Application of Finite Element Analysis for Investigation of Intervertebral Disc Degeneration: from Laboratory to Clinic*

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Summary: Due to the ethical concern and inability to detect inner stress distributions of intervertebral disc (IVD), traditional methods for investigation of intervertebral disc degeneration (IVDD) have significant limitations. Many researchers have demonstrated that finite element analysis (FEA) is an effective tool for the research of IVDD. However, the specific application of FEA for investigation of IVDD has not been systematically elucidated before. In the present review, we summarize the current finite element models (FEM) used for the investigation of IVDD, including the poroelastic nonlinear FEM, diffusive-reactive theory model and cell-activity coupled mechano-electrochemical theory model. We further elaborate the use of FEA for the research of IVDD pathogenesis especially for nutrition and biomechanics associated etiology, and the biological, biomechanical and clinical influences of IVDD. In addition, the application of FEA for evaluation and exploration of various treatments for IVDD is also elucidated. We conclude that FEA is an excellent technique for research of IVDD, which could be used to explore the etiology, biology and biomechanics of IVDD. In the future, FEA may help us to achieve the goal of individualized precision therapy.
Key words: finite element analysis; intervertebral disc degeneration; biomechanics; spine

Intervertebral disc degeneration (IVDD) is commonly responsible for low back pain, which poses a significant economic burden on patients[1–3]. Hence, the research related to the etiology and treatment of IVDD is essential. The current research methods for IVDD include cell experiment, animal model, organ culture, cadaveric samples test and so on[4–7]. Nevertheless, due to the complex anatomical structure of intervertebral disc (IVD) and anfractuous mechanism of IVDD, all existing methods have limitations more or less, which will inevitably result in the departure of the conclusion from the real situations in human[8]. For instance, with cell experiments, it is hard to simulate the complicated microenvironment of the disc; the reproducibility of the results of the animal model or organ culture is low; and the cadaveric samples are rare and often restrained by ethical issue. Meanwhile, for the therapeutic strategies of IVDD such as surgical interventions and biotherapy, the biomechanics influence and long-term efficacy of different operations are hard to evaluate, and the biotherapy is virtually impossible to test directly on patients[9]. Therefore, seeking new research approaches to study the etiology and curative treatment of IVDD is of great significance.

The finite element analysis (FEA) method seems to be a cost-effective alternative tool for the investigation of disc degeneration. FEA is a numerical method simulating and analyzing the behavior or mechanism of structures or components, which is initially developed in the 1950s in the aircraft industry[10]. Hereafter, FEA is widely used in many other fields. Considering that it could well evaluate the external and internal responses of living tissue, Brekelmans *et al* primarily introduced it into the analysis of biomechanics in 1972[11]. Then, it is applied to design prosthesis and determine the material properties of tested subjects such as intra-abdominal tissues, cartilage, annulus fibrosus (AF),

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muscle, skin, or polymer gels[12]. With the computing power increasing, FEA is further applied to investigate the spine and its components. Ever since Belytschko *et al* first applied the FEA for the biomechanics investigation of the spine, the FEA study of spine has been developed from two dimensional linear model to nonlinear model and further to the three dimensional nonlinear model[13]. Regarding to the investigation of IVD, FEA is an alternative for the quantitative or qualitative study of IVDD and regeneration. FEA could provide complex biological, chemical, electrical and mechanical information of the disc under physiological or pathological conditions, which are difficult to measure directly. Accordingly, FEA has been employed to explore the etiology of IVDD, analyze the influences of IVDD, design and assess the new instruments for spinal operation and evaluate the impacts and efficacy of the operation or biotherapy for IVDD[14–17]. Although FEA has been widely used in IVDD research, systematic review of the specific application of FEA in the investigation of IVDD is scarce.

In this review, we summarize the current finite element models (FEM) used for the investigation of IVDD. In addition, we also discuss the application of FEA in the research of IVDD pathogenesis, and the biological, biomechanical and clinical influences of IVDD. Finally, we elaborate the use of FEA in the evaluation and exploration of various treatments for IVDD.

