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A Nanotechnological Approach to the Management of Alzheimer Disease and Type 2 Diabetes

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Abstracts: Alzheimer's disease (AD) and type 2 diabetes (T2D) are both prevalent in older individuals and have gained significant attention due to alarming rates of increase. The high incidences of these diseases pose a great socioeconomic burden and cause major public health concerns worldwide. A number of studies have established potential links between AD and T2D, supporting the hypothesis that T2D is linked with an increased risk of AD and that controlling diabetes could have a positive impact on the prevention of AD. At present, both diseases lack precise diagnostic approaches for early intervention and effective cure. Further, the currently available diagnostic tools for AD screening are insufficiently sensitive and robust for preventive measures. Although several drugs are used for the treatment of both these diseases, none of these drugs offers complete remission of the disease, merely symptomatic relief. Moreover, these drugs have limited efficacy because of problems such as conventional drug delivery systems beyond the blood brain barrier, a lack of target specificity and diminished potency. From this perspective, the emerging field of nanotechnology has offered new techniques and tools to overcome these challenges. In this review, we discuss the direct and indirect limitations of existing therapies and describe alternative potential nanotechnological approaches that could be utilized to overcome these limitations. New insight in the field of nanomedicine is necessary for early diagnosis, the development of novel drug therapies, the action of drugs and prevention, as well as for gaining an in-depth understanding of the complex biology of both diseases.

Keywords: Alzheimer's disease, type 2 diabetes, insulin, amyloid, nanotechnology, nanoparticle, nanodiagnostics, nanomedicine, targeted drug delivery, chelation therapy, metal dysregulation.

INTRODUCTION

The German psychiatrist and neuropathologist Alois Alzheimer first defined the term "senile dementia" more than a century ago and later became the namesake for Alzheimer's disease (AD) [1]. AD is a multifactorial, irreversible, progressive neurodegenerative condition [2] characterized by impaired cognitive function, diffuse deposition of amyloid plaques and neurofibrillary tangles [3]. The incidence and prevalence of AD is age related, and this disease is responsible for the most common form of dementia. AD is most often diagnosed in people over 65 years of age, although the less-prevalent early-onset form of Alzheimer's can occur much earlier [4]. Like AD, Type 2 diabetes mellitus (T2D) is more prevalent with aging, is increasing at an alarming rate and has become a major public health concern worldwide [5, 6]. Various multi-disciplinary studies (epidemiologic and clinical) have been carried out in an effort to identify the etiology, pathogenesis and risk factors linked with AD. These studies provide strong evidence that AD is related to T2D and that both diseases share the same pathophysiology, leading to the hypothesis that AD might be type 3 diabetes [7]. Emerging evidence has revealed many similarities between the two diseases: protein conformational disorders; association with obesity, insulin resistance, inflammation and endoplasmic reticulum stress; en-route initiation; and/or stage aggravation [8]. Currently, evidence suggests that patients with hyperinsulinemia, insulin resistance and T2D are at an increased risk of memory impairment and AD [9-11]. As life expectancy is increasing worldwide due to better health management, AD is rapidly becoming one of the most urgent global healthcare problems [12] and affects the social and behavioral skills of people living with it [13]. Apart from the social impact, AD also puts greater financial burdens on patients, families, and the community as a whole. According to one estimate, there are more than 24 million patients with

