Review Article

NANOTECHNOLOGY THERAPY FOR T2DM: CHALLENGES AND FUTURE PERSPECTIVES, 2024.

Abstract

Nanotechnology, the study and application of materials and systems at the nanometer scale (1–100 nm), has revolutionized multiple fields, including medicine. Nanoscience examines structures on this scale, and nanotechnology transforms them into practical applications. The historical development of nanotechnology traces back to ancient times, with early civilizations unknowingly applying nanoscience principles in metallurgy, textile production, and art. However, modern nanotechnology emerged in the 20th century, gaining momentum through key discoveries, government programs, and global research initiatives. Pioneers like Norio Taniguchi and Richard Feynman laid the foundation for today's advancements, which now integrate nanomaterials like nanoparticles, nanowires, and quantum dots in fields ranging from disease diagnostics to targeted drug delivery. Nanomedicine leverages nanoscale phenomena for healthcare applications, including artificial nanostructures for disease treatment and detection. Despite its ancient roots, nanotechnology has rapidly evolved, driven by modern scientific research and national initiatives aimed at economic and healthcare breakthroughs.

Keywords: Nanotechnology, Nanoscience, Nanoparticles, Quantum dots, Nanowires
Targeted drug delivery

1. INTRODUCTION

Diabetes Mellitus (DM) is a chronic disease characterized by impaired metabolism of glucose[1]. The two most common forms of diabetes are type 1 diabetes (diminished production of insulin) and type 2 diabetes (impaired response to insulin and β-cell dysfunction). Both lead to hyperglycemia, excessive urine production, compensatory thirst, increased fluid intake, blurred vision, unexplained weight loss, lethargy, and changes in energy metabolism[2].

T2DM is a complex heterogeneous group of metabolic conditions characterized by increased levels of blood glucose due to impairment in insulin action and/or insulin secretion[2]. about 462 million people worldwide (4.4% of those in the 15–49 age group, 15% of those in the50–69 age group, and 22% of those over 70) had type 2 diabetes and 1.4 million deaths and 2.5% of total Deaths are attributed to diabetes in 2017[3]. This represents 6.28% of the global Population and a prevalence rate of 6059 cases per 100,000 people[4].

Diabetes alone is responsible for almost a million deaths annually, it is among the top 10 causes of death in adults[5]. Males show a slightly higher prevalence than Females (6219 compared with 5898 cases per100, 000) and the incidence peaks at around 55 years of age[3]. By 2030, the number of people with type2 diabetes worldwide is expected to reach 7079 per 100,000, indicating a persistent increase incases Worldwide[6]. The prevalence of type 2 diabetes varies greatly Throughout Ethiopia; it ranges from 0.34% in rural Amhara to 15.8% in thriving Addis Ababa, with a 6.5%national average[7].

1.1 Pharmacological Intervention of DM

Metformin and insulin have historically been primary treatments for T2DM, assisting in controlling blood sugar levels and managing weight. Recently approved for youth T2DM, a GLP-1 Receptor Agonists (Glucagon-Like Peptide-1 Receptor Agonists), encourages insulin release and modest weight reduction. While it necessitates daily injection, forthcoming formulations might simplify administration. Remaining anti-hyperglycemic medications lack approval for youth, underscoring the importance of exercising caution in their use until further research confirms safety and efficacy outside clinical trials[8].

1.2 Non pharmacological Interventions of DM

Non-pharmacologic interventions play a crucial role in managing youth with T2DM. Weight loss, achievable through dietary changes and increased physical activity, improves insulin sensitivity and glucose control [9].

Very low-calorie diets have shown promising results in adolescents, albeit with challenges in long-term sustainability and nutrient deficiencies. Goals include a 7%-10% reduction in BMI or maintaining a BMI below the 85th percentile for age and sex, emphasizing gradual changes in diet and daily activity[10].

Individualized dietary plans, focusing on nutrient-rich foods and portion control, alongside regular consultations with a dietitian, are essential. Similarly, increasing physical activity to at least an hour daily, including aerobic and strength exercises, while minimizing sedentary behaviors, is recommended for improved outcomes in youth with T2DM.

1.3 Limitations/ disadvantages of current treatment

The disease with its several complications brig ups the immediate need to act with a comprehensible strategy. The primary platform is aimed at receiving complete glycemic regulations, possible through estimation of present glycemic status and Study of associated disorder would aim at issuing the healthcare facilities to the patient.

i. The new generation of drugs like sulphonylureas or insulin results in hypoglycaemia and weight gain as well.
ii. Biguanide like metformin can show gastrointestinal effects like diarrhea, nausea and sometimes lactic acidosis.
iii. Thiazolidinedione used is also results in weight gain, which is an issue of concern as type2 diabetes patients are already obese
iv. Drug like incretions mimetic may Show nausea, vomiting and diarrhea.
v. Drugs showing ability to cure diabetes have been used individually and in combination With Different oral agents and also with insulin but obtaining total glycemic control is tough[11].

2. INTRODUCTION TO NANOTECHNOLOGY

Nanotechnology is the study, design, synthesis, creation, manipulation, and application of materials, devices, and systems at the nanometer scale (One meter consists of 1 billion nanometers)[12]

Nanoscience is the study of structures and molecules on the scales of nanometers ranging between 1 and 100 nm, and the technology that utilizes it in practical applications such as devices etc. is called nanotechnology[13].

As a comparison, one must realize that a single human hair is 60,000 nm thickness and the DNA double helix has a radius of 1 nm[14].

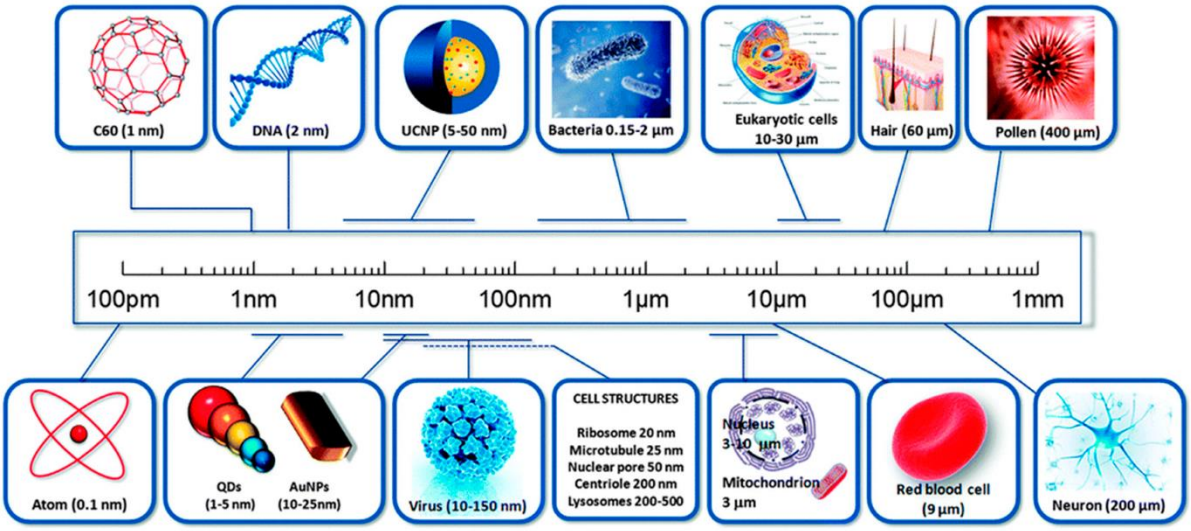

Figure 1;The size of nanoparticles as compared to other biological relevant compounds[14]

Nanotechnology offers sensing technologies that provide more accurate and timely medical information for diagnosing disease, and miniature devices that can administer treatment automatically if required[15].