1 FEM for Investigation of IVDD

As a kind of computer technology using the method of model simulation, the accuracy of FEA mainly depends on the veracity and approximation of modeling. However, considering the complicated structure of IVD, a series of simplifications are always applied to the IVD FEM[18]. Therefore, simulating the real situation as much as possible is fundamental for the FEA of IVD. Consistent with this notion, several types of FEM based on various theories have been developed. According to the purpose of researches, IVD FEM can be classified into the models for the study of biomechanics and those for biology-associated research. Furthermore, degenerated disc models are always simulated on basis of normal disc models[14, 19, 20].

1.1 The IVD Models for Biomechanics Analysis

Even though the FEM has been developed from two-dimension to three-dimension and from linear to non-linear, there still exist some similarities unchanged for the biomechanics analysis models. Because slight variation in the model may result in distinctly different results, to simulate real IVD in either geometry or property as much as possible is fundamental for all models for biomechanics analysis. At present, the most commonly used model for biomechanics analysis is three-dimensional poroelastic nonlinear FEM[21, 22]. The basic theory of this model is that the structure is assumed as biphasic materials consisting of porous solid matrix saturated with water. Generally speaking, this model incorporates all major and peripheral anatomical structures of disc, including vertebral bodies, the bony posterior elements, the structures of the facet joints, the intervertebral disc, and the seven major ligaments at each level[23–25]. All above structures should be organized as real disc. For instance, vertebrae consists of cancellous bone and its surrounding cortical bone; nucleus pulposus (NP) is simulated as a fluid constitutive model which is incompressible; AF is composed of seven concentric rings of ground substance reinforced by collagen fibers; the surfaces of facet joints are modeled by a cartilaginous layer; the contact between the facet joints is regarded as surface-to-surface contact elements without friction[24, 26–29]. To guarantee the similarity, the anatomical characteristics of the above structures are usually obtained from CT scan of living person or cadaveric samples[25, 28]. The biomechanics properties (e.g. Young's modulus, Poisson's ratio) of the above structures are usually obtained from the published literature[28]. However, there are also other methods to define the material properties. Nikkhoo *et al* developed a material property updating protocol, which was efficient and effective in defining material properties of a complex structure such as the IVD[12]. To better simulate real situation, some researchers also defined parameters of FEM using data averaged from the literature or cadaveric samples[22, 30]. The poroelastic nonlinear FEM includes not only changes in geometry of the disc and the nucleus altered mechanical properties but also changes in permeability and porosity of various disc components and the reduction in nucleus water content[21]. Poroelastic nonlinear FEM has been widely used to describe the time-dependent behavior of the disc tissue[22]. In addition, osseo-ligamentous non-linear FEM and strain-adaptive bone remodeling related theory are also used in the biomechanics study of IVD[29, 31].

1.2 IVD Models for Biology Associated Research

The models based on diffusive-reactive theory and cell-activity coupled mechano-electrochemical theory are the most commonly used models for biology associated research. Different from the models for biomechanics analysis, the models related to biology research mainly focus on the simulation of physiological process, and meanwhile, high degree of morphological fidelity is always not necessary. Moreover, due to the symmetry of the disc, only the right upper quadrant of IVD is modeled in most cases[17, 32]. In addition, although both the two theories could be applied to investigate the phenomenon involving biology, there are some differences between them. For diffusive-reactive model, a series of parameters acquired from

the published literature are incorporated into the model, which usually involve the diffusion rate of solutes [e.g. oxygen, insulin-like growth factor 1 (IGF-1), lactate, glucose *etc*.], the reaction between solutes with cells or receptor; the anabolism and catabolism of proteoglycan; and threshold of intervertebral disc cell death and so on[17, 32–34]. The diffusive-reactive model can only be used to investigate the biology phenomenon of IVD, such as IVDD induced by nutrition deprivation or therapy of IVDD by exogenous administration of IGF-1[17, 20]. Nevertheless, the typical truth is that compression is always tightly associated with the biology of IVD, so the biomechanics analysis and biology research could not be absolutely separated from each other[35]. Cell-activity coupled mechano-electrochemical mixture theory can compensate the above described drawbacks of diffusive–reactive model to couple the biology and biomechanics of IVD within one model. In this model, IVD is simulated as an inhomogeneous, porous mixture consisting of three phases: a charged solid phase, an interstitial fluid phase, and a solute phase with multiple species including charged (e.g. sodium ion, chloride ion), and uncharged solutes (e.g. glucose, oxygen, and lactate)[20, 35]. Some biology and biomechanical parameters including cell activity, relationship between solutes with cells as well as deformation-dependent tissue properties that include tissue porosity, fixed charge density, hydraulic permeability, and solute diffusivities are incorporated into the model in order to more accurately reflect the *in vivo* environment in the disc under compression[36, 37]. Hereby, the mechano-electrochemical mixture model is always employed to analyze the reciprocity between compression and biology of IVD[14, 38].

