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Orthobiologics: An Updated Definition

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Abstract

Orthobiologics is a subset of regenerative medicine, which focuses on treating the musculoskeletal system. The main therapeutics utilized include platelet-rich plasma, stem cells, exosomes, and scaffolding matrices. Continuous discoveries and new innovations have led to an increase in both popularity and usage of these therapeutics by various medical and scientific communities. Despite its potential, however, the field is viewed with significant skepticism secondary to poor documentation, a lack of standardization, vague nomenclature, disorganized research protocols, and an absence of a clear understanding of the mechanisms underlying the effects of the various therapeutics. This ambiguity led to a surge in direct-to-consumer marketing by "Stem Cell Clinics", putting patient's health at risk and further delegitimizing the field. These shortcomings led to a recent push for standardization by both professionals and organizations alike; a move that has put Orthobiologics on the path toward becoming a guideline-driven, protocol-based, and research-backed specialty. And with these rapid changes comes the need for an updated definition of "Orthobiologics", a crucial element of any legitimate and standardized medical field.

Keywords

Orthobiologics, Cell Therapy, Musculoskeletal, Regenerative Medicine, Regenerative Rehabilitation, Platelet Rich Plasma, Stem Cells

1. The Field of Orthobiologics

Regenerative medicine is an umbrella term that describes an area of medicine focused on using cells or proteins derived from the human body to treat, repair, or regenerate human tissues [1]. Some major areas of focus of regenerative medicine today include diabetes, autoimmune disease, neurodegenerative disorders like Parkinson's or Alzheimer's Disease, as well as cancer. Greenwood and colleagues offer one of the more robust definitions of regenerative medicine, defin-

ing it as an emerging interdisciplinary field focused on, "the repair, replacement, or regeneration of cells, tissues or organs to restore impaired function resulting from any cause, including congenital defects, disease, trauma and aging." [2]. Orthobiologics is a subset of regenerative medicine, focused on using naturally occurring biological substances and harnessing their potential to bring about favorable clinical outcomes for musculoskeletal ailments. Although orthobiologics have recently gained increasing attention, their use in clinical practice has a long history [3] [4]. In 1939, orthopedic surgeons documented the use of bone marrow aspirate to improve the implantation of bone chips into nonunion fractures [5]. Platelet-rich plasma (PRP) was used during heart surgery in 1987, [6] before it became an orthobiologic staple, when Marx et al in 1998 demonstrated increased maturity and consolidation of mandibular bone grafts which were coated in it [7]. With the turn of the millennium, evolving technology and improved scientific understanding of healing processes led to a shift from a focus on fixation and reconstruction to the possibility of regeneration [8]. And while the aforementioned treatments still comprise the bulk of the field, discoveries and innovations continue to arise. Arguably, the future of the field of musculoskeletal medicine is orthobiologics [9]. However, given the rapid advancement of the field, creating a consensus definition has proved difficult. In this editorial review we hope to provide an updated definition that will stand the test of time and remain relevant throughout the evolution of the field.

2. Various Therapeutic Modalities

The field of orthobiologics is growing rapidly, regarding both its clinical application and the pace of relevant scientific discovery [10]. It is important to reflect on the origins and current state of the field to shape its future direction more effectively. The term orthobiologics refers to naturally occurring bodily substances, that are specifically used to treat orthopedic-related conditions. The most prevalent current orthobiologic treatments that fall within this broad definition include:

Platelet-rich plasma, or PRP, is the most well-known of the blood-derived treatments. It involves the removal and centrifugation of venous blood to separate it into layers, which consist of platelet poor plasma, platelet rich plasma, red blood cells, buffy coat, supernatant, leukocytes etc.; the content of the centrifuged vial is dependent on the number of centrifugations [11] [12] [13]. To be labeled as PRP, the platelet count should exceed 3 - 5× that of normal physiologic platelet values, although a range of 1.5× - 7× is commonly reported [7]. These platelets are rich in growth factors, anti-inflammatory molecules, and other anabolic substances. These include: platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), and transforming growth factor beta (TGF-b), to name a few of the most abundant growth factors [14] [15]. These substances, in supraphysiological concentrations, are released from the platelet's a-granules

and play a pivotal role in the anabolic mechanisms of the healing cascade [16].

Stem cells are undifferentiated cells that can self-replicate and, in certain circumstances, differentiate into other cell lineages [17]. They are usually aspirated from either the bone marrow (commonly the posterior iliac crest) or from adipose tissue, but can be derived from other sources, such as adipose fat grafts, and amniotic fluid and tissues [18] [19] [20] [21]. The stem cell class most referenced in connection with orthobiologic treatments is the mesenchymal stem cell (MSC's) [22]. These cells are multipotent and have shown the in-vitro capacity to form into a variety of musculoskeletal tissues, including bone, tendon, cartilage, and fat [16] [23] [24] [25]. MSC's, when injected into an injury site, however, do not replicate and turn into new tissue. Instead, they can augment tissue healing and repair in a multitude of ways, including functioning as super-signaling molecules, sending out homing signals for reparative and regenerative substances to activate the healing cascade [16] [26]. One of the proposed mechanisms by which stem cells affect their microenvironment is via the release of exosomes [27].