Nanomedicine integrates nanotechnology into healthcare, exploring atomic and molecular levels within the 1-100 nanometer range. Its goal is to harness nanoscale phenomena and materials to create unique structures and systems. Nanotechnology components mimic biological structures,

with quantum dots resembling proteins and drug-carrying nanostructures resembling viruses. This alignment enables innovations like synthetic nanostructures that detect and repair biological damage, resembling natural processes found in white blood cells and wound-healing molecules[16].

2. 1 Historical Background of nanotechnology.

Nanotechnology is a science field that involves both synthesis and the production of different nanomaterials. Nanoparticles are classified as objects of 1-100 nm size that may vary from the bulk material because of their volume. Copper, zinc, titanium, magnesium, gold, alginate and silver are used to produce various metallic nanomaterials[17].

The development of nanoscience can be traced to the time of the Greeks and Democritus in the 5th century B.C, when scientists considered the question of whether matter is continuous, and thus infinitely divisible into smaller pieces, or composed of small, indivisible and indestructible particles, which scientists now call atoms[18].

The word “nanotechnology” was introduced for the first time into a scientific world by Norio Taniguchi at the international conference on industrial production in Tokyo in 1974 in order to describe the super thin processing of materials with nanometer accuracy and the creation of Nano-sized mechanisms[19]. Ideas of nanotechnological strategy, which were put forward by Feynman, were developed by E. Drexler in his book “Vehicles of creation: the arrival of the nanotechnology era” published in 1986[19].

In the second half of 1980s to the early 1990s a number of important discoveries and inventions was made, which created an essential impact on the further development of nanotechnology. Since then, a considerable intensification of nanotechnological researches and designs is underway, the number of publications on nanotechnological subjects increases sharply, practical

application of nanotechnology expands; project financing in nanotechnology increases significantly, as well as the number of organizations and countries involved in it[20].

In 1991, the US launched its first nanotechnology program through the National Scientific Fund. By 2001, the National Nanotechnological Initiative (NNI) was ratified, emphasizing collaboration across federal departments. The initiative aimed to prioritize nanotech for economic and national security interests in the 21st century. Before NNI's approval, a committee surveyed global nanotech trends, disseminating findings to US experts during 1996-98[20].

In 1999 the session of the Interbranch group on nanoscience, Nano engineering and nanotechnology (IWGN) took place, the result of which was the forecast on research in nanotechnology for the next 10 years. The same year the IWGN conclusions and recommendations were supported by the Presidential Council on Science and Technology (PCAST), whereupon NNI was officially approved in 2000[21].

In a preamble to NNI the US president Clinton declared: “I earmark 500 million dollars in the current fiscal year for the state nanotechnology initiative, which will enable us to create new materials in the future , to diagnose cancer in a few affected cells and to achieve other amazing results[21].

The initiative being offered is for at least twenty years and promises to lead to important practical results”. As in the USA, considerable attention to nanotechnology development is given in Japan[21].

In 2000 the Japanese Economic Association organized a special department on nanotechnology under the auspices of the Industrial and Technical Committee, and in 2001 the Framework Plan of nanotechnology research was developed[21].

In Western Europe, countries conduct nanotechnology research through national programs. In Germany, the Ministry of Education, Science, Research, and Technology primarily supports nanotech research. England's nanotech development is overseen by the Council of Physics and

Technology Research and the National Physical Laboratory. France's strategy is guided by the National Center of Scientific Research. Additionally, China, South Korea, and other emerging nations are increasingly focusing on nanotechnology. Recently, nanotech research has also commenced in CIS countries, typically within state scientific programs[22].

The nanotechnology paradigm emerged in the 1960s, with its own development beginning in the 1980s and 1990s. Preceding this, the period up to the 1950s can be viewed as nanotechnology's pre-history. Managed nanotech development conditions arose at the end of this period, spurred by the scientific and technical revolution spanning the late 19th and early 20th centuries' [21].

2.2 Nanotechnology of the Past

Before the "Nano era," people encountered Nano-sized elements, utilizing them practically despite lacking a full understanding of their processes. Intuitive nanotechnology artifacts emerged spontaneously, showcasing unique properties of small particles, yet their underlying causes remained obscure. Individuals engaged in nanotechnology without realizing they delved into Nano world phenomena.

Throughout history, ancient techniques were often transmitted from one generation to the next without an understanding of why certain materials and resulting products possessed distinctive characteristics. Millennia ago, individuals utilized natural fibers such as flax, cotton, wool, and silk, yet the underlying principles behind their properties remained unexplored.

Ancient civilizations utilized natural fibers like flax, cotton, wool, and silk, known for their nonporous structure with pores ranging from 1 to 20 nanometers. These fabrics boasted practical benefits, such as efficient sweat absorption and quick drying. Additionally, fermentation processes mastered since antiquity produced staple food items like bread, wine, beer, and cheese, functioning at the Nano level.

In ancient Egypt, black hair dyeing was prevalent, initially thought to involve natural vegetative dyes like henna. However, recent studies by Ph. Walter analyzing hair samples revealed a

mixture of lime, lead oxide, and water used for black dyeing, forming galena nanoparticles during the process. Natural black hair color, containing melanin, dispersed within keratin, was enhanced by Egyptians' innovative use of sulfur in the dyeing paste, producing uniform galena particles for consistent and lasting dyeing effects.

In the British Museum's collection stands Licurgus's bowl, a remarkable artifact crafted by Ancient Roman glassmakers. Notably, this bowl, adorned with the likeness of Licurgus, the Edonian king, possesses unique optical properties: its color shifts depending on the light source's location, whether indoors or outdoors.When exposed to natural light, the bowl appears green, but when lit from within, it transforms into a red hue. Initial analysis conducted in General Electric laboratories in 1959 revealed the bowl's composition to be typical soda-lime-quartz glass with traces of gold, silver (around 1%), and manganese (0.5%).

Researchers initially speculated that colloidal gold contributed to its unique color and dispersion. Subsequent advancements in research techniques unveiled gold and silver particles ranging from 50 to 100 nanometers in size, identified through electron microscopy and X-ray imaging, as responsible for the bowl's distinctive coloring.

In a 2007 Scientific American article on Plasmons, H.A. Atwater attributed the phenomenon to the excitation of electrons by metal nanoparticles. During the Middle Ages, European engineers achieved significant advancements in the manufacturing of multi-colored stained-glass windows for churches. Recent research indicates that these windows included additives of gold and nanoparticles of other metals.

From the 9th to the 17th centuries, Islamic and later European ceramic glazes, known as "luster," incorporated nanoparticles like silver (Ag) and copper (Cu). Renaissance pottery in Italy during the 16th century also utilized nanoparticles, influenced by Ottoman techniques. In the 13th to 18th centuries, nanowires of cementite and carbon nanotubes were employed in creating "Damascus" saber blades for enhanced strength and sharpness. Despite intentionally producing

these colors and properties for centuries, medieval artists and forgers remained unaware of the underlying causes behind these effects[24].