1.3 Simulation of Degenerated Disc

There are various methods to simulate the degenerated disc, which could be divided into two manners according to changed parameters based on normal IVD model, thus changing the geometry and material properties of the normal model. The above two manners are always applied conjunctively. Methods of changing the geometry usually include reducing the height of disc; increasing the disc area and decreasing the NP area; making the inferior facet oblique to the superior facet; reducing the thickness of cartilage endplate (CEP); adding some lesions such as osteophyte, rim lesion, radial tear, or circumferential tear and so on[26, 27, 39]. Transforming the material properties includes decreasing the water content or fixed charge density in the NP and AF regions; altering the elastic moduli, bulk modulus, Young's modulus and Poisson's ratio of NP and AF tissues; increasing the stiffness of disc and other methods[24, 40–42].

1.4 Validation of the Models

After the construction of the model, the established disc must be validated to avoid under- or overestimating the calculated results. The principle of validating the model is to compare some parameters of the model with the real situation. For models used for biomechanics analysis, the axial displacement, range of motion, quality of motion, disc pressure and cortical strains are always used to validate the model by comparing them with the experimental data and literature[22–24, 26, 29]. For models used for biology associated research, they can be validated by comparing some parameters predicted by the models, such as the water content and glycosaminoglyca (GAG) content distributions, with experimental data[35, 38, 43]. However, we must notice that some parameters such as the distributions of lactate and oxygen are difficult to validate as it would require invasive and complicated experimental procedures[14]. Therefore, we must make sure that our initial assignment to each parameter is precise enough.

2 Application of FEA to the Investigation of IVDD Pathogenesis

IVDD is a complex process involving a variety of intricate mechanisms, which result in the fact that both in vivo and *in vitro* studies are powerless to examine interactional pathogenesis. Therefore, the technique to investigate the effects of a single influencing factor is necessary. Consistent with this notion, FEA manifests its advantages in analyzing the contribution of single factor to the pathogenesis of IVDD, and some mechanisms hard to illustrate using traditional methods have been elucidated.

2.1 Analysis of Nutrition Distribution and Transport in IVD

Compression and impaired nutrition supply play pivotal roles in the pathogenesis of IVDD. However, the *in vivo* research about the nutrient distribution as well as the specific role of compression in IVDD are quite difficult, especially in human discs[44]. FEA can therefore serve as an important supplement, which can help us to fully understand the *in vivo* environment of IVD. By virtue of FEA, several researchers have revealed that compression can affect the nutrition distribution. Specifically, dynamic compression could increase the oxygen concentration, reduce the lactate accumulation. In contrast, static compression exhibited inverse effects on transport and metabolism of oxygen and lactate[37, 45, 46]. As for the underlying mechanism of compression influencing the nutrition distribution, Malandrino *et al* demonstrated that external force-induced large volume changes modified diffusion distances and diffusivities, which ultimately influenced the oxygen and lactate regional distributions within the IVD. Furthermore, for the healthy disc, nutrient concentration patterns depended mostly on the time of sustained compression and recovery[14]. Although

compression influences the nutrient distribution, results from FEA also indicate that dynamic compression-induced changes of nutrition distribution do not affect the cell density in non-degenerated IVD[36, 37].

