Biomechanical properties of polyvinyl alcohol hydrogel as a nucleus pulposus replacement in intervertebral disc herniation: A systematic review

EKO AGUS SUBAGIO[1], GALIH INDRA PERMANA[1], ABDUL HAFID BAJAMAL[1], MUHAMMAD FARIS[1], NUR SETIAWAN SUROTO[1], AMALIYA RASYIDA[2] and BUDI UTOMO[3]

[1]Department of Neurosurgery, Faculty of Medicine, Airlangga University-Dr. Soetomo General Academic Hospital, Surabaya, East Java 60286; [2]Department of Materials and Metallurgy Engineering, Sepuluh Nopember Institute of Technology, Surabaya, East Java 60111; [3]Department of Public Health, Faculty of Medicine, Airlangga University, Surabaya, East Java 60286, Indonesia

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Abstract. The best artificial disc material must closely resemble the viscoelasticity, biomechanics and bioavailability of a natural human intervertebral disc. Currently, there is a lack of reviews discussing the characterization of polyvinyl alcohol (PVA) hydrogel as a nucleus pulposus (NP) replacement in intervertebral disc herniation. The present study systematically reviewed the biomechanical characterization of PVA hydrogel as a potential ideal candidate for the replacement of NP. The PubMed, Google Scholar, Science Direct, and Cochrane Database of Systematic Reviews databases were searched according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline. Data from the literature regarding study design, sample size, materials and biomechanical properties were collected. The literature search identified seven publications, which were read to obtain information about the biomechanical characteristics of PVA hydrogel material used with different compounds. Stress, strain and Young's modulus testing outcomes were all evaluated. The biomechanical characteristics of the materials were evaluated to determine how closely they resemble those of the NP. The results revealed that the PVA hydrogel and NP share similar biomechanical characteristics. In order to enhance its biomechanical capabilities, the PVA hydrogel may be combined with other materials.

Correspondence to: Dr Eko Agus Subagio, Department of Neurosurgery, Faculty of Medicine, Airlangga University-Dr. Soetomo General Academic Hospital, Mayjen Prof. Dr. Moestopo Street No. 6-8, Surabaya, East Java 60286, Indonesia
E-mail: eko.agus@fk.unair.ac.id

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Introduction

The most common cause of radicular pain and one of the most common reasons for spinal surgery is intervertebral disc herniation (IDH). This condition is caused by the displacement of the nucleus pulposus (NP) to the outside of the intervertebral disc (IVD) space. The progressive degeneration of a disc is considered to cause IDH (1). The degenerative process is influenced by various factors, including mechanical, behavioral and genetic factors. The IVD allows flexibility and transmits physiological loads across the spine. By sending signals to cells that control appropriate matrix homeostasis, the mechanical load plays a critical role in preserving a healthy IVD (2,3). Conversely, ongoing exposure to high loading is associated with disc degeneration. Degenerative alterations in the annulus lead to IDH. A weakness caused by annulus fissures makes it possible for disc material to expand or move outside the annulus margins (1,4). A recent trend in the surgical management of degenerative disc disease is to preserve the spinal mobility segment and reduce soft-tissue dissection. The intradiscal replacement of the NP or artificial discs may be used instead of performing spinal fusion (2,4,5). This strategy aims to restore the NP, while maintaining the integrity of the cartilaginous endplate and the biomechanics of the anulus fibrosis. The objectives of using NP implants are to stabilize spinal ligamentous structures, improve disc space height, relieve or reduce transmission of shear pressures on the remaining annulus, and stabilize motion (4,6,7).

The ideal implant for the NP must have the same biomechanical characteristics and bioavailability as the human NP. Polyvinyl alcohol (PVA) hydrogel materials for use as implants are designed to have the characteristics of structural integrity, biocompatibility, biodegradability, safety, viscosity and mechanical strength. PVA hydrogel compounds, which have specific material properties, can be used to replace a disc artificially (6,8,9). The present study systematically reviews the biomechanical characterization of PVA hydrogel materials resembling the NP and evaluates these materials as an NP replacement in IDH.