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dementia worldwide, and this number is expected to increase to forty-two million by the year 2020 and to eighty-one million by 2040 [14]. The National Institutes of Health (NIH) estimate suggests that 4.5 million Americans are affected by AD, and the management of these patients could cost $100 billion annually. This situation may become alarming, as one of the estimates indicates that by 2050, approximately 13.2 million older Americans are expected to have AD if this trend continues and no preventive treatment becomes available [15]. In an attempt to investigate the etiology of AD, a number of risk factors have been predicted to trigger its development. Strong evidence from epidemiological research has emerged supporting the hypothesis that T2D is associated with an increased risk of AD [16] and that controlling diabetes could have a major impact in the prevention of the disease [17]. The management of AD patients is greatly dependent on the currently available treatments, which usually offer only symptomatic benefits. Therefore, there is a need to develop a better strategy that can lead to disease-modifying therapeutics. This approach requires robust diagnostic tools for early-stage detection of AD. Further, it is crucial both to evaluate drug efficacy in clinical trial settings and to implement the finest patient management strategies. Unfortunately, there is no reliable diagnostic method for the early and accurate detection of AD [18]. Further, the current diagnostic methods of AD have several limitations such as low sensitivity, low accuracy, dependence upon brain reserves and disease severity. These limitations complicate timely therapeutic intervention in AD patients and necessitate the use of new technology in for diagnosis [19]. In this respect, a nanotechnological approach in diagnosis has gained prominence because of its potential to detect ultra-low concentrations of biomarkers. There are currently many drugs available or under development for the treatment of AD, with different targets and mechanisms of action. However, none of these drugs have proven to be significant in terms of efficacy due to their various limitations, such as conventional drug delivery systems, lack of target specificity, altered effects and diminished potency due to drug metabolism [20]. Therefore, overcoming these hurdles requires an alternative approach to drug delivery. Nanotechnology has become an important potential choice due to its substantial popularity in the field of nanomedicine. There are a number of biocompatible nanoparticles reported to be effective to overcome these limitations that could serve as an effective drug delivery system with slight optimization of physical, chemical and biological properties. These newer generations of drug delivery systems have major advantages over conventionally available drug delivery systems [21]. Notably, nanoparticles offer a great potential for drug delivery to the brain due to their small size and ease of surface modification (active and passive targeting).

EMERGING NANOTECHNOLOGICAL APPROACHES IN FUTURE MEDICINE

Currently, there are several drugs used in the treatment of these diseases, with limitations such as drug delivery, efficacy, cytotoxicity and, most importantly, drug resistance. Further, combinatorial drug approaches have been tried during the past few decades to improve treatment, but the outcomes have been discouraging because of the major side effects and diminished potency in patients due to the development of drug resistance. Therefore, there is a need to adopt a new, safer approach in the 21st century for the effective treatment of AD. Nanotechnology is an emerging multidisciplinary field that is revolutionizing medicinal research. It has immense potential to radically advance the treatment and prevention of several diseases. Notably, there have already been significant advancements in the application of various nanotechnology-based approaches toward cancer diagnostics and therapeutics [22]. In this review, we focus on the challenges with the current treatment of AD and T2D. We have shed some light on the amazing potential of nanotechnology in providing more effective treatment and prevention for these diseases by advancing the efficacy and drug targeting of the delivery systems.

In general, nanotechnology is defined as the manipulation of matter on an atomic and molecular level with at least one dimension in the 1 to 100 nanometers length scale. In 1959, the renowned physicist Richard Feynman first discussed the idea of nanotechnology; later, in 1961, he discussed the concept of nanotechnological applications in medicine. After several decades, it became possible to manipulate the direct interactions between nanoscale devices and biological molecules through molecular engineering and biotechnological approaches that have led to the creation of a new discipline called 'nanobiotechnology' [23, 24]. This emerging branch of science is gaining substantial popularity in the field of nanomedicine and particularly in medical diagnostics by exploiting the unique properties of nanomaterials for various applications (e.g., contrast agents for cell imaging and therapeutics for treating cancer). Nanomaterials can be useful for both *in vivo* and *in vitro* biomedical research and applications because the size of nanomaterials is similar to that of most biological molecules and structures. Interestingly, the wonderful amalgamation of nanomaterials with biological molecules has led to the development of drug delivery vehicles, analytical tools, physical therapy applications, contrast agents and diagnostic devices. Several nanodiagnostics technologies such as nanoscale visualization, nanoparticle biolabels, biochips/microarrays, nanoparticle-based nucleic acid diagnostics, nanoproteomic-based diagnostics, Bio-barcode assays, nanopore technology, DNA nanomachines, Nanoparticle-based immunoassays, and nanobiosensors are gaining popularity in the field of medical diagnostics [25].

APPLICATION OF NANOTECHNOLOGY IN THE DIAGNOSIS OF AD

At present, the goal is to improve the diagnostic methods for the early detection and effective treatment of AD by utilizing novel nanotechnological approaches to reduce death and suffering from this disease. It is known that the neurodegeneration process begins in the brain well before AD becomes symptomatic. Therefore, to prevent progression and complications in AD, it is crucial to detect AD pathology before symptoms or signs of the disease appear. Currently, there are a number of methods used for the diagnosis of AD, including neuroimaging, clinical assessment, neuropsychological testing and detection of

cerebral spinal fluid (CSF) biomarkers [26, 27]. Unfortunately, these methods have major drawbacks: the first method depends upon the severity of the disease [28]. The second and third methods are dependent upon brain reserve and thus are not sensitive enough to be used for screening [29]. The fourth method is presently less clinically common due to unacceptable invasiveness. Thus, it is now very clear that none of these approaches is appropriate for the early diagnosis of AD; such diagnostic tools require independence from both disease severity and brain reserve [28, 29].

