Thinking on the Application of Nanotechnology in the Mechanism Research on the Traditional Chinese Medicine Diagnosis and Treatment of Diabetes Mellitus

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Abstract. Nanotechnology is an advanced scientific technique in the 21st century and diabetes mellitus (DM) is a commonly seen chronic disease, which seriously threatens the health of human beings. By analyzing the relationship between nanotechnology and biological medicine, nanotechnology and traditional Chinese medicine (TCM) and the advances and the existing problems of TCM diagnosing and treating DM, the application of nanotechnological methods for the mechanism research on TCM diagnosis and treatment of DM was discussed. It is indicated that nanotechnology is one of the fastest developmental, the most potential and the far-reaching high and new technologies in current world, and it greatly promotes the development of biological medicine and TCM. With the application of nanotechnology of medical diagnostics and medical materials, it will make the development of TCM possess an unprecedented field, which consequently could integrate the macroscopical and microscopical syndrome differentiation. It’s pointed out that breakthrough will be achieved from the research of the administration route, the improvement of medical biological availability and the selection of the acupoint prescriptions on mechanism research on TCM for the diagnosis and treatment of diabetes mellitus.

Key words. Nanotechnology; Biological Medicine; Traditional Chinese Medicine (TCM); Diabetes Mellitus; Mechanism Research

1. Introduction
Diabetes mellitus (DM) is a metabolic disorder characterized by chronic hyperglycemia induced by multiple complicated reasons, which has seriously threatened the health of human beings. With the development of people’s living standard, the incidence of DM grows year by year. According to a WHO report [1], the number of global DM patients was 120 million in 1994, 175 million in 2000 and may rise above 300 million by 2025. This has drawn much attention from scientists. Complications are the cause and pathological mechanism of DM, so the conventional research methods are time-consuming and labor-intensive with low therapeutic effects. In clinic, traditional Chinese medicine (TCM) has its own advantages and characteristics in the treatment of DM and its complications. By introducing advanced scientific techniques such as nanotechnology, it could
provide thinking on the application of nanotechnology on TCM diagnosis and treatment of DM hence further understanding of the mechanism.

2. Nanotechnology and Biomedicine
Nanotechnology refers to an advanced new technique used to study the specificity and interactions of materials such as the management of atoms and molecules, which is a new scientific technology integrated with high techniques and multiple disciplinary cross [2]. Since the basic thoughts and methods of nanotechnology have been introduced into all the subjects, diverse newly-developing fields related to nanotechnology have grown, which demonstrates its great potential and superiority.

In the beginning, nanotechnology was just utilized in the techniques of micro-electron and micro-motor. However, at present, it has been penetrated to all the fields of bio-technology and biomedicine. Compared with the traditional electronic equipment based on Silicon, it could be applied to bio-materials, fluids and chemical materials as raw materials for biochips, which determines the diversity of the biochips. On the other hand, with the reduction of the area and size of the micro-bio-system, it could improve the functions, increase the production and save the cost of the system [3]. The researches and application of nanotechnology in biomedicine could be classified into the following three aspects.

2.1. Nano-biological Materials
Nano-materials have great impacts on biomedicine. To some extent, the development of nano-materials determines the future (or richness?) of nano-medicine. At present, nano-materials have been successfully applied in the medical field. Among them, drug carrier is the most attractive, which could be safely and effectively utilized to the target organs and gene therapy, or to be processed into the human biomedical materials such as artificial kidneys, artificial joints, etc.

2.2. Diagnostic Techniques of Nano-medicine

2.2.1. Optical Coherence Tomography (OCT).
With the resolution of a micron and 1000 times more accurate than CT and MRI, OCT is also called Molecular Radar by scientists, which could make the dynamic imaging of the living cells in the body 200 times per second, observe the dynamic state of living cells and detect the morbidity of single cell without killing living cells like X-ray, CT or MRI. Based on this, people could diagnose the cases in advance and avoid detecting the carcinoma of the late phase.

2.2.2. Laboratory Test.
Laser monatomic molecule detection is hypersensitive, which could be applied to obtain one of the one hundred billion atoms or molecules in the gaseous substance. Based on this, scientists who wish to can now detect bio-molecules in the human body to find out clues which influence human health. With the saliva, blood, stools and the gas breathed out, it could detect numerous kinds of pathogenic molecules or marks among the one hundred billion ones in time [4].

