Abstract:

Chronic diseases are long-lasting in their effect and could be persistent even for years. The slow progressing, but all the more lethal chronic diseases have caught eye of scientists all over the world. Accounting for over 63% deaths all over the world, it is high time that these are kept at bay. The high expectations for an improved life and health care are increasing greatly and there is a dire need to implement advanced diagnostics and therapeutic tools for the treating several chronic diseases. Nanotechnology is a field with the potential to take over early diagnostics, effective treatment and prevention of major chronic diseases afflicting the world. This report presents the advancement in nanotechnology for the diagnosis and cure of some chronic diseases such as Diabetes, Hypertension, Cardiovascular disorders and Asthma, focusing on molecular imaging, targeted drug delivery including controlled release, regenerative medicine and futuristic applications.
Diabetes:

Diabetes or diabetes mellitus is a disease in which due to the non-availability of insulin hormone inside our body, the glucose balance is disturbed which can lead to serious complications such as lower limb amputations, blindness and cardiovascular disease. Around 150 million suffer from this multifactorial polygenic disease and the number will rise in the coming future. Although there is no cure for diabetes, patients can reduce complications which arises through the tight control of blood glucose levels. It can be caused by the autoimmune destruction of insulin producing beta cells or via tissue wide resistance which decreases the number of beta cells and also affect the activity of existing beta cells.

Various kind of diabetes besides causing acute glucose level abnormalities, also have various other risks to health that are the characteristic long-term complications. These include various cardiovascular disease, chronic renal failure, retinal damage, nerve damage, and micro vascular damage, dysfunction and poor healing.

Nanotechnology and diabetes:

Nanotechnology has been advancing in the mainstream biomedical application at a rapid rate including the areas of gene therapy, imaging and novel drug discovery delivery in the treatment of diseases like diabetes, cancer etc. Previously a lot of problems like target specificity, cytotoxicity of certain anti-carcinogenic pharmacological agents etc. are faced during drug development process. Thus to cater these problems biocompatible nanoparticles have been introduced and are being effectively used as drug delivery system. A lot of research is going on development of biosensors for glucose monitoring and a lot of success has been achieved. In this report we are going to discuss various glucose monitoring as well as drug delivery approaches aimed at releasing insulin hormone at the required sites.

Diagnostic approaches: Nanotechnology had benefitted a lot in the field of glucose monitoring and diabetes management. Some of the glucose monitoring techniques has been discussed below:

1) Nanoscale biosensors or nanobiosensors: These biosensors works on the same principle as electrochemical biosensors which works by entrapment of glucose oxidase enzyme in polymers or membranes on a metal or carbon working electrode to be used as transducer, and it is linked to a electron transporter. The liberation of electrochemical species, as hydrogen peroxide, in the enzymatic reaction was measured at the working electrode surface. These biosensors when
incorporated with nanoparticles dramatically improve the stability and specificity of the detection system. These nanobiosensors are able to perform both glucose monitoring as implantable devices, and high throughput analyses as lab-on-chip devices for low concentration detection. Various types of nanomaterials ranging from nanoparticles to nanotubes, nanowires, nanorods, nanofibres, as well as nanocomposites, have been employed to enhance the performance of detection system and lowering the detection limit. Some of them are discussed below:

a) Nanoparticles: Metal nanoparticles (NPs) have been largely employed in electrochemical biosensing, more precisely gold nanoparticles may serve as surface for the attachment of biocomponents in platforms setup which provides a higher stability of the biosensor in.

b) Nanowires, nanofilms and nanofibres: Nanowires have been used as a immobilizing platform for glucose oxidase enzyme, nanofibres have also been widely used as electrode or as conducting molecular wires for the immobilization of biological material for sensors.

c) Nanotubes: Nanotubes have attracted a great attention since they allow biocomponent loading on higher surface area and have higher conductivity, improving electrical communication between surfaces and immobilized biocomponents.

d) Nanocomposites: These consist of different nanomaterials for particles to tube, wires or fibres. The resulted nanostructure, have high purity and high surface area, showed good electrocatalytic activity toward oxidation of glucose, as well as high sensitivity and stability.

2) Quantum dots: Semiconductor QDs have excellent optical properties for its use in sensors, such as narrow fluorescence peaks and lesser photobleaching. Since these quantum dots cannot interact with glucose hence there are incorporated with a recognition element for glucose for example cadmium telluroid.

This biosensor architecture allows the rapid optical detection of glucose. However as a replacement of electrochemical sensors these are quite expensive but have an ideal long term implantation.

3) Field effect transistor (FET): These type of electrochemical biosensors measures the change in a particular property affected by charges near the surface of the sensor or the pH of the solvent causing the sensor to register a change in the measured property. This allows the indirect quantification of glucose level but at the same time pH change in the bulk affect the response.

4) Fluorescent polymeric nanosensors or “smart tattoo”: This approach involves biosensing through the skin rather than having an electrode system implanted. Accordingly the fluorescence property change in response to blood glucose level and this change can be noted base on optical interrogation through the skin. In this glucose binding proteins are incorporated on the
microsphere surface through layer by layer assembly of a nanofilm to encapsulate the components, e.g. Polyethylene glycol beads.