CEP pathway is the major pathway to transport nutrition into IVD. However, solely detecting the influence of CEP on nutrition transport is extremely difficult due to the existence of other nutrition pathways. Wu *et al* simulated the endplate calcification by reducing the tissue porosity, and results showed CEP calcification dramatically decreased the nutrient levels such as glucose and oxygen in human IVD[47]. Furthermore, Jackson *et al* illustrated that CEP calcification more strongly affected glucose concentrations in the nucleus than in AF region[48]. Besides the endplate calcification, Shirazi-Adl *et al* demonstrated loss of endplate permeability, as well as changes in geometry and fall in diffusivity associated with fluid outflow could also decrease nutrition supply, which caused the nutrient concentration too low to maintain cellular activity or viability, resulting in cell death and disc degeneration[49].

2.2 Investigation of IVDD Pathogenesis

The intrinsic relevance between impaired nutrition supply and IVDD can be elucidated through FEA. Malandrino *et al* analyzed the effects of cell density on metabolic transport, and demonstrated that the disturbance of cell number was a possible onset of disc degeneration via altering the metabolic balance[14]. In order to explore the effects of nutrition imbalance on the pathogenesis of IVDD, they further reduced supply of solutes at the bone-disc interface to simulate the IVDD. The results showed that a reduction in metabolite concentrations at the bone-disc boundaries induced an increasing cell death, and even an increase in exchange area made no sense[50]. Other results from Zhu *et al* and Gu *et al* also revealed roughly the same effects of impaired nutrition supply on pathogenesis of IVDD[36, 43].

There are two pathways, the CEP-NP pathway and the AF periphery pathway, for IVD nutrition supply. However, the specific roles of each pathway have not been elucidated[51]. In a FEA conducted by Zhu *et al*, they simulated the impairment of different nutritional pathways. The results demonstrated that different types of IVDD would happen depending on the impaired nutritional pathway. Thus, the sole impairment of CEP-NP pathway would mainly cause the NP degeneration, impairment of AF pathway only was characterized by degeneration of outer AF, while impairment of both CEP-NP and AF pathways would lead to the degeneration of NP and AF simultaneously[20].

Besides impaired nutrition supply, researchers also employed FEA to investigate the influence of smoking on IVD homeostasis. Elmasry *et al* found that the GAG concentration at the CEP was mostly influenced by nicotine-mediated downregulation of cell anabolism, while the decrease of solutes exchange between blood vessels and disc tissue mainly influenced the NP, leading to the reduction of cell density and GAG levels[32].

3 Biological, Biomechanical and Clinical Influences of IVDD

The degeneration process of IVD is a cascading event owing to the fact that IVDD will further aggravate the progression of degeneration through transforming the biology and biomechanics conditions of IVD. Due to invasive procedures and ethical concerns, traditional methods can seldom obtain the data related to changes happening within human degenerated disc. As a numerical simulation method, compared to traditional methods, the greatest advantage of FEA is that it can non-invasively and repeatedly detect the biology, biochemical, and biomechanical characteristics of degenerated disc.

3.1 Degeneration-induced Changes in IVD

IVDD has significant influence on biology and biochemical characteristics of disc. Several FEA studies have revealed that IVDD could result in the decrease of water content, proteoglycan content and fixed charge density in disc[20, 35, 38, 43]. Degeneration could also diminish the supply of glucose. Through analyzing the nutrient distribution and cell viability in IVD, Jackson *et al* found that both IVDD and compression-induced static deformation could change the glucose distribution. Disc degeneration would result in glucose levels falling below the levels necessary for maintaining cell viability, which caused decrease in cell density, and this effect was further exacerbated by compression-induced deformation of the degenerated IVD[37]. Degeneration related changes in CEP may be responsible for variation in nutrition supply. Results from FEA performed by DeLucca *et al* revealed that accompanied with degeneration, permeability of CEP decreased about 50%–60%, resulting in severe inhibition of nutrition transport[52].