2.2.3. Pathologic Diagnosis.
Generally the sizes of nanoparticles are much smaller than cells and erythrocytes in living organisms, which provides a new research direction for biological study. That is, to make cell separation and cellular staining, or to process into some special drugs or antibody-free with nanoparticles and local-oriented therapy.

2.2.4. Diagnosis of Implantable Sensor Array.
Taking advantages of the nano-probe technique, it could be embedded in the body. According to different diagnosis and detections, it could locate in different regions of the body. With the blood flowing, it could move in vitro and produce feedbacks of biological information onto the in vitro record device [5].
2.2.5. Genetic Diagnosis.
Due to the great analytical skills of the gene chips, few samples applied, convenience, hypersensitivity and specialty, it could obtain abundant information, which is significant in the diagnosis of gene mutation and some genetic diseases with the copy number variations.

2.3. Therapeutic Techniques of Nano-medicine

2.3.1. Nanoscale Robot.
With the nanoparticles, scientists have produced the nanoscale robot, which could be injected in the vessels and makes the general physical examination possible. It could move in the microcosm of the organism, clear any harmful substances and activate the cell energy, which consequently keeps human beings healthy and long live.

2.3.2. Gene Therapy.
Gene therapy is thought to be the only method in treating genetic diseases. Nowadays, the critical challenge is, firstly find out the DNA chains of the abnormal cells; then with the nanotechnology, transmit the DNA chains applied into the abnormal cells and replace the abnormal DNA chains. With the nanotechnology, it could deliver the new-style genetic materials into the existing DNA without creating any immune reactions.

2.3.3. Drug Delivery and Nano-controlled Release System.
With the nanotechnology, the drug delivery could easily transmit to any regions of the body, release the drugs, kill the pathogens and eliminate the focus [6], which could apparently save the dosage, prevent the adverse effects after general administration and improve the therapeutic specialty. Nano-controlled system has great potential in the aspect of drug delivery, which could release drugs and prolong the drug effects, reduce the dosage, decrease or avoid the side-effects and improve the stability of the drugs. In addition, it could be applied to build up some new routes of administration, including in vivo local drug delivery, administration with mucous membrane absorption, oral administration with polypeptide drugs, etc [7].

3. Nanotechnology and Traditional Chinese Medicine

3.1. Nano-Chinese Materia Medica
In 1998, some scholars firstly came up with the definition of Nano-Chinese Materia Medica, which refers to the particles of the effective components, regions, raw materials and compound preparation of Chinese Materia Medica with nanotechnology, with diameter smaller than 100 nm [8]. Compared with the traditional Chinese Materia Medica, it has the following five advantages: (1) Improve the biological availability and save the limited resources of the Materia Medica; (2) Strengthen the target-oriented therapeutic effects; (3) Add up more pharmaceutical preparation choices; (4) Promote the standardization and internationalization of the Chinese drug preparation.

3.2. Application of Nanotechnology in the Acupuncture & Tuina
Acupuncture & Tuina is the specialty of TCM. With the nanotechnology, it could further study and understand the essence of Meridians and Collaterals, which consequently provides the theoretical and technical support for them and enlarges the research fields and indications.

3.2.1. Application of Nano-sensing Needle in Acupuncture & Tuina.
The research and development of needling sensor is a key technique in the mechanism study of Acupuncture & Tuina. Nano-sensing needle is based on the integrated techniques of acupoints people understand and the modern biomedical sensor, which has the functions of needling, delivering the bioinformation and detecting the changes of substances in the acupoints during the meridian qi transmission, the changing rules of the environment in the acupoints after taking the needling techniques and the relationship between human biorhythm and the meridian qi transmission, etc [9].
3.2.2. Nanotechnology and Acupoint Embedding.
Traditional catguts have the advantages of being absorbed without foreign matters. However, due to the individuals, after embedding excessive and thick catguts, the local regions would create inflammation and the pain obviously appears. Hence, taking advantages of drug-loaded nano-controlled release techniques, or finding new types of nano-materials to replace traditional catguts provide new methods and directions for the existing problems of application of catguts.

3.2.3. Nanotechnology and Acupoint Application.
Nano-Chinese Materia Medica could change the disadvantages of traditional acupoint application, which is to put the western or Chinese medicine onto the pathway of meridians, or to process them into various types of aerosols and penetrate directly into the body through the skin. On one hand, it could enlarge the drug administration methods of acupoint application; on the other hand, it could be more suitable for more groups of people.