The goals for these tools are to detect AD pathology at its earliest stages, to pinpoint its size of etiology, to deliver AD drugs to specific brain locations, and to determine the efficacy of these drugs in clearing the lesion. There are a number of nanodevices being evaluated in clinical trials, and scientists have predicted that nanotechnologies will be useful as multifunctional tools in diagnostics and therapeutics for the treatment and prevention of many diseases. Thus, it seems that nanotechnological approaches are minimally dependent upon the severity of the disease because of their potential of detecting ultra-low concentrations of AD biomarkers. In addition, the majority of nanotechnological tools are capable of detecting multiple biomarkers simultaneously, whether *in vivo* or *in vitro*. These capabilities make these nanotechnology-based tools a plausible choice for AD diagnosis [30]. Several nanoparticle-based diagnostic tools and assays are reported in the literature (Table **1**), and a few of those relevant to AD are discussed below.

Use of DNA-Nanoparticle Conjugates (Bio-Barcode Assay)

The nanoparticle oligonucleotide bio-barcode assay is a robust diagnostic technique with a sensitivity of several orders of magnitude lower than the concentrations of protein biomarkers detectable by Enzyme-Linked Immuno Sorbent Assay (ELISA) [31]. The high sensitivity of the assay is achieved by specific antibodies for the target biomarkers as well as hundreds of DNA barcodes coated on engineered gold nanoparticles [31]. In this way, a single molecule of biomarker can be traced by hundreds of DNA barcodes. Moreover, these DNA barcodes can also be amplified by polymerase chain reaction (PCR) [32]. Notably, this assay has been used by Georganopoulou *et al*. to detect amyloid-beta-derived diffusible ligands (ADDL) with high sensitivity in CSF samples from AD patients [30]. This finding is highly significant because the bio-barcode assay is a million times more sensitive, as reflected by remarkable difference in the concentration of biomarkers of AD in the CSF [24, 33], than the detection of ADDL in the CSF samples by ELISA. Thus, the bio-barcode assay is a suitable choice for the diagnosis of AD (Fig. **1**).

USE OF LOCALIZED SURFACE PLASMON RESONANCE (LSPR) NANOBIOSENSOR

Over the last two decades, there has been a rapid development of highly sensitive and selective nanobiosensors in the field of diagnosis, drug discovery and detection of biological agents [34]. These optical sensing techniques based on various sensing transduction mechanisms include LSPR triangular silver nanoparticles (SNPs). This optical sensing technique is ultra-sensitive, capable of quantitative detection of biomolecular interactions and biological targets, making it a suitable choice for wide use in medical diagnosis. The sensing principle is based on the high sensitivity of the LSPR spectrum of silver nanoparticles to adsorbate-induced changes in the dielectric constant of the surrounding environment. In the LSPR nanobiosensor method, changes in the nanoparticle's external nanoenvironment lead to a change in the refractive index of the

Table 1. Various Nanotechnology Tools for AD Diagnosis

Technology	Biomarker	Signal Detection	Documentation	Sensitivity	Ref.
Bio-barcode Assay	ADDL	Sandwich assay (Monoclonal Anti ADDL Ab):	Scanometric Recording	NA	[30]
Localized surface plasmon resonance	ADDL	Sandwich assay (Monoclonal & Polyclonal Anti ADDL Ab):	Spectroscopy	NA	[35]
Scanning Tunneling Microscopy	Aβ(1-42)	Sandwich assay (Monoclonal Anti Aβ Ab)	Frequency of pulse-like peaks	10 fg/ml	[37]
Two Photon Rayleigh Scattering Assay	Tau protein	Monoclonal Anti Tau Ab	TPRS Spectroscopy	1 pg/ml	[38]
Optical (Fluorescent) Imaging	Aβ plaques	NIAD-4	multiphoton microscopy	NA	[39]

ADDL: Amyloid-derived diffusible ligands.
TPRS: Two Photon Rayleigh Scattering Assay.
NA: Not available.
Aβ: Amyloid-β.