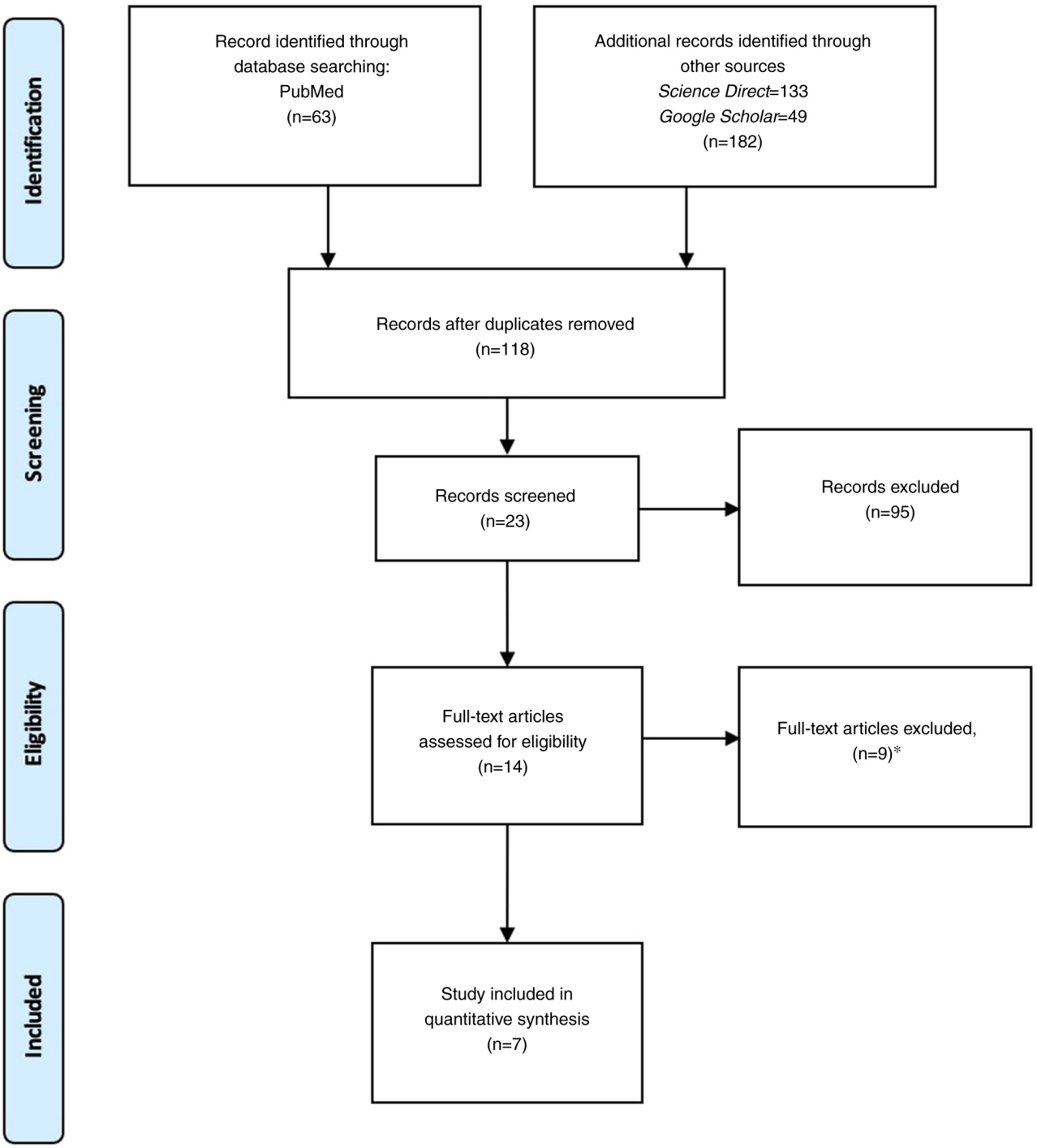

Figure 1. Flow diagram of the included and excluded studies in the present systematic review. *The present systematic review was unable to include nine articles due to their study designs, with the following details: Two studies did not substitute for NPs, one study was conducted on animals and six studies had inconsistent variables.

Data and methods

The present systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline (10).