3.2.4. Application of Nanotechnology in the Drug Meridian Distribution and Qi Meridian Transmission.
Thanks to the good magnet-controlled location of the magnetic nano-particles, it could trace the in vivo movement of nanoparticles with the photosensitive detecting device and the external magnetic field. Based on this, we could take the drug meridian transmission with the combination of drug and magnetic nano-particles. Nano-magnetic fluid materials could be applied in the mechanism research of meridian transmission of the basic subjects of acupuncture & Tuina. If we could process the solution applied in the acupoint injection into the nano-magnetic solution, it could provide a new research method for the mechanism study of meridian transmission.

4. Advantages and Existing Problems of TCM Diagnosing and Treating DM and its Complications

4.1. The advantages mainly indicate as follows.

- **Holistic Bi-directional Regulation.** Under the theoretical guidance of TCM, the effective components of herbs could treat DM by the entire regulation to the body hence apparently improve the clinical symptoms. Meanwhile, it could bi-directionally regulate endocrine functions and maintain the homeostatic equilibrium.

- **Individualized Diagnosis and Treatment.** With the syndrome differentiation to individuals of TCM and according to different constitutions, symptoms, even different characteristics, seasons and climates, select different suitable prescriptions and adopt different treatments and herbs, which could consequently improve the clinical symptoms and the quality of life.

- **Multiple Therapies of TCM.** Besides Chinese Materia Medica, other therapies such as acupuncture, Tuina, Qigong, physical therapy, psychotherapy, mental suggestion, etc, could be applied. Among them, acupuncture has many therapies such as filiform needling therapy, electro-acupuncture, moxibustion, acupoint catgut embedding, acupoint injection, acupoint application, integrated acupuncture and herbs, etc, all of which could be applied to treat type 2 DM and the complications caused by the diabetic neurovasculopathy, with definite therapeutic effects, convenient acupoint location and simple manipulation. Acupuncture combined with decreasing dosages of western medicine could satisfactorily control the glycemia and blood fat of the patients. As a result, it could reduce the adverse reactions caused by the drugs and prevent the complications caused by the neurovasculopathy, which has been widely applied in clinic and further studied [10].

- **Advantages of Chinese Materia Medica.** (1) Due to the diversity of prescriptions and herbs, it provides more choices for new-drug exploitation and treatments. (2) As most of the herbs are organics, which elements approach the human food, the toxic-side effects are lower than that of chemotherapy. (3) The herbs could strengthen the constitutions and improve the immune system. (4) Some herbs may control the glycemia from multiple perspectives without the
occurrence of hypoglycemia reactions. (5) The herbs could directly complement the Vitamin, microelements, electrolytes, mineral substances, cellulose, etc, and rectify the complications caused by the nutrient deficiency. (6) It could bi-directionally regulate the body, keep the homostatic equilibrium, maintain the osmotic pressure and protect the membrane functions. (7) Modern researches have found that there are numerous microelements such as Zinc, Co, etc, in the herbs, which participate in the synthesis of insulin and the decrease of glucose. There are rich vegetable fibers in many herbs, which could prolong the absorption of the glucose. Besides that, some herbs may stimulate the secretion of insulin.

4.2. There are also some Existing Problems as follows.

- In clinic, it’s difficult for TCM diagnosing DM and its complications at the initial stage, especially some type 2 DM patients don’t have the typical symptoms and are just diagnosed when take the physical examination. Before the occurrence of the complications, the organism of many patients could have the pathogenic changes, which affect the heart, brain, kidney, eyes, peripheral nerves, vessels, etc. So it’s difficult to find out diabetic complications just with the simple TCM diagnosis.
- There are no standards for the syndrome types and the therapeutic effect evaluation. With the TCM macroscopical syndrome differentiation, the symptoms, signs and the evaluation couldn’t be objective and accurate, which makes it difficult to be standardized.
- There are many herbs applied to treat DM and its complications. However, the actions of target glycemia-decreasing of herbs couldn’t be swift and strong like that of western medicine, even the therapeutic effects couldn’t be stable like insulin.
- Most of the Chinese herbs are compound decoction or Chinese patent drugs. Due to the slow effects and weak dependence of the patients, it brings much inconvenience for the DM patients.
- The mechanism study of traditional Chinese Materia Medica, acupuncture, Tuina and other traditional therapies in treating DM and its complications is still at the initial stage, which focuses more on the clinical observation and mechanism speculation and needs further deeper researches.