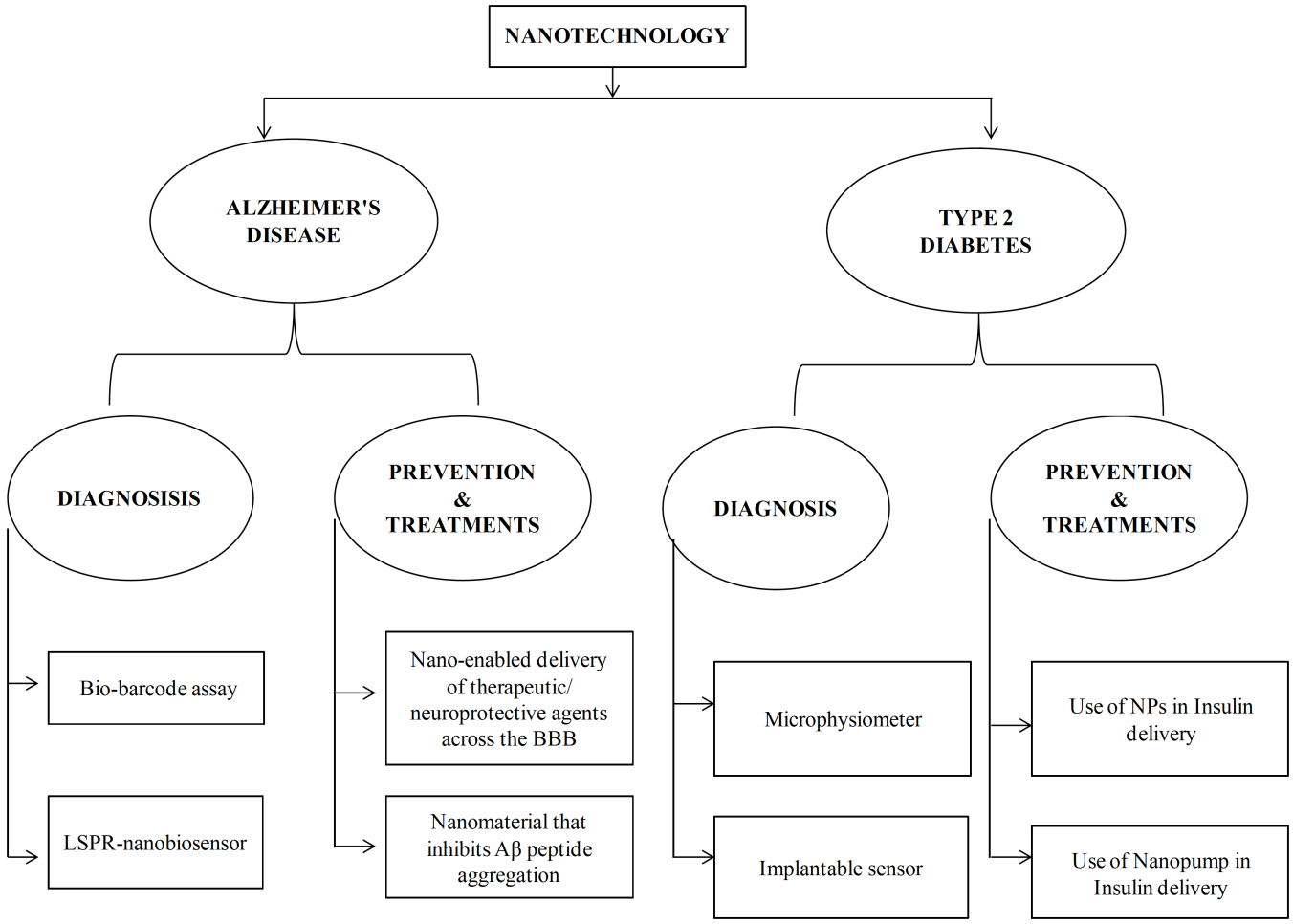

Fig. (1). A flow chart showing applications of nanotechnology in diagnosis and treatments.

surrounding magnetic field. This change subsequently changes the SNPs λ max that can be detected *via* spectroscopy [35]. The LSPR nanobiosensor has been reported in the detection of molecular biomarkers in AD [33, 35]. This method is sensitive to different concentrations of target bio molecule (ADDL) because the solution concentration directly changes the refractive index of the medium; therefore, different wavelength shifts are detected for different concentrations [36]. Therefore, the LSPR nanobiosensor is highly suitable for the wide range of applications in medical diagnosis, including detecting different biomarkers and monitoring disease and biological agents. The use of the LSPR nanobiosensor has recently been demonstrated in the diagnosis of AD in various applications [35]. Researchers have exploited these techniques to screen patients for AD and to study the oligomerization of A*β* in ultra-low concentrations similar to *in vivo* conditions. Moreover, LSPR nanobiosensors may be well applied in revealing the interactions between pharmacological inhibitors and their target molecules in the field of drug discovery [35].