Search strategies. The PubMed, Google Scholar, Cochrane (CENTRAL) and Science Direct databases were searched for relevant systematic reviews, original articles and randomized clinical trials (RCTs) of PVA hydrogel materials as NP replacements. The key words used for the search were herniated NP, IVD herniation, NP replacement, IVD substitution, PVA hydrogel and injectable hydrogel. The corresponding author will provide the detailed search strategy upon request. Additional studies were found by searching the references of the retrieved publications and relevant overview articles.

Inclusion criteria. All reviews, original articles and/or RCTs written in the English language were considered eligible for

Table I. Characteristics of the primary studies included in the present systematic review.

No.	Author(s), year of publication	Test method	Crosslinking	Stress (MPa)	Strain (%)	Young's modulus (MPa)	(Refs.)
1.	Kita, 2010	Unconfined uni-axial compression test	PVP	0.01	15	0.05	(21)
2.	Binetti *et al*, 2012	Unconfined uni-axial compression test	PEG-DGE	5.71	35	2	(11)
3.	Mahanta *et al*, 2013	Unconfined uni-axial compression test	$FeCl_3$	0.000006	47	0.000012	(22)
4.	Binetti *et al*, 2014	Unconfined uni-axial compression test	PVP, PEG-DGE	0.18	30	0.6	(23)
5.	Neo *et al*, 2014	Unconfined uni-axial compression test	Silk	0.06	45	0.13	(19)
6.	Charron *et al*, 2017	Unconfined uni-axial compression test	PEG 1% (w/v) gelatin	0.02	25	0.1	(20)
7.	Heo and Park, 2022	Unconfined uni-axial compression test	Phosphate-buffered saline	0.17	25	0.7	(24)

PVP, polyvinyl pyrolidone; PEG, polyethylene glycol; diglycidyl ether.

inclusion if they fulfilled all of the following criteria: i) The study population consisted of patients with IDH and NP replacement or IVD substitution; ii) the study population (*in vitro*, *in vivo* and *ex vivo*) had undergone NP replacement or IVD substitution with PVA hydrogel materials; iii) PVA hydrogel material biomechanics, including stress, strain and Young's modulus, had been characterized. Studies that matched the inclusion criteria for any groups were included, as were subgroups provided that the subgroup findings were presented separately.

Study selection. The inclusion criteria were applied to the references found by the literature search independently by two reviewers to select relevant studies from the titles and abstracts or, if necessary, from the whole publication. A third reviewer was engaged to settle disputes, if necessary.

Categorization of the relevant literature. Relevant literature was categorized with biomaterial testing of the PVA hydrogel as an NP replacement. The literature could be in the form of RCTs, reviews, original articles and material biomechanical testing. All of the selected literature contained stress, strain and Young's modulus as the biomechanical properties of the PVA hydrogel materials.

Data extraction. The data were extracted independently by two reviewers. Information was collected on the PVA hydrogel compound, biomechanical characterization, stress, strain and Young's modulus. Biomechanical testing in reports was required to have been performed on a testing machine. The materials used to replace the NP in IDH cases fulfilled all of the criteria described above.

Outcome measurements. The literature was selected if it reported the test method, crosslinking materials, stress (MPa), strain (%) and Young's modulus (MPa). The ASTM standard test method and crosslinking materials were those used to measure the composition of the PVA hydrogel material mixture. The stress (MPa), strain (%) and Young's modulus (MPa) were of the biomechanical properties of a material were collected. These biomechanical properties were then compared with the value of human NP biomechanical properties with the goal of identifying an ideal PVA hydrogel compound biomaterial similar to the NP.

Results

Study selection. The initial search identified 245 references. A total of 222 articles were excluded on the basis of duplication and/or the abstract, title and key words. After reading the complete articles, 16 articles were excluded for the following reasons: The reports did not describe PVA hydrogel as the main material (nine studies), no biomechanical properties (stress, strain and Young's modulus) were reported, no outcome results were provided (four studies), and there was no explanation of the mechanical testing procedure (three studies). As a result, only seven articles were included in the present systematic review (Fig. 1).