Due to the changed extracellular matrix constituent and geometry of degenerated disc, material characteristics will also be altered. Nikkhoo *et al* compared the material properties of intact and degenerated discs using FEA, and the results suggested that the hydraulic permeability significantly decreased while Poisson's ratio dramatically increased in the degenerated discs[12]. With the progression of degeneration, Zhu *et al* found that the Von Mises stress would increase within the disc and this increase was more obvious in the outer AF region. In the meanwhile, both the disc volume and height decreased with the degeneration[35]. Ayturk *et al* showed that disc degeneration could specifically affect the functional

effectiveness of the collagen fiber network in the annulus, leading to changes in the biomechanical behavior at both the tissue level and the motion-segment level[53]. In addition, Galbusera *et al* further explored the influence of different IVDD parameters on mechanical characteristics of disc. The results indicated that reduced disc height, water content, and external pressure had the highest influence on the spine biomechanics, while changing the disc permeability and endplate sclerosis made no difference[54]. Consistent with above results, Chagnon *et al* also proved that disc height, changes in the annulus stiffness, as well as in the annulus and nucleus permeability had significant influence on load sharing of degenerated discs[39]. All above conclusions derived from FEA suggest that IVDD might transform the biology and biomechanics behavior of IVD, which perhaps deteriorates the progression of IVDD.

3.2 Influences of IVDD on Vertebrae

Due to changed biomechanics property and geometry of disc, vertebrae could also be influenced by IVDD. According to the Wolff's law, changed stress in vertebrae would lead to adaptation in the vertebrae, and a series of FEA studies have verified this theory. Homminga *et al* demonstrated that disc degeneration, especially the degeneration of NP, transferred the load from the nucleus to the annulus. Subsequently, this would result in decreased density in the trabecular core, and the increased density in the anterior and posterior wall of vertebrae. However, the lateral walls were almost unaffected. These adaptive changes would increase the occurrence of vertebral fractures[31]. Similar to the results of this study, a FEA performed by Maquer *et al* indicated that higher disc degeneration grade reduced the failure load and increased damage in the vertebral body[55]. IVDD can also affect facet joint. For instance, Hussain *et al* found that posterior facets (PF) were more easily influenced than discs owing to decrease in segmental flexibility. Therefore, IVDD might result in the overload of PF joints[27]. They further employed FEM to investigate the effect of disc height on loading of PF. The results revealed that IVDD could apparently affect articulating facets of cervical spine at flexion and extension motions. In moderate IVDD, PF loading was more affected by posterior disc (PD) height loss than anterior disc (AD) height gain, whereas in severe IVDD, it was more affected by AD height gain than PD height loss[19, 56].

3.3 Influences of IVDD on Adjacent Segments

Accumulating evidence indicates that IVDD can alter the loading and motion patterns of adjacent discs, and even lead to onset of degeneration in adjacent segments. By using FEA, we can specifically investigate the influences of IVDD on adjacent levels. Kim *et al* established a lumbar FEM to analyze the effects of degenerated L4-L5 level on the adjacent L3-L4 level. The results displayed that L4-L5 disc degeneration could result in increased intradiscal pressure and the simultaneous increase of disc bulge in posterior region of L3-L4 level, which could trigger the degeneration of L3-L4 segment[57]. Similarly, Ruberte *et al* demonstrated that degeneration in L4-L5 level could increase the range of motion in adjacent L3-L4 and L5-S1 segment. Meanwhile, the maximum von Mises stress and shear stress in the annulus would increase too. These changes often increased the injury risk of the adjacent levels[58]. In addition, in a FEA of cervical spine, Hussain *et al* also stated that degenerated C5–C6 segment brought about higher motion changes in normal C6-C7 segment immediately inferior to it[42].

3.4 Association between IVDD and Clinical Features

IVDD is usually accompanied with a series of symptoms such as disc prolapse, pain and Schmorl's nodes. By virtue of FEA, we may illuminate the mechanism of some clinical symptoms. Lu *et al* demonstrated that axial compressive load, bending, twisting, and disc saturation were all necessary for the initiation and propagation of anulus failure. If one of above factors was lacking, anulus failure was harder to achieve[59]. Qasim *et al* used a FEM to predict the initial damage of degenerated disc. Results indicated that in grade Ⅲ degenerated discs, the damage initiated at the posterior inner annulus adjacent to the endplates and propagated outwards towards its periphery, while in grade Ⅳ degenerated discs, damage initiated at the posterior outer periphery of the annulus and propagated circumferentially[23]. For the association of IVDD with pain, von Forell *et al* showed that compared to contiguous multilevel disc degeneration cases, skipped-level disc degeneration caused lower stress and force for the surrounding ligaments, facets, and pedicles at certain vertebral levels of the spine even when the skipped level included more degenerated discs. This conclusion was in consistent with higher incidence and severity of pain in contiguous multilevel disc degeneration patients[24]. For the formation of Schmorl's nodes, von Forell *et al* found that IVDD could increase the strain energy at the center of the vertebral endplate immediately in contact with the degenerated disc. This phenomenon was more obvious in skipped-level disc degeneration, which could be regarded as a predictor for the development of Schmorl's nodes[60].