APPLICATION OF NANOTECHNOLOGY IN THE DIAGNOSIS OF T2D

During the past few decades, efforts have been made to establish a linkage between T2D and AD, and epidemiological data have finally emerged to suggest a strong correlation between these two age-related diseases. It has been quite evident for some time that diabetes, particularly T2D, may be associated with impaired cognitive function. A number of studies indicate that impairment of neurotrophic factors such as insulin, IGF-1 and NGF, which occurs in both diabetes and AD, may offer a mechanistic link between these two disorders. T2D is commonly characterized by insulin resistance, hyperglycemia, hypercholesterolemia, hyperlipidemia and hypertension [40]. Therefore, the combination of these factors becomes the "metabolic syndrome", and some of these factors have been implicated as risk factors of cerebrovascular disease, accelerated cognitive dysfunction and dementia, characteristic hallmarks of AD [41, 42]. Most early-stage T2D patients are asymptomatic, and the routine diagnostic methods are not highly sensitive to the genetic changes at the very beginning of the disease. Therefore, there is a need to implement the newer, ultra-sensitive diagnostic tools for early and accurate diagnosis at molecular levels. Such diagnostic methods can have promising outcomes in detecting risk factors in pre-diabetic patients and can offer benefits to individual health by reducing the relative risk of high blood sugar, a measure of being diabetic, through medical counseling. Further, it can also enable the prediction of risk of a T2D individual for susceptibility to AD at an early stage. Fulfilling such a promise requires a revolution in the medicinal research through the adoptation of nanotechnology, an emerging multidisciplinary field, in

diagnostics and drug delivery. This technology undoubtedly has enormous potential to markedly advance the treatment and prevention of many complex diseases. In this subsection of the review, our focus is to address current nanotechnology-based methods used in T2D disease for rapid, early and effective *in vitro* diagnostic tests.

Use of Microphysiometer

The microphysiometer, a multi-walled carbon nanotube, is composed of many flat sheets of carbon atoms stacked and rolled into very small tubes [43]. The nanotubes are electrically conductive, and they directly measure the current at the electrode with respect to the concentration of insulin in the chamber. Microphysiometers work at physiological pH levels characteristic of living cells [44]. The microphysiometer method of detection is based on the nanosensor, which measures the insulin level. The sensor continuously detects the insulin level by measuring the transfer of electrons produced when insulin molecules are oxidized in the presence of glucose. When the cells produce more insulin molecules, the current in the sensor increases proportionally to the insulin concentration, allowing the monitoring of insulin concentrations in real time [45].

Use of Implantable Sensor

The implantable sensor is developed to offer diabetes patients an alternative for constant monitoring of blood sugar levels. It limits the dangerous glucose level fluctuations known as glucose excursions often encountered by finger-sticking or short-term glucose sensors [46]. In this method, polyethylene glycol beads coated with fluorescent molecules are injected under the skin and allowed to remain in the interstitial fluid. When the glucose in the interstitial fluid drops to dangerous levels, glucose displaces the fluorescent molecules and creates a glow. This glow is seen in a tattoo placed on the arm [47].