3. APPLICATIONS OF NANOTECHNOLOGY

3.1 Applications of Nanotechnology in Diagnosis

3.1.1 Nanowires

Nanowires (NW) are Nano sized channels that allow passage of electrical current at very low amplitude and can be constructed from carbon nanotubes, metal oxides or silicon. Their very small size and minute diameter, usually 10nm, makes them sensitive to any minute change in electrical properties at any slight adjustment for example when an additional molecule is bonded to it[25].

Nanowire-based devices offer versatile platforms for highly sensitive electrical detection of biological and chemical substances. By placing nanowires across microfluidic channels, they can detect molecular signatures of particles passing through, aiding in disease diagnosis by identifying altered genes. These systems enable researchers to locate genetic changes associated with diseases with high precision[25].

3.1.2 Nanotubes

These are small electrically insulated tubes or pores which can detect a single molecule when this passes through the tube or pore. The molecule's detection is based on the change of the ionic current of the electrolyte solution containing the molecules of interest, which results in a change of the electrical current (translocation event signal)[26]

Nano fluidic devices integrating biochips and nanopores aim to revolutionize DNA sequencing by detecting unique molecular structures of DNA bases. This approach enables enhanced sizing

of DNA molecules through multiple measurements on single molecules, improving accuracy. Techniques integrating nanopore-containing membranes into microfluidic devices reduce noise and facilitate the design of nanopore networks for clinical applications[27]

3.1.3 Quantum Dots

Quantum dots (QD) are semiconductor nanocrystals that are readily synthesized and provide characteristic properties that are intermediate between the properties of bulk semiconductors and discrete molecules. The diameters of QDs range from 2 to 10 nm. They display quantized energy levels and size-dependent fluorescent properties[28].

The fluorescent properties of QDs are suitable for cancer targeting and imaging applications. Due to the small size and EPR effect, they can penetrate tissues well, but need to be coated with PEG to evade immune system and prolong their half-life. Quantum dots linked to tumor-specific antibody were applied in imaging of different cancers[29].

Their ability to absorb wavelengths of broad spectrum and emit narrow spectrum is especially beneficial, as one light source can be used and therefore the costs are significantly lower and the analysis of data is easier. In addition, no signal amplification is necessary. Moreover, it is possible to quantify signal, but comparison between individual signals is not possible[29]. Quantum dots can also be linked covalently with fluorescence microscopy to observe cells in living animals; immune fluorescent labelling of breast cancer marker Her2 have been achieved with the specific cancer 18antibodies covalently linked to quantum dots covered by polyacrilate cap and quantum dots with detectable luminescence encapsulated in carbohydrate are useful in cancer imaging[28].

3.1.4 Nanobots

Also known as nanorobotics, are robots of nanometer (10−9m) scale, that has been applied in medicine for early diagnosis as well as targeted drug-delivery for treatment of cancer, pharmacokinetic monitoring of diabetes and healthcare. Nanobots dentifrices (dentifrobots), for

instance, when used as mouthwash or toothpaste can cover all sub gingival surfaces, thereby metabolizing any trapped organic matter into harmless and odorless vapors[30].

Pathogenic bacteria that exist in dental plaque are identified and destroyed, using properly configured dent if robots in fact, Nanobots have been predicted to be injected into patients so as to perform work at the cellular level. Biochips and Nanobots are good examples of Nanobots[30].

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3.1.5 Silica Nano spheres

Just like QDs, inorganic dye-loaded silica particles are characterized by good photo stability, sharp emission peaks, and long-lasting fluorescence lifetimes. They are appropriate for dispersion aqueous solutions, due to their hydrophilic surface. They are usually used to conjugate optical labels in order to increase the detection signal, such as organic or inorganic dye molecules (lanthanide-based and ruthenium-based)[31].

3.1.6 Nano biosensors

Biosensors are chemical sensors, in which recognition processes rely on biochemical mechanisms utilization. They consist of a biological element (responsible for sampling), and a physical element (often called transducer, transmitting sampling results for further processing[32]. Nanomaterials serve as sensitive sensors for medical diagnostics, identifying specific cells or regions in the body. They utilize various forces and parameters to distinguish cancer cells at the molecular level, facilitating targeted treatment delivery. Additionally, Nano sensors detect external changes and relay information to enhance diagnostic accuracy within the body..[32]

3.2 Applications of Nanotechnology in Treatment.

3.2.1. Role of nanotechnology in gene therapy

Gene therapy is a procedure to replace a defective gene in the DNA (which is responsible for causing a disease) with a normal gene. The gene is usually inserted into the stem cells using a vector[33]. Stem cells have long life and a self-renewal ability; therefore, they are the most suitable targets for gene therapy[34].

The vector used should be highly specific and efficient in releasing the gene or genes of variable sizes. It should not be recognized as an antigen by the host immune system. The vector must have the ability to express the inserted gene throughout the life of that organism When the gene is correctly inserted into the cells, it inhibits and corrects the functions of the mutated gene and induces the normal functioning of cells[35].

Viral vectors, fundamental in gene therapy for years, leverage host machinery for protein synthesis via DNA encoding. Their stable integration into host genomes enables long-term transgene expression. Common vectors like lentiviruses, retroviruses, and adenoviruses are efficient. Risks include immune responses, inflammation, and off-target changes, impairing efficacy[36].

Immune responses may render therapy ineffective and trigger rapid viral clearance upon subsequent exposure. Inflammation, as seen in a case study where a leukemic patient died from adenovirus overdose, highlights potential dangers. Insertional mutagenesis, especially with retroviruses, poses tumor risks by activating oncogenes. Selecting suitable viruses for diverse cell types remains a challenge in gene therapy[37]

Gene therapy using non-viral nanostructures is safe, as compared to therapy using viral vectors. They are also much less oncogenic and rarely trigger immune responses. Their preparation is much easier than that of viral vectors. There is no risk of virus recombination and no limit on the size of the gene to be loaded. NPs are one of the many nanostructures that are used for non-viral gene delivery. The presence of a positive charge, small size, and high surface-to-volume ratio enables them to penetrate deep into the membranes, thus making them ideal vectors for gene delivery[38].

3.2.2 The role of nanotechnology in targeted drug delivery

Nano vectors facilitate precise drug delivery, crucial for avoiding toxic solvents' release elsewhere in the body and minimizing contamination. Their diminutive size enables deep penetration into tumor cells, enhancing cancer treatment efficacy through targeted and localized drug release. This approach allows for continuous controlled drug release at desired levels, reducing overall drug doses and improving therapeutic outcomes. Nanostructures hold promise for overcoming barriers in target-specific drug delivery, offering a viable solution for treating various diseases with minimal side effects[38].

The NPs used for drug delivery must contain some important components, including a particle core, an outer biocompatible protective layer and a linking molecule for increased bioactivity (it attaches the core of NPs to bioactive molecules because of the reactive compounds present at both of its ends). Nano vectors are modified before drug delivery and this modification includes coating with ligands such as peptides, folic acid, and antibodies. Ligands are attached to NPs so that they can bind specifically to targeted sites to enhance the specificity even more[39].

It is essential to attach more than one ligand because if only one ligand is attached, there is a possibility that it may bind to receptors present in places other than on the targeted site. In addition, tumor cells are usually overexpress, i.e., they have more than one type of surface receptor. Since Nano vectors possess unique properties and various modifications can be performed during drug loading[40].