4 Evaluation and Exploration of Treatment for IVDD by Use of FEA

At present, the golden standard for the treatment of disc degeneration is the surgical removal of the diseased disc followed by fusion of the adjacent vertebral bodies. In the meanwhile, biological therapeutics is also proven to be effective[61]. Nevertheless, for surgical therapy, what kind of fixation should be adopted

following surgery and how to fill the NP after removal are still controversial. For biology therapy, due to ethical issue, the effectiveness in human is hard to evaluate. Therefore, numerical simulation may be a new method for evaluation and exploration of treatment for IVDD.

4.1 Surgical Treatment for IVDD

Many surgical methods have been developed to stabilize and depressurize the degenerated disc, while different surgical procedures will result in various clinical outcomes. To evaluate the effectiveness and biomechanics influence of operation, and to further explore new surgical methods, FEA technique is adopted.

Spinal fusion is the dominant method for IVDD treatment; however, there are various fusion methods. Zagra *et al* compared the biomechanics between posterior oblique lumbar interbody fusion (POLIF), posterior lumbar interbody fusion (PLIF) and transforaminal lumbar interbody fusion (TLIF) by use of FEA. The results showed that POLIF was a viable and safe surgical technique, which manifested a biomechanical property comparable to PLIF and TLIF[62]. Nevertheless, spinal fusion is also thought to be able to trigger the adjacent segment degeneration. Tang *et al* demonstrated that anterior lumbar interbody fusion (ALIF) had more adverse biomechanical influences than disc degeneration on adjacent upper disc, which led to higher intradiscal pressures, and intersegmental rotation ranges. These adverse effects might aggravate the degeneration of adjacent upper segment[26]. They further verified that TLIF could aggravate adjacent segmental degeneration more severely than ALIF[16]. In order to avoid the adverse effects of spinal fusion on adjacent segment, some improvements have been made, and the efficiency is verified using FEA. Erbulut *et al* demonstrated that dynamic construct consisting of a dynamic rod and a dynamic screw was superior to rigid rod constructions, which could prevent the adjacent segment from excessive motion[63]. For dynamic fixators, Chien *et al* demonstrated that Dynesys system was more suitable for a healthy or mildly degenerative transition segment, while Cosmic system was preferable for severely degenerative transition segments[64].

Besides spinal fusion, interspinous implant device is also a commonly used operation alternative. Song *et al* evaluated a novel interspinous implant device through FEA. It was reported that implantation only slightly changed the range of lumbar motion. In addition, the spine stability was effectively preserved without undue restriction of spine activity. Furthermore, it could reduce the pressure of L4/5 end plate, NP and facet joint[15]. In addition, Cegonino *et al* showed that the cage insertion seemed to be a better way to treat IVDD, in that it could reduce the stress and strain in affected disc, and preserve the disc height at long-term in a more evident way than fusion with autograft[65]. For multilevel degeneration, it is sometimes difficult to choose suitable operation procedure. Faizan *et al* found that compared to fusion plus disc replacement and bi-level fusion, bi-level disc replacement almost had no adverse mechanical effects on adjacent levels[66]. Accordingly, Chung *et al* demonstrated that compared to PP (2 peek cages) and AA (2 artificial discs), PA (peek cages and artificial discs) construct had optimal biomechanics due to minimal ASD and implant failure, whereas the AP (artificial discs and peek cages) strategy was only preferable when cranial degeneration was the major problem[67]. However, there are also some limitations. Schmidt *et al* exhibited that with the increased number of implanted artificial discs, the motion in flexion and extension would augment more than intact condition. Moreover, deviations from the optimal implant position would lead to unfavorable kinematics, high facet joint forces and even lift-off phenomenon[29].