APPLICATION OF NANOTECHNOLOGY FOR THE TREATMENTS OF AD

During the past couple of decades, efforts have been made to understand the cause(s) of AD for the development of safe and effective treatments [48]. One of the main challenges faced by researchers in treating this disease is its complex nature; multiple changes have been observed in the brains of AD patients, including the accumulation of amyloid plaques, tau protein hyperphosphorylation, mitochondrial dysfunction, and oxidative and inflammatory stress. A large number of drugs with different targets and mechanisms of action are available or under development for the treatment of AD. For example, Phase III trials of nonsteroidal anti-inflammatory drugs (NSAIDs), phenserine, tolserine, cymserine, bisnorcymserine, statins, tarenflurbil, tramiprosate, Ginkgo biloba and xaliproden have been completed. However, none of them has demonstrated a significant efficacy [49-60]. The current medications for AD, such as the anticholinesterase inhibitors and the latest N-Methyl-D-aspartic acid or *N*-Methyl-D-aspartate (NMDA) receptor inhibitor Namenda, offer moderate symptomatic relief at various stages of disease, but they do not halt the progression of this neurodegenerative disorder [61]. Therefore, considering the multifactorial nature of the disease, a number of factors must be considered while tackling AD. There is a need to adopt new strategies such as nanotechnological approaches for targeted drug delivery, as well as pharmacological compounds with many properties that could be able to exert their effect heterogeneously on multiple factors implicated in AD [62, 63]. It is very clear that the targeted delivery of drugs in neurodegenerative disease is of foremost significance for treating AD and Parkinson's disease [64]. One of the major problems in treating such CNS disorders is the inability to surpass the natural CNS protective barriers, mainly the Blood-Brain Barrier (BBB) [65]. To overcome the obstacle of the BBB, polymeric biocompatible drug carriers have been applied to the CNS for many applications [66]. Polymeric nanoparticles are promising candidates in the investigation of AD because nanoparticles are capable of opening tight junctions and crossing the blood brain barrier, and they have high drug-loading capacities that could be targeted to the mutagenic proteins of Alzheimer's [67, 68].

The use of nanoparticle-based drugs has many advantages over conventional drug delivery. The entrapment of drugs with appropriate polymeric biocompatible nanoparticles could enhance either delivery to or uptake by target cells and/or reduce the toxicity of the free drug to non-target organs. In this way, nanoparticle-based drug delivery will result in an increase in the efficacy of drugs with reasonably high therapeutic index [69]. Furthermore, solid nanoparticles may be used for drug targeting and applied to the diseased site in the body where the drug carried must be released. In addition, when nanoparticles are exclusively used as a carrier, the possible adverse effects of residual material after the drug delivery should be considered as well. In this respect, biodegradable nanoparticles with a limited lifespan would be optimal [70]. Unfortunately, the currently available drugs provide symptomatic improvements or delay the breakdown of acetylcholine, vital for nerve cell communication, in early stages of the disease [71, 72] but fail to stop or reverse the progression of cognitive, behavioral, and functional deficits in the brains of AD patients. However, recent research has been shifted towards developing nanoparticles based on other promising methods of treatment for AD such as anti-inflammatory drugs [73, 74], antioxidants [75], amyloid-targeted drugs, and even a drug (rosiglitazone) to treat insulin resistance [76]. It is evident from the literature that AD is a multifactorial phenomenon and that the etiology of this disease is not well understood. So far, however, the accumulating evidence supports the hypothesis that oxidative stress caused by a number of mechanisms may be among the major risk factors that initiate and promote neurodegeneration [77-79]. It has been shown that the CNS is particularly susceptible to oxidative damage compared to other tissues in the body [80, 81]. Although elevated concentrations of various metals can be responsible for oxidative damage leading to neurodegeneration, this complex pathophysiological system is not yet fully understood. Despite all these odds, metal dysregulation may in fact be a promising approach for healing AD, by employing chelation therapy. The results are encouraging, as in the case of desferrioxamine, a specific iron chelator with high affinities for aluminum, copper, and zinc, which has demonstrated some therapeutic benefits for

patients with AD [82-85]. Another finding suggesting the involvement of iron metabolism in AD is its elevated concentration in the brain of AD patients [86, 87]. Similarly, aluminum has also been found in high concentrations in both senile plaques and intra-neuronal neurofibrillary tangles in the brains of subjects with AD, suggesting its involvement in the etiopathology of AD [86-88]. Interestingly, ongoing studies are using nanoparticles to offer an exciting therapeutic option that will demonstrate nanoparticles' safety and effectiveness for chelator delivery. The potential use of nanoparticles conjugated to chelators, which mimic lipoprotein particles and transfer iron chelators in and out of the brain by selected apolipoprotein absorption, provides not only a useful means of treatment but also insight into the mechanism of AD [89].