3.2.3Treating cardiovascular diseases through Nano systems

Millions of deaths worldwide are attributed to cardiovascular diseases. Despite advancements in treatments that have improved survival rates among heart disease patients, complete cardiac regeneration, especially following cardiac infarction, remains elusive. Stem cell therapy presents a promising approach for therapeutic angiogenesis[41]. Incorporating anti-apoptotic and pro-angiogenic genes into genetically engineered stem cells can extend their lifespan and enhance

their paracrine secretion. Due to limitations in gene capacity and immunogenicity, viral vectors are unsuitable for gene delivery to stem cells. Bio-compatible nanoparticles demonstrate efficacy in transferring genes to stem cells[42].

A diverse range of nanostructures facilitate gene delivery to stem cells. Liposomes excel due to their ability to prevent nonspecific gene binding and degradation. Polymers offer enhanced target specificity and efficiency. Chitosan alginate nanoparticles, in a study, delivered growth factors to placental cells, enhancing cardiac tissue function at myocardial infarction sites through continuous growth factor release[43]. NPs possess the capability to track and monitor stem cells, with superparamagnetic iron oxide Nano systems (SPIONs) designed to bind to cell surfaces for cellular entry through endocytosis. Additionally, quantum dots offer a means to monitor living cells over extended periods[44]

Hypertension presents numerous complications, such as myocardial infarction, heart failure, stroke, elevated blood pressure, and organ damage like to the eyes, kidneys, and brain. Despite the availability of antihypertensive medications, challenges persist, including short half-lives, limited bioavailability, low water solubility, and adverse effects. Targeted drug delivery via nanotechnology has emerged as a promising solution to address these issues[45]

Nanotechnology offers diverse carriers for hypertension treatment, including lipid carrier NPs, solid lipid NPs, polymeric NPs, liposomes, and Nano emulsions. These exemplify its potential in cardiovascular therapy, particularly non-viral stem cell-based treatments. However, extensive studies on Nano vectors' effects in living cardiovascular models are necessary for safe human application[45].

3.2.4 Nanotechnology in the treatment of ocular diseases

Nanoparticles (NPs) overcome ocular delivery challenges due to their small size and variable surface properties, efficiently navigating barriers like the tear film and ocular surface epithelium.

Their biodegradability eliminates the need for surgical removal post-delivery, offering a promising solution for targeted drug transport in the eye with minimal toxicity[46].

Anterior eye diseases, such as cataracts, conjunctives, keratitis, dry eye, corneal injury, etc., are usually treated using eye drops but the corneal barrier causes drugs to have poor bioavailability. However, Nano systems can increase the bioavailability by prolonging the retention time of the drug on the surface of the eye and improving the penetration of the drug[47].

On the other hand, posterior eye diseases in the choroid and retina include retinoblastoma, glaucoma, choroidal neovascularization, macular degeneration, and posterior uveitis. Eye drops are not usually effective in treating these diseases, so intraocular injections are performed, which leads to many unwanted side effects[48].

However, Nano systems have improved the delivery of drugs to the posterior portion of eye and the various Nano systems used for this purpose include Nano vesicles, Nano implants, NPs, and hydrogels[48].

3.2.5 Nanotechnology in the Treatment of Brain Diseases

Brain diseases can be treated efficiently if we can overcome the issue of the blood– brain barrier (BBB). The BBB is a boundary between circulating blood and the neural tissues of the brain. The presence of the BBB is the major hurdle in the treatment of brain diseases because it does not allow the drugs to enter the central nervous system (CNS) and maintains homeostasis in the brain[49].

Disturbances to the BBB lead to neuro-inflammatory and neurodegenerative diseases like Parkinson's and Alzheimer's. Despite this, damaged BBBs impede drug delivery to the brain. Nanoparticles (NPs) offer a solution, crossing the BBB efficiently to deliver drugs. NPs utilize both organic (e.g., PLA, PLGA) and inorganic (e.g., silica, gold) materials for penetration. Their small size, high drug-loading capacity, and imaging prowess make NPs effective in treating such diseases.

4. ADVANCEMENT OF NANOTECHNOLOGIES IN TYPE 2 DM.

Diabetes is a metabolic disease characterized by chronically elevated blood glucose levels (BGLs) and an inability to maintain BGL homeostasis. Type 2 diabetes is characterized by insulin resistance, or a deficiency in cellular response to insulin in the bloodstream[50].

Diabetes has grown to become one of largest public health challenges globally, affecting 25.8 million in the United States and 382 million worldwide; and this number is expected to grow to 592 million by 2035[51]

Daily insulin injections are painful and lead to patient noncompliance, and can lead to dangerous insulin overdoses[52]. Additionally, periodic measurement of blood glucose may not detect large fluctuations in BGLs which occur between points of measurement. Therefore, systems which improve blood glucose monitoring, or "close the loop" between glucose measurement and insulin delivery, are highly desirable.

4.1. Use of nanotechnology in the detection of insulin and blood sugar (Diagnosis):

A new method that uses nanotechnology to rapidly measure minute amounts of insulin and blood sugar level is a major step toward developing the ability to assess the health of the body's insulin-producing cells. It can be achieved by following ways

4.1.1 Microphysiometer

The microphysiometer, constructed from multi-walled carbon nanotubes, functions as a sensor for continuous insulin monitoring. Its electrically conductive nature allows direct measurement of insulin concentration by assessing the current at the electrode. Unlike traditional methods that sample insulin intermittently, this sensor detects insulin levels continuously, responding to changes in glucose-induced insulin oxidation. This real-time monitoring enables precise insulin concentration tracking, offering significant advancements in diabetes management.[53].

4.1.2 Implantable sensor

Accurate and frequent glucose measurements are the basis of contemporary diabetes management. However, it is commonly acknowledged that contemporary clinical glucose measurement systems are a nuisance to the patient as a result of frequent and painful needle sticks, and the current standard of intermittent testing can miss dangerous fluctuations in blood glucose concentration. Therefore, one of the most significant challenges in diabetes research is the development of glucose sensors which achieve accurate glucose measurements painlessly and frequently, with the goal of continuous glucose measurement. The improved glucose sensor technology has an immediate and significant impact on the health of diabetics, as improved sensing will lead to more accurate insulin dosing and diabetes management.

Use of polyethylene glycol beads coated with fluorescent molecules to monitor diabetes blood sugar levels is very effective in this method the beads are injected under the skin and stay in the interstitial fluid. When glucose in the interstitial fluid drops to dangerous levels, glucose displaces the fluorescent molecules and creates a glow. This glow is seen on a tattoo placed on the arm[54]. Sensor microchips are also being developed to continuously monitor key body parameters including pulse, temperature and blood glucose. A chip would be implanted under the skin and transmit a signal that could be monitored continuously[55].

4.2. Use of Nanotechnology in the Treatment of Diabetes

Diabetes management traditionally involves injecting insulin due to oral insulin's ineffectiveness. A new approach involves inhaling insulin and achieving controlled release into the bloodstream, eliminating manual dosage adjustments. Nanotechnology offers solutions for insulin delivery, including oral insulin development and microsphere systems for enhanced absorption and targeted release, promising advancements in diabetes treatment.[56]. The treatment of diabetes

includes the proper delivery of insulin in the blood stream which can be achieved by nanotechnology in the following ways:

4.2.1 Development of oral insulin

Production of pharmaceutically active proteins, such as insulin, in large quantities has become feasible. The oral route is considered to be the most convenient and comfortable means for administration of insulin for less invasive and painless diabetes management, leading to a higher patient compliance[57]. Nevertheless, the intestinal epithelium is a major barrier to the absorption of hydrophilic drugs, as they cannot diffuse across epithelial cells through lipid-bilayer cell membranes to the bloodstream[58]. Therefore, attention has been given to improving the paracellular transport of hydrophilic drugs. A variety of intestinal permeation enhancers including chitosan (CS) have been used for the assistance of the absorption of hydrophilic macromolecules. Therefore, a carrier system is needed to protect protein drugs from the harsh environment in the stomach and small intestine, if given orally[59].