4.2 Biological Therapy for IVDD

Surgical treatment mainly aims at severe IVDD patients. For mild degeneration, biological therapy may be more appropriate. Death of NP cells is the primary inducement for IVDD; therefore, IGF-1, which can promote cell proliferation, seems to be a good choice for improving or even retarding IVDD process. Huang *et al* explored the effects of IGF-1 administration on distribution of glucose and oxygen in IVD. Their results displayed that with higher concentration of IGF-1 binding proteins, the region affected by IGF-1 was smaller and the duration of the therapeutic IGF-1 level was longer in the degenerated disc. Additionally, IGF-1 injection could reduce the glucose concentration and increase the lactate accumulation in IVD[41]. Furthermore, Travascio *et al* found that exogenous administration of IGF-1 was only effective in well-nourished regions of IVD, and even accelerated cell mortality in malnourished regions. This research revealed that adequate nutritional supply was essential for the successful IGF-based therapy for IVDD[17]. Cell transplantation is another way to save the disc degeneration. Whereas, Wu *et al* found that due to impaired nutrition supply in degenerated disc, excessive number of injected cells might cause further deterioration of the nutrient environment in degenerated disc, which might aggravate the degeneration of disc[47]. Zhu *et al* used FEA to evaluate the effectiveness of three kinds of biological therapies: increasing cell density, increasing glycosaminoglycan synthesis rate, or decreasing glucosamine degradation rate of NP. They revealed that increasing cell density could repair mild and severe degeneration, whereas increasing mucopolysaccharide synthesis or inhibiting its degradation could only repair mild degeneration and was ineffective for severe degeneration[68]. Tissue

engineering scaffolds are also effective for IVDD therapy[69]. Yao *et al* used a FEM to explore the optimal mechanical property of scaffold. The results showed that well-designed tissue-engineered scaffold preferably had a modulus in the range of 5–10 MPa and a compressive strength exceeding 1.67 MPa[70]. Furthermore, other results demonstrated that a partial volume fill well above 85% was necessary to restore the compressive characteristics of the disc[71].

5 Conclusion

Traditional methods for investigation of IVDD-associated diseases, including *in vivo* and *in vitro* studies, have inherent deficiencies. As a numerical simulation technique, FEA is an excellent method for the research of IVDD. In this review, we conclude that FEA can mainly investigate the following problems: (1) the etiology of IVDD, including biological and biomechanical pathogenesis; (2) the biology, biochemical and biomechanical influences of IVDD on disc, vertebrae and adjacent segment; (3) the evaluation and exploration of biological and surgical treatment for IVDD. The results derived from FEA are reliable, precise and comparable to traditional research methods, which could well represent the molecular, pathological and biomechanical features of degenerated discs. Compared to traditional research methods, the calculated results of FEA are more quantitative and visualized. Furthermore, FEA is mainly used to explore some phenomena that are difficult to interpret only by traditional technology and it could simulate the results of very long time spans. Moreover, because of the non-invasion and repeatability, it is even superior to traditional research methods at some respects.

There are still some limitations for FEA. For example, as a numerical simulation method by which the precision of results largely depends on the similarity of the model and accuracy of the parameters, the results might not be the real value of the human spine owing to the assumptions and simplifications. Furthermore, because of the specimen-specific nature of the geometry used in generating the model, perhaps results derived from the model are only suitable for the geometries of this particular spine. In addition, the model usually neglects the muscles surrounding the spine, which also contribute tremendously to the biomechanics property of disc. Finally, FEA could only take limited number of factors into consideration while the real situation is quite complicated. Thus, the results of FEA are not as comprehensive as traditional research methods.

Despite the limitations, we still believe that FEA is an excellent technique for the research of IVDD, and it is especially suitable for the research related to the analysis of the biomechanics properties of degenerated disc. With the advancement in computer technology, FEA will be more and more consummate. In the future, FEA may help us to achieve the goal of individualized precision therapy.

Conflict of Interest Statement

The authors declare that there is no conflict of interest with any financial organization or corporation or individual that can inappropriately influence this work.

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