APPLICATION OF NANOTECHNOLOGY FOR THE TREATMENT OF T2D

The pathophysiology of T2D is characterized by decreased insulin sensitivity [90], impaired regulation of hepatic glucose production, and deteriorating β-cell function eventually leading to β cell dysfunction [91]. T2D is a progressive disorder, often associated with microvascular and macrovascular complications in late stages due to excessive protein glycation and activation of oxidative stress [92]. Therefore, the utmost priority in the course of treatment for T2D is shifted towards the factors responsible for dysglycemia to bring the patients' glycemic level down to normal. Unfortunately, a number of existing drugs used for T2D treatment have failed to attain the reduced level of glycemic fluctuation. Despite this fact, a variety of therapies are currently available for the management of T2D in stepwise manner, such as initial lifestyle modifications, the addition of oral anti-diabetic drugs (OADs), and intake of insulin as supplement [93]. However, the evidence accumulated to date has demonstrated that the progression of diabetes can be checked or even reversed with early and aggressive intervention through a combination of therapies that can act simultaneously upon many mechanisms, a characteristic feature of pathophysiology associated with diabetic individuals. In practice, several diabetic medications and insulin therapy are used to control the blood sugar level. The medication is prescribed in accordance with the individual patient's needs, often determined by analyzing many factors such as blood sugar level and any other existing health issues [94, 95]. In general, newly diagnosed patients receive metformin (Glucophage, Glumetza, others), an antidiabetic drug that helps to reduce the glucose production in the liver and thereby enhances the insulin sensitivity of body tissues [96, 97]. In principle, different anti-diabetic drugs act differently to lower blood glucose level, viz: glipizide (Glucotrol), glyburide (Diabeta, Glynase) and glimepiride (Amaryl), which act selectively on pancreas to produce and release more insulin [96, 97]. Other medications include acarbose (Precose) that block the action of enzymes that break down carbohydrates in the intestine. Similarly, metformin (Glucophage) or pioglitazone (Actos) are used to make body tissues more sensitive to insulin [97, 98]. Additionally, many other oral drugs are available in the marketplace as alternatives to metformin but with better management, e.g., Sitagliptin (Januvia), Saxagliptin (Onglyza), Repaglinide (Prandin) and Nateglinide (Starlix) [99, 100]. Although OADs are very useful for managing hyperglycemia, especially in the early stages of disease, some individuals suffering from T2D are unable to use oral insulin-modulating drugs due to the interference of normal digestion. These patients are prescribed insulin therapy as an insulin injection when OADs have completely failed. The OADs are very helpful in early stages of the disease, particularly for managing hyperglycemia, as with observations of HbA1c reductions of 0.5% to 2.0% [101]. However, there are many limitations that restrict the use of OADs as potential therapeutic agents. For example, they have limited mechanisms of action, which often address the symptoms of diabetes rather than its underlying pathophysiology. Moreover, it has been reported that OADs may also cause undesirable side effects. It has been observed that sulfonylurea (SU)-treated patients experience up to 2.5% and 17.5% of major and minor hypoglycemia, respectively, while GI problems affect up to 63% of metformin-, 36% of thiazolidinedione (TZD)-, and 30% of acarbose-treated patients. Many other side effects are also reported, such as peripheral edema in up to 26% of TZD-treated patients, whereas there is commonly an increase in body weight of up to 1 to 5 kg in both SU and TZD therapy [102]. These side effects can have a negative impact on patient adherence to treatment, resulting in higher HbA1c levels and increased vulnerability to other complicated diseases, eventually leading to hospitalization as well as, sometimes, fatality [103]. Surprisingly, conventional human insulin injected intravenously has a 17-minute half-life, and its short duration of action has limited its potential. Therefore, to overcome all of these problems faced by clinicians in treating the T2D patients, there is an urgent need to adopt the emerging nanotechnological tools as an alternative method in drug delivery and targeting. It is therefore worthwhile to describe the some of the nanotechnological applications in drug delivery.

USE OF NANOPARTICLES IN INSULIN DELIVERY

The concept behind using nanoparticles in insulin delivery is to minimize the half-life of insulin by direct administration in the blood stream. In these methods, the insulin molecules are encapsulated within the nanoparticles as a dry powder formulation that can easily be administered into the lungs by inhalation. Interestingly, the nanoparticles being used for this purpose are small enough to pass through the lungs uninterrupted, resulting in the direct delivery of insulin molecules to the bloodstream without degradation [104]. Notably, porous hydroxyapatite nanoparticles have also been tested for the intestinal delivery of insulin. Such a method of administration has been encouraging in animal studies. In preclinical studies, insulin-loaded poly (lactide-co-glycolide) nanospheres administered to guinea pigs *via* the lungs induced a significant reduction in the blood glucose level compared with insulin solution; remarkably, the effect of the nanospheres was observed for up to 48 hours [104].