CS nanoparticles improve protein absorption in the intestines, especially when compared to CS solutions. Insulin-loaded CS-coated nanoparticles extend their stay in the small intestine, penetrating the mucus layer and temporarily opening tight junctions between epithelial cells due to their pH sensitivity or degradability. This facilitates insulin release into the bloodstream through the paracellular pathway, enhancing its effectiveness[60].

4.2.2 Microsphere for oral insulin production:

The most promising strategy to achieve oral insulin is the use of a microsphere system which is inherently a combination strategy. Microspheres act both as protease inhibitors by protecting the encapsulated insulin from enzymatic degradation within its matrix and as permeation enhancers by effectively crossing the epithelial layer after oral administration[61].

4.2.3 The nano pump

The nanopump is a powerful device and has many possible applications in the medical field. The first application of the pump, introduced by Debiotech, is Insulin delivery. The pump injects Insulin to the patient's body in a constant rate, balancing the amount of sugars in his or her blood. The pump can also administer small drug doses over a long period of time[62].

Figure 2 Nanopump

Source; from https://www.medtrum.com/Nanopump

Generally NPs have Advantages of

- Selective targeting
- Enhancing cellular intake and accumulation at the target site
- Enhancing stability
- Enhancing solubility
- Preventing offsite degradation
- Enhancing the half-life of the active agents in circulation
- Minimizing off target cytotoxicity
- Stimuli responsive drug release, prevents premature drug releases

5. CHALLENGES AND FUTURE PERSPECTIVES.

Understanding challenges, failures and successes of nanoparticles for clinical applications is key to future Nanomedicine success. Although nanoparticles have many useful properties, there are concerns that these same properties may increase the toxicity of nanoparticles compared with that of the bulk material[63].

5.1 Challenges.

5.1.1 Safety challenges in nanomedicines development

In recent years there has been increasing attention to toxicities unique to nanoparticle-based medicines. In general, the standard battery of formal toxicology analyses in the preclinical setting that are conducted for any new drug should be sufficient to catch any tissue specific adverse outcome with a Nanomedicine[64].

This may be a good guiding principle; however, it should be recognized that additional testing in the preclinical setting may be required that is specific for the behavior of the particular product. As an example, in case of the materials that are persistent, not readily excreted, eliminated or metabolized, or reside in particular tissues for extended periods, it is reasonable to expect a regulatory agency to require that the consequences of the longer persistence be fully evaluated[65].

In contrast, nanomaterials that can be proven to be rapidly eliminated from the body may not require protracted testing. Important and unique to nanomedicines is the safety of the Nano particulate system as a whole. International standard-setting bodies have recognized this implication and agreed that “as a minimum set of measurements—size, zeta potential (surface charge), and solubility” of nanoparticles should be used as predictors of nanoparticle toxicity (74).

The biological effects of nanoparticles can vary based on particle size and material composition. While smaller nanoparticles may induce inflammation and oxidative stress, the relationship between size and effect is complex. For instance, certain nanomaterials, like carbon nanotubes, exhibit carcinogenicity at specific sizes. Relying solely on size-based comparisons between micro and nanoparticles may not accurately assess their biological effects, leading to potential underestimation or overestimation of risks.[63].

5.1.2 Biological effect

The biological effects of nanoparticles are considered to be a result of increased tissue penetration due to their decreased particle size compared with the bulk material. That is, the biological effects of nanoparticles increase as particle size decreases[66].

Recently, we examined the relationship between particle size and acute toxicity of intravenously administered silica nanoparticles in mice (in submitted). We found that the severity of several acute toxicities such as acute lethal toxicity or liver damage increased as particle size decreased[66].

Reproductive Toxicity of Nanoparticles Fetuses and infants are particularly vulnerable to the effects of nanoparticles because their defense mechanisms, such as the blood–brain barrier and the immune system, are not yet fully developed. In fact, nanoparticles may be toxic to fetuses and infants at concentrations that have no negative effects in adults(diameter of 2.5 μm or less during pregnancy or lactation increases the risk of children developing an autism spectrum disorder)[67].

Reproductive toxicities of nanoparticles in males. Epidemiological studies have shown or less reduces sperm motility. In addition, animal experiments have revealed that exposure to -rich diesel exhaust particles disrupts the secretion of sex hormones, and that injected silver nanoparticles (20 and 200 nm) reduce sperm count, increase the rate of sperm malformation, and induce DNA damage in germ cells[65].

In addition to previous reports that some nanoparticles migrate to the testes, we have found that intravenously treated silica nanoparticles with diameter of 70 nm cross the blood–testis barrier and distribute in germ cells. we have also observed the accumulation of the silica nanoparticles in Sertoli cells[65].

5.1.3 Immunological challenges of nanomedicines

However, one set of toxicities that cannot readily carry over from preclinical testing to humans is immunotoxicity. The immune response can be elicited by different sources. Biologics such as proteins, peptides, antibody fragments, and nucleic acids in nanoparticles can serve as antigens[68].

Interaction of drug and carrier can result in conformation changes that increase immunogenicity. For example, immunological issues can arise from paclitaxel interacting with albumin. In the case of nabpaclitaxel, an immunological type response was observed in pigs with nab-paclitaxel drug but not the albumin control, supporting the observations[68]

The conjugation of C60 fullerene derivatives to bovine serum albumin (BSA) resulted in the generation of particle-specific antibodies and was used for immunization. Polyamidoamine dendrimers conjugated to BSA also showed increased antigenic potentials and induced dendrimer-specific antibody. The complex manufacturing process of nanoparticle-based medicines presents many opportunities for endotoxin contamination, which is also a source for immune response[68].

Nanoparticles exhibit varying degrees of immunogenicity, influenced by factors like size, surface properties, and charge. Certain nanoparticles can trigger the activation of the complement pathway, prompting rapid clearance by macrophages in organs like the liver and spleen. For instance, superparamagnetic iron oxide nanoparticles like Ferumoxtran-10 and ferumoxytol can be swiftly eliminated through this mechanism. [69].

5.1.4 Regulatory Challenges to nanomedicines developments

Due to the complexity and large potential diversity of nanoparticle-based products, it may seem apparent that the regulatory pathway for nanomedicines may face several hurdles. Currently, the FDA, EMA, and other regulatory agencies examine each new nanoparticle-based drug on a product-by-product basis[68].

There is generally a lack of standards in the examination of nanomedicines as a unique category of therapeutic agents. Recent movements towards establishing some definitions and guidelines are first steps in determining if additional regulation will be applied to nanomedicines[68].

The complex nature of nanoparticle-based medicines with their multiple components, where more than one component can affect pharmacological behavior of the active, contrasts against standard drugs where there is usually a single active agent and the other components mostly serve as inactive formulation aids (excipients). It is reasonable to expect that nanomedicines raises complicated regulatory strategies, and processes are likely to be significantly more complex[68].