Various nanobiosensors have been developed using this property of fluorescent signals like the one using forster resonance energy transfer (FRET) and one using highly plasticized hydrophobic polymers.

5) Nanorobots: Nanorobots have been so designed to flow in the blood vessels along with RBCs detecting the glucose level. The nanorobots hardware is designed so that as soon as it receives the signal for glycemic management through some wireless communication. Each time the glucose achieves critical levels, the nanorobot indicate the person by emitting an alarm about their increased glucose level through the cell phone, allowing the patient to quickly take medications prescribed by his doctor.

Sensor microchips are also being developed to continuously monitor fundamental body parameters like pulse rate, body temperature and blood glucose level. A specially designed chip would be implanted under the skin and transmit a signal that could be monitored continuously.

Therapeutic techniques: Drug-delivery and nano-controlled release system of insulin hormone

1) Controlled insulin release via multilayer encapsulation system: In this technique solid insulin nano aggregates have been prepared and encapsulated via layer by layer adsorption of two or more oppositely charged biodegradable and biocompatible layers and the deposition is carried on layer by layer sequentially over a charged substrate. The insulin release is pH controlled. Amount of insulin released from the system depends on the range of pH because of the negative charge developed on insulin and hence the varied interaction with differently charged layers.

2) Nano-network approach to controlled drug release: Here the insulin nanoparticles are contained in a solid core covered with modified dextran and glucose oxidase enzymes. These core nanoparticles are given either a positive biocompatible covering made up of chitosan or negative covering made up of alginate. When the final solution is prepared these oppositely charged structures attract each other and formed a nano-network which holds the particles together and prevents them from dispersing. When the glucose oxidase enzyme is exposed to high glucose content it converts glucose to gluconic acid which further attacks dextran which results into the release of insulin which monitors the glucose level. However this experiment is restricted for human use till now.

3) Artificial Nanopancreas: It was designed to contain insulin in its inner chamber and a glucose sensor on its surface. This sensor electrode would continuously measures the glucose level in the blood and any abnormality would be fed back into a small computer controlling infusion pump responsible for insulin release in the blood stream and thereby bringing the glucose level down. Due to its large size it is not yet commercially available.
4) **Silicon box containing pancreatic beta cells:** In this the box containing pancreatic beta cells is surrounded by a material with a very specific nanopore size (about 20 nanometers in diameter). These allow the passing of glucose and insulin but inhibit the entrance of other immunosuppresant cells. These are implanted under the skin of patients.

5) **Nanopumps:** These insulin pumps use islet beta cells to create insulin and deliver it as needed. The pump is nanoetched with silicon membranes with spores that allow only insulin to move out whereas inhibits other unimportant cells to move inside that would attack implanted beta cells. A nanoinsulin pump would be much smaller than existing implantable insulin pumps and would be much longer lasting and easier to insert into the patient.

6) **Oral and subcutaneous absorption of insulin nanoparticles:** Submicroscopic polymeric pluronic acid particles are produced enclosing insulin which can be taken via subcutaneous injections or oral doses.

**Hypertension**

For flow of blood through arteries, it requires some force which is measured in terms of blood pressure. When flow of blood changes than blood pressure may elevate or lower according to the flow. When blood pressure is elevated then heart has to work harder than normal for proper flow of blood through blood vessels. This chronic medical condition, in which the blood pressure in the arteries is elevated, is known as Hypertension or High Blood Pressure or Arterial Hypertension.

In normal conditions, blood pressure at rest is within the range of 100-140mm Hg systolic (top reading) and 60-90mm Hg diastolic (bottom reading). If blood pressure is at or above 140/90mm Hg, it is termed as High Blood Pressure. Blood pressure greater than 180/110mm Hg is termed as ‘Hypertensive crisis.’

Symptoms of hypertension are headaches, lightheadedness, vertigo, tinnitus, altered vision. Physical examination can be done by examining optic fundus in the back of the eye for presence of hypertensive retinopathy.

**Cause:** Hypertension can be classified as either Primary hypertension or Secondary hypertension. High salt intake, high alcohol consumption, use of high fat products can cause primary hypertension. Stress plays a minor role. For adult primary hypertension, early life events like low birth weight, maternal smoking, lack of breast feeding etc. can be implicate as risk factors. Some risk factors for secondary hypertension are endocrine conditions, sleep apnea, obesity, excessive liquorice, illegal drugs, herbal medicines. Hypertension may result from a complex interaction of genes and environmental factors.