5. Thinking on the Application of Nanotechnology in the Mechanism Research of TCM Diagnosis and Treatment of DM

5.1. Application of Nanotechnology in the TCM Diagnosis of DM and its complications

According to the clinical symptoms of DM and its complications at early phase, emphasize more on the detection to the groups of people with high incidence and take the biochemical indexes and clinical detections. With the techniques of nano-diagnosis such as optical coherence tomography, laser monatomic molecule detection, nano-particles, etc, we could detect the subtle situation of the cells and molecular metabolism in the body of DM patients and the substance metabolism before the occurrence of the complications hence provides the basis for the mechanism study of DM and its clinical diagnosis at early phase. Under the theoretical guidance of Surface Plasmon Resonance (SPR), the biosensor could detect the interactions among the protein, nuclein and other biological macromolecules without labels and stain. With the nano-particles such as polyactice acid (PLA), etc, some Japanese scientists have produced the detecting device, which could be applied to detect the signal substance neurotransmission and test the blood glucose and lactate levels related with the fatigue of the body and contributes to the prevention and diagnosis of DM. What’s more, we could study the relationship between TCM syndrome types of DM and the objective biochemical indexes with the techniques of nano-diagnosis, which combines the traditional macroscopical syndrome differentiation with the modern microscopical nanotechnology and hopes to achieve the standards of syndrome types and therapeutic effect evaluation.

GAO, et al [11], studied the gene expression profile related with the types of kidney deficiency (dual yin-yang deficiency) and blood stasis of a DM family with the techniques of gene chips and
made the detection and comparison between the 3 DM patients and the other 2 healthy family members. The result showed that there were totally 446 pieces of different genes. Among them, there were 8 pieces of up-regulated expressed genes and 438 pieces of down-regulated expressed genes, which indicated the close relationship between the deficiency type of DM and the down-regulated expression of genes. With the techniques of gene chips, the combination of TCM macroscopical syndrome differentiation with the microscopical gene functions provides a new research method in the modern study of TCM diagnosis of DM.

5.2. Application of Nanotechnology in the mechanism research of TCM treatment of DM and its complications

In the clinic, there are many Chinese herbs effectively treating DM. However, due to the slow actions and absorption, inconvenient administration, etc, they just play an auxiliary role in the treatment. With the advanced nanotechnology, the nano-Chinese Materia Medica could improve the biological availability and the therapeutic effects, take the convenient target-oriented administration, release the functions, reduce the dosage, etc, which would apparently improve the therapeutic effects, avoid the adverse effects caused by the long-term drug administration, enhance the quality of life and more importantly explore more prosperous markets for the Chinese Materia Medica treatment of DM and its complications. With the drug-loaded nanoparticles, deliver the herbs (mainly the effective components, regions or the extracts) to the focus, which could accelerate the solubility of the herbs and improve the effects and the amphipathic property of the surface of the drug-loaded nanoparticles and enhance the biological effectiveness, target orientation and specialty of Materia Medica. With the integration or interactions of nanoparticles and the human protein, it could prevent the progress of DM or treat its complications.

The pharmacological actions of Chinese Materia Medica have the characteristics of multiple approaches and targets. Hence, with the techniques of gene chips, it’s significant to set up the technological platform for the herbal study, evaluate the therapeutic effects of the herbal treatment of DM, select the herbs and access the metabolism and the toxic-side effects. LI, et al [12], studied the gene expression changes of Gliguidone Capsule on the diabetic rats with the techniques of gene chips and set up the difference profiles of the gene expression for the pharmacological actions of Gliguidone. The techniques of gene chips integrate TCM, the related pathogenic gene expression of modern genomics with the pharmacological actions of modern chemical substances, which link TCM with the gene expression and explain the TCM pharmacological theories and the mechanism for the TCM treatment of DM and its complications from the perspective of gene expression.

The development of acupuncture promotes the further research of needling sensors, which was proposed with the requirement of modernization of traditional Materia Medica. Compared with the biomedical sensors at home and abroad, the sensing needle could be utilized in vivo at fixed positions, points and time with dynamic measurement, which could be applied as the sensor and the actuator [13]. With the techniques of Langmuir-Blodgett Films, it could assemble the bioactive molecules into the ultrathin membrane steadily and could be processed into the bio-sensor with special recognition functions. For instance, with the diffusion-absorption techniques, it could absorb the glucose oxidase onto the lipid Langmuir-Blodgett Films. With the membrane modified onto the golden matrix of the electrode of H₂O₂, it could be processed into the glucose sensor [14]. Hence, with the techniques, we could absorb the glucose oxidase, insulin receptors, etc, onto the hypersensitive Langmuir-Blodgett Films and fix them onto the golden-plating acupuncture needles, they could be processed into the glucose sensing needle, insulin receptor sensing needle, etc. With the sensing needles applied in the treatment of DM and its complications, it could play an important role in the selection of acupoint prescriptions and the mechanism study of acupuncture therapeutics.