The most important limitations of nanoparticles are that their production requires serious time and cost also, they have challenges in industrial applications. At the same time, repetitive applications and slow release may cause pulmonary inflammation, carcinogenicity, and toxicity on the cardiovascular system. The treatment cannot be terminated at any time and tissue targeting may not be fully achieved[70].

5.1.5 Ethical issues

The ethical issues involve the identification and assessment of hazards and risks, nonmaleficence (doing no harm), autonomy (self-determination), justice (fairness in distribution of risks), privacy (in handling of medical information), and respect for persons[71]. The ethical issues that most affect workers in jobs involving nanomaterials are linked to identification and communication of hazards and risks by scientists, authorities, and employers; acceptance of risk by workers;

implementation of controls; choice of participation in medical screening; and adequate investment in toxicologic and exposure control research[72]. Health effects data on workers involved with nanotechnology are limited because of the incipient nature of the field, the relatively small number of workers potentially exposed to date, and the lack of time for chronic disease to develop and be detected[72].

The most relevant human experience deals with exposures to ultrafine particles (which include particles with diameters < 100nm) and fine particles (particles with diameters < 2.5 μm). Ultrafine and fine particles have been assessed in epidemiologic air pollution studies and in studies of occupational cohorts exposed to mineral dusts, fibers, welding fumes, combustion products, and poorly soluble, low-toxicity particulates such as titanium dioxide and carbon black[72] Animal studies reveal risks associated with exposure to engineered nanoparticles, highlighting their correlation with lung inflammation and cytotoxicity due to oxidative stress. Accurate interpretation of these findings relative to human exposure levels is imperative. Evidence suggests that increased PM2.5 air pollution is linked to adverse health effects, particularly in susceptible populations, despite ongoing debates regarding concentration thresholds[72].

Animal studies show risks of engineered nanoparticles, correlating surface area with oxidative stress and lung inflammation. Higher oxidative stress heightens inflammation and cytotoxicity risks. Interpretation should account for human exposure doses. Evidence links increased PM2.5 air pollution with health effects, particularly in vulnerable populations like the elderly with respiratory and cardiovascular diseases..[72] Animal studies highlight potential hazards of engineered nanoparticles, including pulmonary fibrosis and translocation to the brain and circulation. Concerns arise over platelet activation and vascular thrombosis, indicating possible health risks for exposed workers.[72]

5.2 FUTURE PERSPECTIVES.

5.2.1 Personalized Nanomedicine

Personalized medicine may be defined as the tailored individualized management approach to achieve the right drug at the right dose to the right patient. The approach was driven by multiple factors including unjustifiable drug adverse effects in many patients as well as lack of unity in drug efficacy that can vary from 25 to 80% according to drug classes[73].

Personalized medicine involves proteomic, genomics, and epigenetic studies, as well as specific patient health conditions and environmental influence. In turn, nanotechnology is a broad term that encompasses systems in the range of 10–100 nm. The term also implies the ability to control structures at this Nano-range towards a desirable outcome[73].

Molecules at the Nano size range could interact with cells at the subcellular and molecular levels as the size allows for this otherwise unattainable interaction at a larger scale (e.g., larger than 1 μm scale). Nanomedicine had been implicated in the prevention, monitoring, diagnosis, and treatment of disease, and many of these inventions are used every day in the current clinical practice [4].

The intersection between Nano and personalized medicine lies at multiple points. Firstly, the diagnostic area, and here nanotechnology has a lot to offer in areas of exploring the status of specific drug targets, the pharmacogenetic testing, and the ability to perform both in vitro and in vivo testing. Secondly, the therapeutic area, as the Nanomedicine can tailor the drug to a specific target identified for a specific disease in a specific patient[74].

In addition, with Nanomedicine, due to its targeting capability, it is possible to achieve much higher doses than the maximum tolerated dose for the non-formulated drug. Hence, the dose can be tailored based on individualized patient conditions. Finally, Nanomedicine can circumvent two major determinants in individualized drug response related to the variability in cytochrome-P enzymes (CYP) and drug transporters in different populations. Nanomedicine drug formulation could effectively render formulated drugs as stealthy to metabolizing enzymes as well as make it intracellular in the endocytic process, which is independent of the transporter[75].

5.2.2 Nanotechnology and Artificial Pancreas Development

Nanotechnology offers transformative possibilities in Type 2 diabetes management, enabling personalized Nanomedicine for improved drug delivery and precise glucose control. The integration of Nano sensors and Nano carriers in artificial pancreas systems holds the potential to revolutionize diabetes care, enhancing patients' wellbeing and treatment outcomes[74].

Development of artificial pancreas could be the permanent solution for diabetic patients. The original idea was first described in 1974. The concept of its work is simple: a sensor electrode repeatedly measures the level of blood glucose; this information feeds into a small computer that energizes an infusion pump, and the needed units of insulin enter the bloodstream from a small reservoir[74].

An alternative approach to regulating blood glucose involves utilizing a small silicon container housing pancreatic beta cell derived from animals, encased in a material featuring precisely sized nanopores. These nanopores permit the passage of glucose and insulin while preventing larger immune molecules from entering. Implanted subcutaneously in diabetic individuals, these containers offer a temporary means of restoring the body's glucose regulation without requiring potent immunosuppressive drugs, thus reducing the risk of infection[74].

Figure 3; artificial pancreas

Sources; from https://www.canadianinsulin.com/artifial pancreas

CONCLUSIONS

Diabetes Mellitus (DM) encompasses both type 1 and type 2, characterized by symptoms such as hyperglycemia, excessive urination, thirst, and weight loss.

Type 2 Diabetes Mellitus is a global concern, with prevalence expected to rise, particularly in urban areas of Ethiopia. Treatment options range from traditional drugs like metformin and insulin to newer alternatives such as GLP-1 receptor agonists.

Non-pharmacological interventions like diet and exercise are crucial, despite challenges in maintaining them. Nanotechnology, focusing on materials at the nanometer scale, presents significant advancements in medical diagnostics and treatments, building upon historical applications.

In modern medicine, nanotechnology enhances diagnosis through sensitive sensors and facilitates treatment via gene therapy and targeted drug delivery systems. In T2DM diagnosis, nanotechnology enables highly precise sensors for insulin and glucose monitoring, while in treatment, it revolutionizes insulin delivery with alternatives like oral insulin and nanopump.

Challenges include safety concerns, biological effects, immunological challenges, and regulatory hurdles that must be addressed. Looking forward, personalized nanomedicine and advancements in artificial pancreas development hold promise for improving patient outcomes and revolutionizing diabetes management.

REFERENCES.

1. Ayelign B, Genetu M, Wondmagegn T, Adane G, Negash M, Berhane N. Tnf-α (− 308) gene polymorphism and type 2 diabetes mellitus in ethiopian diabetes patients. Diabetes, metabolic syndrome and obesity: targets and therapy. 2019:2453-9.
2. Lin Y, Sun Z. Current views on type 2 diabetes. The Journal of endocrinology. 2010;204(1):1.
3. Abdul Basith Khan M, Hashim MJ, King JK, Govender RD, Mustafa H, Al Kaabi J. Epidemiology of type 2 diabetes—global burden of disease and forecasted trends. Journal of epidemiology and global health. 2020;10(1):107-11.
4. Garus-Pakowska A: Metabolic Diseases—A Challenge for Public Health in the 21st Century. In., vol. 20: MDPI; 2023: 6789.
5. Kumar GV, Usha N, Sandyashree B. Risk Assessment for Type-2 DM among the OPD patients attending at JSS Hospital Chamarajanagara. International Journal of Nursing Education and Research. 2021;9(3):297-300.