Description of study characteristics. No reviews were found in the search. A total of seven articles on biomechanical testing from PVA hydrogel were found. All seven articles were on the PVA hydrogel used as the base material that was crosslinked with other materials, described unconfined uni-axial compression mechanical testing, and reported the biomechanical properties results.

Data extraction. The relevant information from the studies selected according to the inclusion criteria described above is presented in Table I. The information explained the

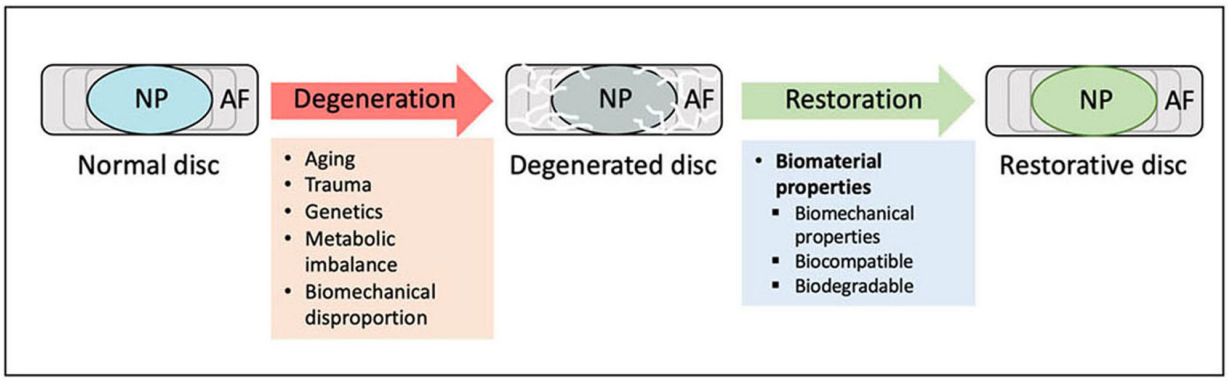

Figure 2. Treatment objectives following tissue deterioration inside the NP are influenced by potential biomaterial characteristics. NP, nucleus pulposus; AF, annulus fibrosus.

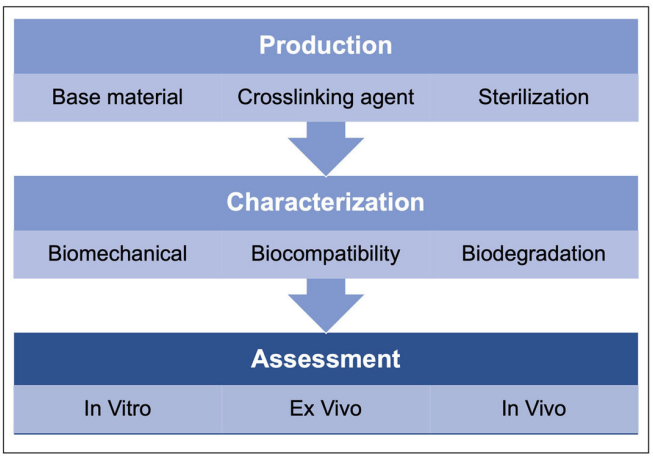

Figure 3. Biomaterial system parameters that need to be examined for restoration of the nucleus pulposus.

Table II. Intradiscal pressure values for different positions and exercises.

Position	Stress (MPa)
Lying	0.10-0.12
Standing	0.5
Sitting	0.46-0.55
Walking	0.53-0.65
Lifting 20 kg (rounded back)	2.3
Lifting 20 kg (straight back)	1.7

mechanical testing procedure, crosslinking materials, and biomechanical properties. The literature search identified the materials with the biomechanical properties most similar to those of the NP. The study by Binetti *et al* (2012) (11) demonstrated that a PVA hydrogel with polyethylene glycol-diglycidyl ether (PEG-DGE) had a Young's modulus of 2 MPa. This result is similar to the Young's modulus of human NP (1.43-32.85 MPa) (12).

