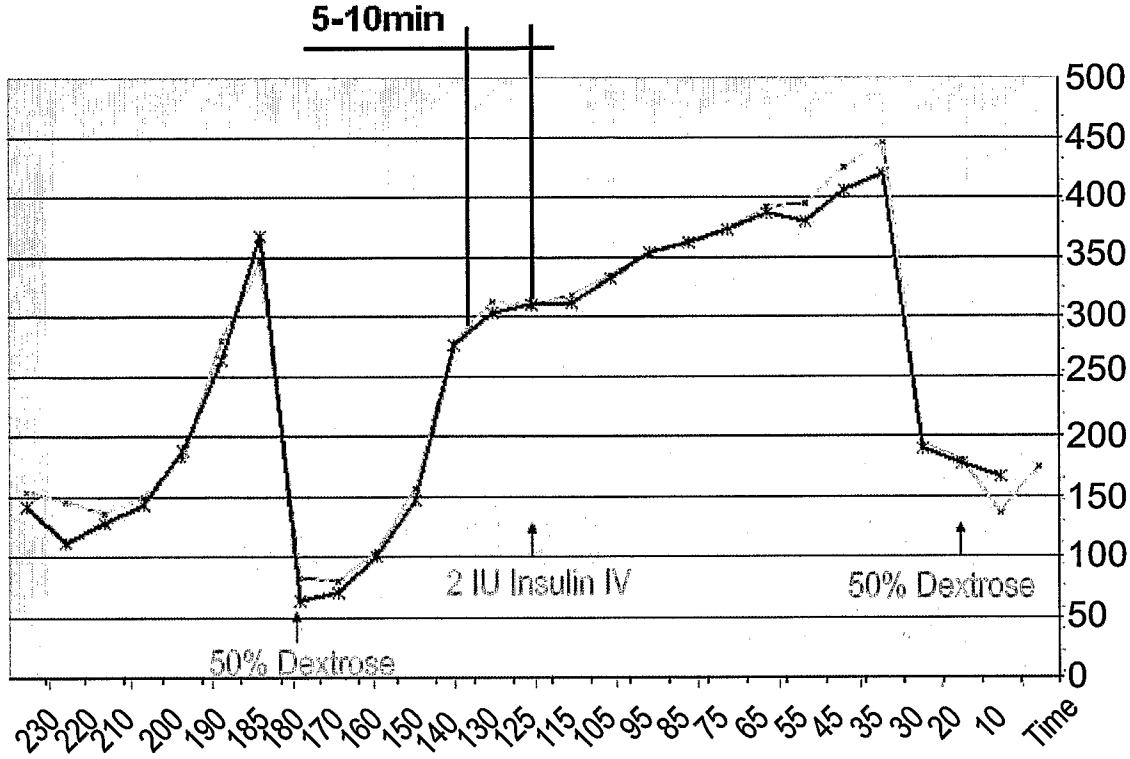

5-10min
500
450
400
350
300
250
200
150
100
50
0
2 IU Insulin IV
50% Dextrose
50% Dextrose
230 220 210 200 190 185 180 170 160 150 140 130 125 115 105 95 85 75 65 55 45 35 30 20 10 Time
Time (min)

Fig. 4c