6. Mushait K, Arabia S. Predictors and Associated Risk Factors of Development of Type 2 Diabetes Mellitus. 2022.
7. Zeru MA, Tesfa E, Mitiku AA, Seyoum A, Bokoro TA. Prevalence and risk factors of type-2 diabetes mellitus in Ethiopia: systematic review and meta-analysis. Scientific reports. 2021;11(1):21733.
8. Jones KL, Arslanian S, Peterokova VA, Park J-S, Tomlinson MJ. Effect of Metformin in Pediatric Patients With Type 2 Diabetes: A randomized controlled trial. Diabetes Care. 2002;25(1):89-94; doi: 10.2337/diacare.25.1.89.
9. Serbis A, Giapros V, Kotanidou EP, Galli-Tsinopoulou A, Siomou E. Diagnosis, treatment and prevention of type 2 diabetes mellitus in children and adolescents. World Journal of Diabetes. 2021;12(4):344.
10. Di Figlia-Peck S, Feinstein R, Fisher M. Treatment of children and adolescents who are overweight or obese. Current problems in pediatric and adolescent health care. 2020;50(9):100871.
11. Terse PP, Pawaskar P, Pawar PK, Samant SS, Teli A. Nanotechnology and Nanocapsule-Based Approaches for the Diagnosis and Therapeutics of Diabetes Mellitus: A Concise Survey. Journal of Drug Delivery and Therapeutics. 2023;13(9):151-9.
12. Sahu MK, Yadav R, Tiwari SP. Recent advances in nanotechnology. International Journal of Nanomaterials, Nanotechnology and Nanomedicine. 2023;9(1):015-23.
13. Mansoori GA, Soelaiman TF. Nanotechnology--An introduction for the standards community. ASTM International; 2005.
14. Gnach A, Lipinski T, Bednarkiewicz A, Rybka J, Capobianco JA. Upconverting nanoparticles: assessing the toxicity. Chemical Society Reviews. 2015;44(6):1561-84.
15. Thwala LN, Ndlovu SC, Mpofu KT, Lugongolo MY, Mthunzi-Kufa P. Nanotechnology-Based Diagnostics for Diseases Prevalent in Developing Countries: Current Advances in Point-of-Care Tests. Nanomaterials. 2023;13(7):1247.
16. Gordon N, Sagman U, Alliance C. Nanomedicine taxonomy. Canadian Institutes of Health Research Canada; 2003.
17. Aeila ASS, Sai TM, Kumar AR. Nanoparticles—the future of drug delivery. J. Pharmaceutical Res. 2019;9.

18. Bayda S, Adeel M, Tuccinardi T, Cordani M, Rizzolio F. The history of nanoscience and nanotechnology: from chemical–physical applications to nanomedicine. Molecules. 2019;25(1):112.
19. Omran BA, Omran BA. Fundamentals of nanotechnology and nanobiotechnology. Nanobiotechnology: A Multidisciplinary Field of Science. 2020:1-36.
20. Nasrollahzadeh M, Sajadi SM, Sajjadi M, Issaabadi Z. An introduction to nanotechnology. In: Interface science and technology. Elsevier; 2019. p. 1-27.
21. ARILESERE AO. NANOTECHNOLOGY IN MEDICAL SCIENCE. 2019.
22. Isigonis P, Afantitis A, Antunes D, Bartonova A, Beitollahi A, Bohmer N, et al. Risk governance of emerging technologies demonstrated in terms of its applicability to nanomaterials. Small. 2020;16(36):2003303.
23. Bayda S, Adeel M, Tuccinardi T, Cordani M, Rizzolio F. The History of Nanoscience and Nanotechnology: From Chemical–Physical Applications to Nanomedicine. Molecules. 2020;25(1):112.
24. Reibold M, Paufler P, Levin AA, Kochmann W, Pätzke N, Meyer D. Carbon nanotubes in an ancient Damascus sabre. Nature. 2006;444(7117):286-.
25. Garnett E, Mai L, Yang P. Introduction: 1D nanomaterials/nanowires. Chemical reviews. 2019;119(15):8955-7.
26. Robertson JW, Ghimire ML, Reiner JE. Nanopore sensing: A physical-chemical approach. Biochimica et Biophysica Acta (BBA)-Biomembranes. 2021;1863(9):183644.
27. Lyberopoulou A, Efstathopoulos EP, Gazouli M. Nanotechnology-based rapid diagnostic tests. Proof and concepts in rapid diagnostic tests and technologies. 2016:89-105.
28. Agarwal K, Mondal S, Rai H. Quantum dots: An overview of synthesis, properties, and applications. Materials Research Express. 2023.
29. Gil HM, Price TW, Chelani K, Bouillard J-SG, Calaminus SD, Stasiuk GJ. NIR-quantum dots in biomedical imaging and their future. Iscience. 2021;24(3).
30. Jackson TC, Patani BO, Ekpa DE. Nanotechnology in diagnosis: a review. Advances in Nanoparticles. 2017;6(03):93-102.
31. Reisch A, Klymchenko AS. Fluorescent polymer nanoparticles based on dyes: seeking brighter tools for bioimaging. Small. 2016;12(15):1968-92.

32. Bhatia D, Paul S, Acharjee T, Ramachairy SS. Biosensors and their widespread impact on human health. Sensors International. 2024;5:100257.
33. Cavazzana M, Bushman FD, Miccio A, André-Schmutz I, Six E. Gene therapy targeting haematopoietic stem cells for inherited diseases: progress and challenges. Nature reviews Drug discovery. 2019;18(6):447-62.
34. Shomali N, Gharibi T, Vahedi G, Mohammed RN, Mohammadi H, Salimifard S, et al. Mesenchymal stem cells as carrier of the therapeutic agent in the gene therapy of blood disorders. Journal of cellular physiology. 2020;235(5):4120-34.
35. Ma C-C, Wang Z-L, Xu T, He Z-Y, Wei Y-Q. The approved gene therapy drugs worldwide: from 1998 to 2019. Biotechnology advances. 2020;40:107502.
36. Croze RH, Kotterman M, Burns CH, Schmitt CE, Quezada M, Schaffer D, et al. Viral Vector Technologies and Strategies: Improving on Nature. International Ophthalmology Clinics. 2021;61(3):59-89.
37. Goswami R, Subramanian G, Silayeva L, Newkirk I, Doctor D, Chawla K, et al. Gene Therapy Leaves a Vicious Cycle. Front Oncol. 2019;9:297; doi: 10.3389/fonc.2019.00297.
38. Zu H, Gao D. Non-viral vectors in gene therapy: recent development, challenges, and prospects. The AAPS journal. 2021;23(4):78.
39. Harish V, Tewari D, Gaur M, Yadav AB, Swaroop S, Bechelany M, et al. Review on nanoparticles and nanostructured materials: Bioimaging, biosensing, drug delivery, tissue engineering, antimicrobial, and agro-food applications. Nanomaterials. 2022;12(3):457.
40. Hefnawy A, Khalil IH, Arafa K, Emara M, El-Sherbiny IM. Dual-ligand functionalized core-shell chitosan-based nanocarrier for hepatocellular carcinoma-targeted drug delivery. International Journal of Nanomedicine. 2020:821-37.
41. Bian X, Ma K, Zhang C, Fu X. Therapeutic angiogenesis using stem cell-derived extracellular vesicles: an emerging approach for treatment of ischemic diseases. Stem cell research & therapy. 2019;10:1-18.
42. Wang Y, Bruggeman KF, Franks S, Gautam V, Hodgetts SI, Harvey AR, et al. Is viral vector gene delivery more effective using biomaterials? Advanced Healthcare Materials. 2021;10(1):2001238.