Discussion

New approaches supporting IVD regeneration that are clinically practical and can enhance the quality of life of patients need to be developed. Since the NP is the location at which early IVD degeneration is most commonly observed, the NP is a prospective target for future treatments. Tissue engineering with NP bioinstructive materials is an alternative to currently available therapies (7,13,14). In addition, to helping to restore NP functionality by increasing its disc height, biologically suitable materials to repair injured tissue can also serve as a delivery system for cells and/or biomolecules to help regenerate healthy tissue. This distinction between NP restoration and regeneration imposes various critical constraints on the relevant biomaterials (Fig. 2) (4,11,13,15). Ideally, biomaterials need to restore the height and biomechanical properties similar to those of the undamaged NP and be able to withstand typical physiological loads on the disc (Table II). From a mechanical point of view, mostly unconfined compression tests and rheology are performed to understand a biomaterial's behavior under physiologically relevant stresses. Consequently, a broad range of parameters regarding their effects on the material's efficacy and performance over time within the disc need to be considered during development (Fig. 3) (4,9,13,16).

In the present systematic review, the literature was systematically selected to evaluate the biomechanical properties of PVA hydrogels with various crosslinking materials. All the selected literature described similar mechanical testing procedures for the study materials. The biomechanical properties results were for stress (MPa), strain (%) and Young's modulus (MPa) (9,17,18). A total of seven articles were identified for the qualitative analysis. The analysis revealed that knowledge on NP replacement is limited, particularly with PVA hydrogel material, which is an ideal substitute as its biomechanical properties are similar to those of the NP. This condition may be affected by several factors, such as the crosslinking materials, mechanical testing procedures and material composition ratio.

In the literature search, the PVA hydrogels were described as being crosslinked with polyvinyl pyrrolidone (PVP), PEG-DGE, $FeCl_3$, polyvinyl pyrrolidone (PVP)/PEG-DGE, silk, PEG 1% (w/v) gelatin and phosphate-buffered saline (PBS). Notably, the studies by Neo *et al* (2014) (19) and

Charron *et al* (2017) (20) demonstrated that the PVA hydrogel could be crosslinked with natural materials, such as silk and gelatin. Hydrogels crosslinked with natural materials are very interesting to study due to their biocompatibility, biodegradability and safety (7,14). The studies by Kita (2010) (21), Binetti *et al* (2012) (11), Mahanta *et al* (2013) (22), Binetti *et al* (2014) (23), and Heo and Park (2022) (24) demonstrated that PVA hydrogels crosslinked with synthetic materials, such as PVP, PEG-DGE, $FeCl_3$, PVP/PGE-DGE and PBS, lacked bioactivity. However, those materials have the advantages of being able to be engineered and formed to generate the appropriate mechanical properties. The present systematic review found that the biomechanical properties of natural crosslinking agents were less similar than those of synthetic crosslinking agents to those of NP (14,15,25). Synthetic hydrogel crosslinking has exhibited improved Young's moduli values than those of natural materials. Young's modulus is a metric that evaluates resistance to changing the shape of a material in response to an applied force, which is essentially a measurement of a material's stiffness; the higher the value of Young's modulus, the more inelastic the material is, making it more difficult to deform (14,18,15,25). The ratio of stress to strain yields Young's modulus. Due to its association with the amount of load that a material can withstand while keeping its shape, Young's modulus is crucial in defining the biomechanical characterization of a material. The study by Binetti *et al* (2012) (11) demonstrated that the PVA hydrogel with PEG-DGE possessed the omptimal Young's modulus value among other materials and that value was similar to that of the NP. PVA hydrogel with PEG-DEG crosslinking is an ideal candidate for NP replacement.

In conclusion, the biomechanical properties of the NP and of PVA hydrogel are similar. The PVA hydrogel can be combined with various substances to improve its biomechanical properties. The most promising materials for NP replacement were found to be PVA and PEG-DGE hydrogel. The materials were tested *in vivo* to determine their resistance and mechanical strength in the body. The biocompatibility of PVA hydrogel needs to be further evaluated.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

EAS, GIP, AHB and MF were involved in the conception and design of the study, in data collection and analysis, as well as in the writing, revising and reviewing of the manuscript. NSS, AR and BU were involved in the conception and design of the study, and in the revising and reviewing of the manuscript. EAS, GIP, AHB, MF, NSS, AR and BU confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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