**Diagnosis and Drugs:** Diagnosis of hypertension is done on the basis of a persistently high blood pressure. Some typical tests performed in hypertension are-
<table>
<thead>
<tr>
<th>System</th>
<th>Tests</th>
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<tbody>
<tr>
<td>Renal</td>
<td>Microscopic urinalysis, Proteinuria, BUN, Creatinine</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Serum sodium, calcium, potassium, TSH</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Fasting blood glucose, HDL, LDL, Total cholesterol, triglycerides</td>
</tr>
<tr>
<td>Others</td>
<td>Hematocrit, Chest radiograph, Electrocardiogram</td>
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</tbody>
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Source: Harrison’s principles of internal medicine

For treatment of hypertension, health care provider (Doctor) will advice to lose weight, stopping smoking and exercising. Some medicines for high blood pressure are

- Diuretics- These pills help kidneys in removing of salt from blood. eg. Chlorthalidone, hydrochlorothiazide.
- Beta blockers- These pills will help heart beat slow and lower the pressure.
- Angiotensin-converting enzyme inhibitors (ACE Inhibitors) – These inhibitors make blood vessels relax, hence blood pressure goes lower.
- Angiotensin II receptor blockers- These blockers works same as ACE Inhibitors. eg. Olmesartan Medoxomil.
- Calcium channel blockers- These blockers stop calcium from entering to the cells that will relax blood vessels.
- Renin Inhibitors- These newer types of medicines act by relaxing blood vessels for controlling of blood pressure.

Sometime patients have to take more than one drug/medicine to control blood pressure. These medicines may have several side effects such as-

- Cough, Diarrhea
- Erection problems
- Feeling tired, weak, nervous
- Skin rash
- Weight loss or gain without trying

**Nanoparticle Based Hypertension Treatment:** In pulmonary artery when pulmonary vascular resistance increases and fatal right ventricular fails, this is known as Pulmonary Arterial Hypertension (PAH). In treatment of PAH currently the most effective drugs have a very short life-cycle, difficult rendering systemic administration. As a future prospective, these difficulties can be overcome by using nanotechnology.

PAH, asthma and COPD (Chronic Obstructive Pulmonary Disease) share pathological features, such as inflammation, smooth muscle contraction. No existing drugs have the potential to deal with these pathomechanism. Using combination of long active VIP analogs with drug delivery systems may provide clinically useful agents for the treatment of pulmonary hypertension in asthma and COPD. Nanoparticles used as drug delivery system-
1. **Liposomes** – Liposomes are nanosize artificial vesicles of spherical shape that can be produced from natural phospholipids and cholesterol. Liposomes size should be big so that they can carry sufficient amount of drugs. After encapsulation of drug, liposomes should protect their payload from degradation in microenvironment at pulmonary artery and a controlled, retarded release of the drugs.

2. **Micelles** – Micelles are self-assembled supermolecular structures consisting of amphiphilic macromolecules. When come in contact of water, these amphiphilic assemble to form nanoscopic core-shell structure that can be used as reservoirs for hydrophobic drugs. PEG-based cationic micelles are used for intratracheal gene transfer to the lung of rats with monocrotaline- induced PAH. Using these nanoparticles, a remarkable therapeutic efficiency was achieved without compromising biocompatibility.

3. **Polymeric Nanoparticles** – From previous studies of microspheres and submicron particles, uses of polymeric nanoparticles was derived. Generating aqueous droplets in the range of 1-3um have the chance of carrying numerous nanoparticles in one droplet. Feasibility of polymeric microspheres as an inhalable carrier for prostaglandin E1(PGE1) for the treatment of PAH was studied using Poly(lactic-co-glycolic acid) (PLGA) microspheres. Another approach for treatment of PAH is using combination of polyethylene oxide-w-lactic acid (PELA) and hydrophilic prodrug (PROLI/NO) is not yet been successful even using nanoparticles. Further studies are going on for success of this method.

   In another approach bioabsorbable polymeric nanoparticles formulated from a PEG-PLGA enabled the delivery of a NF-κB decoy oligodeoxynucleotide which is directed against the Nuclear Factor-KB (NF-KB) binding site in the promoter region. This study in a rat model of monocrotaline- induced PAH showed that these nanoparticles prevent monocrotaline- induced NF-KB activation.

4. **Nanocrystals and Nanoprecipitates** – Nifedipine (hypertension drug) nanoparticles are coprecipitated with steric acid to form a negative surface charged colloid. To achieve agglomerated nanoparticles of a controlled size, destabilization of the colloid was done by using NaCl to disrupt the electrostatic repulsion between the particles. Such nanoparticles are well suited for pulmonary delivery.

   Tranilast, an antiallergic agent that has a potential for the cotreatment of pulmonary inflammation during PAH, can be processed as wet-milled crystalline particle with a mean diameter of 122 nm.

**Benefits of Nanoparticle-mediated Drug Delivery:**- According to a study at National Institute of Pharmaceutical Education and Research, Panjab (India) (Ankola et al) on ‘Development of potent oral nanoparticles formulation of coenzyme Q10 for treatment of hypertension’ indicates the potential of nanobiotechnology in improving the therapeutic value of molecules like CoQ10, facilitating its usage as first line therapeutic agent.
As shown earlier, PAH, asthma and COPD share pathological features, so no drug has potential to deal with these. But using nanoparticles of long VIP analogs, these diseases can be treated.

Study at Kyushu University, Japan (Chen L et al) reveals that by using nanoparticle based drug delivery system, improved survival rate was achieved as compare to control group.