Acupoint catgut embedding belongs to one of the acupuncture therapies, even with better therapeutic effects and long-lasting actions. The retention of the catguts in the acupoints could continuously stimulate the acupoints during the process of being softened, resolved and absorbed hence finally cure the chronic diseases [15]. Acupoint catgut embedding has satisfactory therapeutic effects in the prevention of DM treatment and its complications. CHEN, et al[16], found that early intervention of this therapy could reduce the contents of endothelin (ET) and increase the contents of
NO, which indicates that it could protect the vascular endothelial cells (VEC), improve the functional disorders, protect the peripheral nerves (vagi) and reduce the injury and plays an important role in the early prevention of gastrointestinal dysfunction complicated with DM. Studies[17] indicated that Nano-controlled release system is promising, which is to put the drug powder or solution into the fine particles whose diameter size is measured in nanometer (nm). As carriers, the nanoparticles improve the curative effects and reduce the adverse effects [18]. With the nanotechnology, the catguts could effectively prolong the therapeutic effects in the body and the actions of drug target-orientation, which could remarkably improve the therapeutic effects of acupuncture treatment of DM and its complications.

Acupoint application is also one of the special therapies of acupuncture. SHAO, et al[19], found that to the cases of type 2 DM complicated with hyperlipemia, this therapy could improve the clinical symptoms, reduce the content of glycemia and apparently improve the lipid metabolism disorders, which could decrease the levels of cholesterol, triglyceride, low density lipoprotein (LDL) and increase the content of high density lipoprotein (HDL). With the advantages of convenient, safe, cheap and non-toxic-side effects, this therapy could be applied to the patients in the longer term. At present, one of the challenges of it is how to penetrate more herbs through the skin and into the blood circulation hence improve the therapeutic effects. For this, we could take advantages of the nano-Chinese Materia Medica or the nanoparticles as the herbal carriers hence improve the clinical effects of acupoint application in the prevention and treatment of DM and its complications.

Diverse studies have indicated that insulin resistance (IR) is the basic link of the etiology of DM due to the defect of actions of the insulin onto the receptors. As a result, the ability of muscles and fatty tissues in absorbing the glucose decreases. At the same time, the increase of the content of glucose in the liver shows the decrease of the sensitivity and response of the insulin. Quantum dot is a kind of nanoparticle made of materials of semiconductor crystal with the diameter smaller than 10 nm, which size is smaller than one thousandth of a normal cell and has the characteristics of absorbing large ranges of wavelengths and transmitting small ranges of wavelengths. It is a fluorescent laber indicator. After covalently bonding with the biological macromolecules, it could make the hypersensitive biological detections [20]. In addition, the quantum dot could couple various kinds of molecules such as Protein A, Antibody, Streptavidin, etc, into the fluorescent probes, which could detect the distributions and functions of the specific target molecules [21]. Based on the above mentioned, we could combine the quantum dot probes with the insulin receptors, which could trace the metabolism state in the body hence further explore the mechanism of TCM treatment of DM.

6. Concluding Remarks
With the development of science and technology, the fields of life sciences, information sciences and nanoscineces have been drawn much attention [22]. The history of the technological development indicates that multiple interdisciplinary cross could apparently promote the development of modern science and technology, and the achievements nanotechnology have obtained are the convincing instances. At present, the development of world medicine has the tendency of emphasis on the pharmacological study, exploitation and application of TCM and the TCM research with nanotechnology in the 21st century would become a new fashion, which would become a turning point for TCM to modernization. The etiology of DM is somewhat complicated, which mechanism exploitation and therapeutic targets from the perspective of molecular level are still the emphases. With the rapid development of the nanotechnology in the medical field, it has provided the thinking for the mechanism researches of TCM controlling and treating DM. The authors firmly believe that the mechanism of TCM delaying or checking the progress of DM and its complications would be further well developed with the nanotechnology widely applied in clinic in the longer term.

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