43. Smagul S, Kim Y, Smagulova A, Raziyeva K, Nurkesh A, Saparov A. Biomaterials loaded with growth factors/cytokines and stem cells for cardiac tissue regeneration. International journal of molecular sciences. 2020;21(17):5952.
44. Wagner AM, Knipe JM, Orive G, Peppas NA. Quantum dots in biomedical applications. Acta biomaterialia. 2019;94:44-63.
45. Baishya B, Rahman SS, Rynjah D, Barman K, Bordoloi SS, Islam J, et al. Enhancing of oral bioavailability of poorly water-soluble antihypertensive drugs. Int J Curr Pharm Res. 2021;13(4):42-7.
46. Omerović N, Vranić E. Application of nanoparticles in ocular drug delivery systems. Health and technology. 2020;10(1):61-78.
47. Afarid M, Mahmoodi S, Baghban R. Recent achievements in nano-based technologies for ocular disease diagnosis and treatment, review and update. Journal of Nanobiotechnology. 2022;20(1):361.
48. Nayak K, Misra M. A review on recent drug delivery systems for posterior segment of eye. Biomedicine & pharmacotherapy. 2018;107:1564-82.
49. Bors LA, Erdő F. Overcoming the blood–brain barrier. challenges and tricks for CNS drug delivery. Scientia Pharmaceutica. 2019;87(1):6.
50. Hartuti S, Nasution A, Syafril S. The effect of drug-related problems on blood glucose level in the treatment of patients with type 2 diabetes mellitus. Open Access Macedonian Journal of Medical Sciences. 2019;7(11):1798.
51. Almutairi E: Statistical modelling and machine learning for the epidemiology of diabetes in Saudi Arabia. In.: Brunel University London; 2022.
52. Sugumar V, Hayyan M, Madhavan P, Wong WF, Looi CY. Current development of chemical penetration enhancers for transdermal insulin delivery. Biomedicines. 2023;11(3):664.
53. Zhan Z, Zhang H, Niu X, Yu X, Sun H, Sha X, et al. Microliter sample insulin detection using a screen-printed electrode modified by nickel hydroxide. ACS omega. 2020;5(11):6169-76.
54. Subha G, Kalaiselvi M. Synthesis and characterization of zinc oxide nanoparticles using Curcuma amada and it's in vitro anti-diabetic activity. AIJRSTEM. 2019;26:149-56.

55. Angelov GV, Nikolakov DP, Ruskova IN, Gieva EE, Spasova ML. Healthcare sensing and monitoring. In: Enhanced Living Environments: Algorithms, Architectures, Platforms, and Systems. Springer; 2019. p. 226-62.
56. de Souza Marinho T, Borges CC, Aguila MB, Mandarim-de-Lacerda CA. Intermittent fasting benefits on alpha-and beta-cell arrangement in diet-induced obese mice pancreatic islet. Journal of Diabetes and its Complications. 2020;34(3):107497.
57. Mukhopadhyay P, Kundu P. Stimuli-responsive polymers for oral insulin delivery. In: Stimuli Responsive Polymeric Nanocarriers for Drug Delivery Applications. Elsevier; 2019. p. 525-46.
58. Xu Y, Shrestha N, Préat V, Beloqui A. An overview of in vitro, ex vivo and in vivo models for studying the transport of drugs across intestinal barriers. Advanced Drug Delivery Reviews. 2021;175:113795.
59. Pathomthongtaweechai N, Muanprasat C. Potential Applications of Chitosan-Based Nanomaterials to Surpass the Gastrointestinal Physiological Obstacles and Enhance the Intestinal Drug Absorption. Pharmaceutics. 2021;13(6):887.
60. Garg U, Chauhan S, Nagaich U, Jain N. Current Advances in Chitosan Nanoparticles Based Drug Delivery and Targeting. Adv Pharm Bull. 2019;9(2):195-204; doi: 10.15171/apb.2019.023.
61. Kim JU, Shahbaz HM, Lee H, Kim T, Yang K, Roh YH, et al. Optimization of phytic acid-crosslinked chitosan microspheres for oral insulin delivery using response surface methodology. International Journal of Pharmaceutics. 2020;588:119736.
62. Pethe A, Konda B, Mustyala T, Shah V. Advances in insulin drug delivery systems. Journal of Pharmacy Research. 2009;2(3).
63. Desai N. Challenges in development of nanoparticle-based therapeutics. The AAPS journal. 2012;14(2):282-95.
64. Duvall MN, Knight K. FDA regulation of nanotechnology. Beveridge and Diamond, PG: Washington, DC, USA. 2012.
65. Coleman ME, North DW, Dietert RR, Stephenson MM. Examining Evidence of Benefits and Risks for Pasteurizing Donor Breastmilk. Applied Microbiology. 2021;1(3):408-25.

66. Garcés M, Cáceres L, Chiappetta D, Magnani N, Evelson P. Current understanding of nanoparticle toxicity mechanisms and interactions with biological systems. New Journal of Chemistry. 2021;45(32):14328-44.
67. N'Dea S, Nelson KM, Dang MN, Gleghorn JP, Day ES. Gold nanoparticle biodistribution in pregnant mice following intravenous administration varies with gestational age. Nanomedicine: Nanotechnology, Biology and Medicine. 2021;36:102412.
68. Desai N. Challenges in development of nanoparticle-based therapeutics. Aaps j. 2012;14(2):282-95; doi: 10.1208/s12248-012-9339-4.
69. Wang YX. Superparamagnetic iron oxide based MRI contrast agents: Current status of clinical application. Quant Imaging Med Surg. 2011;1(1):35-40; doi: 10.3978/j.issn.2223-4292.2011.08.03.
70. Xuan L, Ju Z, Skonieczna M, Zhou PK, Huang R. Nanoparticles-induced potential toxicity on human health: Applications, toxicity mechanisms, and evaluation models. MedComm (2020). 2023;4(4):e327; doi: 10.1002/mco2.327.
71. Varkey B. Principles of Clinical Ethics and Their Application to Practice. Med Princ Pract. 2021;30(1):17-28; doi: 10.1159/000509119.
72. Schulte PA, Salamanca-Buentello F. Ethical and scientific issues of nanotechnology in the workplace. Environ Health Perspect. 2007;115(1):5-12; doi: 10.1289/ehp.9456.
73. Clack K, Soda N, Kasetsirikul S, Mahmudunnabi RG, Nguyen NT, Shiddiky MJ. Toward personalized nanomedicine: the critical evaluation of micro and nanodevices for cancer biomarker analysis in liquid biopsy. Small. 2023;19(15):2205856.
74. Mandal D, Sarmah JK, Gupta J. NanoRevolution: Pioneering Applications of Nanotechnology in Type II Diabetes Care. Engineering Proceedings. 2023;56(1):56.
75. Alghamdi MA, Fallica AN, Virzì N, Kesharwani P, Pittalà V, Greish K. The Promise of Nanotechnology in Personalized Medicine. J Pers Med. 2022;12(5); doi: 10.3390/jpm12050673.