USE OF NANOPUMP IN INSULIN DELIVERY

The nanopump is a powerful device, and its first application as a pump was introduced by Debiotech in insulin delivery. The pump generally balances the sugar

level in the patient's blood by injecting insulin into the body at a constant rate. The nanopump can also be used for administering small doses of drugs over a long period of time [105].

CONCLUSION

Recent research indicates that AD and T2D are interlinked and that the progression of disease is proportionate to the age. A number of studies have established potential links between AD and T2D, including dysfunctional insulin signaling, oxidative stress, inflammatory response, altered protein processing and defective roles of advanced glycation end products. This emerging evidence supports a model in which T2D is linked with an increased risk of AD. Thus, the tighter control of T2D, including early screening of individuals at risk, might be beneficial to retard cognitive decline and could help to prevent progression to AD. Therefore, comparison and analysis of the current diagnostic methods and therapies will eventually lead to the development of appropriate preventive and therapeutic strategies that could directly help to reduce the burden of AD and T2D. As discussed above, many drugs are available to treat both these diseases, but they offer only symptomatic benefits, especially to AD patients. More importantly, none of these drugs are fully effective due to their various limitations, e.g., conventionally available drug delivery systems, lack of target specificity, altered effects and diminished potency due to drug metabolism in the body. Therefore, to overcome these hurdles, there is need for an alternative, more effective approach to drug delivery. Nanoparticles offer great potential in drug delivery to the brain due to their small size and ease of surface modification (active and passive targeting). The primary goals for research in nano-bio-technologies in drug delivery include more specific drug targeting and delivery, reductions in toxicity while maintaining therapeutic effects, greater safety, biocompatibility, and faster development of new safe medicines. Numerous biocompatible nanoparticles are reported to be effective to overcome these limitations and serve as an effective drug delivery systems with slight optimization of physical, chemical and biological properties. In this course, a number of nanodevices have been already evaluated in clinical trials. Researchers have predicted that nanotechnology will serve as a multifunctional tool in diagnosis as well as therapy for the treatment and prevention of many diseases. As an example of carrying drugs to their designated locations, carbon nanotubes have offered great promise as an advanced drug delivery system. Nanotubes are like nanoscopic needles, with the capability to penetrate through membranes, thus making them a suitable choice for drug delivery to the AD brain without hindrances such as the blood-brain barrier. Similarly, nanotechnology offers a great potential to detect ultra-low concentrations of multiple bio-markers. A bio-barcode assay for the detection of ADDL has been developed, using magnetic microparticles conjugated with a monoclonal antibody against ADDL along with gold nanoparticles conjugated with a polyclonal antibody against ADDL in combination with DNA strands. This nanotechnology-based tool has a sensitivity of several orders of magnitude higher than immunology-based techniques such as ELISA. Additionally, quantum dot probes can be used for the real-time tracking of molecules and cells over extended periods of time. It is predicted that small molecule ligands can be used to target quantum dots to specific proteins on cells. Despite the potential *in vivo* toxicity issues with quantum dot probes, they offer an ideal solution for the diagnosis of AD pathology. If it is possible to bind quantum dots to ADDLs or neuritic plaques, they might be very helpful for identifying AD at an early stage. Thus, nanotechnology provides tremendous potential for future medical treatment and diagnosis. Nanoparticles are useful against pathogens and for other medical uses such as diagnosis and real-time monitoring of cancer progression. However, one needs to be mindful of the potential toxicity. Therefore, at the time of nanoparticles' application, the pros and cons should be considered [106]. The unique properties of nanotechnology give researchers the opportunity to experiment with new ideas to further enhance the treatment of AD and T2D.

LIST OF ABBREVIATIONS

AD	=	Alzheimer's disease
T2D	=	Type 2 diabetes
CNS	=	Central Nervous System
BBB	=	blood brain barrier
CSF	=	Cerebral spinal fluid
ELISA	=	Enzyme-Linked Immuno Sorbent Assay
ADDL	=	Amyloid-beta derived diffusible ligands
LSPR	=	Localized surface plasmon resonance
SNPs	=	Silver nanoparticles
OADs	=	oral anti-diabetic drugs
TZD	=	thiazolidinedione

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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