Exosomes are membrane bound extracellular vesicles containing signaling molecules that can be programmed to exert a specific regenerative response [28]. The signaling molecules within exosomes can result in a host of downstream effects, including cell growth, differentiation, immunomodulation, and regeneration [29]. It has been shown that exosomes are one of the paracrine mediators released by stem cells to affect downstream signaling. They transfer "functional cargo" including mRNA molecules, proteins, and lipids, additionally they affect intercellular communication, and contribute to the healing of injured or diseased tissues and organs [30].

Scaffolding matrices, like the name suggests, provide structural support to damaged tissue, and allow for improved cell signaling and communication within the tissue's microenvironment [31] [32]. These extracellular matrices can fill a space once occupied by damaged or torn tissue and serve as a structural foundation for cells to adhere to, migrate within, and begin the process of healing and repair. They are often seeded with MSC's to augment tissue regeneration, cell differentiation, and healing. Examples of commonly used scaffolding matrices include fat grafts and amnion/umbilical cord-derived tissue [16].

3. Issues on the Road towards Legitimacy

There has been a significant increase in clinical trials devoted to orthobiologics research in recent years [33]. There have even been several recent accolades from the professional sports industry, with the likes of the NBA and NFL releasing official statements on their stances regarding the legitimacy of orthobiologic intervention and how it can be used to treat their athletes [34] [35]. These professional athletic organizations want to use the most cutting-edge therapeutics to treat their athletes, and therefore cannot ignore the potential efficacy of orthobiologic treatments.

In 2021, a survey was sent out to members of the American Orthopaedic Society for Sports Medicine, which revealed that 66.1% of members used at least one orthobiologic in their practice, 71.6% reported increased orthobiologic utilization, and 71.3% of respondents anticipated increased usage of orthobiologics in the immediate future [36]. Many physicians believe the potential for enhanced tissue regeneration does exist [37]. Whether it be for expedition of bone healing, ligament injury, focal chondral defects, osteoarthritis, tendinopathies, or complete tissue tears, orthobiologics hold tremendous healing potential [38] [39].

Despite its potential, however, the field is viewed with significant skepticism by various medical and scientific communities. Reasons for this skepticism include poor documentation, a lack of standardization, vague nomenclature, [40] disorganized research protocols, unsubstantiated recovery protocols, [41] [42] and an absence of a clear understanding of the mechanisms underlying the effects of these therapeutics. All these factors continue to be obstacles in the path towards legitimacy for the field of orthobiologics.

Despite the lack of a high level of evidence however, the use of orthobiologics has still greatly increased. PRP in particular has garnered much attention in the sports medicine world over the past decade, with many clinical trials underway studying its potential uses [43]. Many, however, have one major flaw in common, which is that they are being launched without full knowledge of what the PRP contains, which "dose" and methods of delivery are most effective, and without comprehensive scientific understanding of the mechanisms by which it may benefit the patient [44]. There is an inherent heterogeneity to PRP given its need to be collected from the individual. Given the heterogeneity in the methods of preparation, it is difficult to assess studies, let alone implement best practices. For example, there are over two-dozen different PRP preparation kits that have been used to create platelet-rich plasma [45] and over 17 different commercial protocols [46]. Additionally, there are notable differences in platelet count, the concentration of red cells and/or leukocytes, the number of centrifuge spins applied to the specimen, the use of anticoagulant primer, the type of anticoagulant used, as well as the time interval between blood draw and injection [47] [48] [49] [50]. To effectively gather data for future scientific research, there must be a certain degree of uniformity in data collection, such as pre-procedural complete blood count analysis for the whole blood and the concentrated PRP, analytical accommodation for patient/sample heterogeneity, as well as post-procedural patient-reported outcome measure collection.

In contrast to PRP, where the primary issue is a lack of uniformity, stem cells largely lack consensus on basic therapeutic mechanics [51] [52]. Not only are there large discrepancies amongst the various orthobiologic stem cell studies, but recently the entire biochemical mechanism underlying the efficacy of stem cell based treatments has been called into question [53]. With recent research dissecting the mechanism of how stem cells mediate tissue repair, scientists and medical professionals alike have become more skeptical of their proposed ability

to accelerate tissue regeneration. Although studies have been able to demonstrate stem cell replication in-vitro, in-vivo studies have not [54] [55]. Also, given the small number of these cells harvested during the extraction process, there are questions as to whether these cells are being transferred successfully into the patient at all. For the cells that do transfer successfully, however, it has been shown that they exert more of a paracrine effect than a replicative or regenerative one [56] [57] [58]. In sum, they change the surroundings they are introduced to via alteration of their microenvironment, but evidence of their ability to differentiate into the desired cell lineage is difficult to demonstrate [59] [60] [61] [62]. Despite the available data, most still believe tissue regeneration to be the main mechanism underlying stem cells as a therapy [63]. Consequently, there have been calls to change the name of "mesenchymal stem cells," to something more representative of their actual mechanism, such as "medicinal signaling cells" or "mesenchymal stromal cells" [58].

Although the lack of consensus as to the mechanism underlying therapeutic stem cell mediated tissue repair is reason enough to be divided on the subject, the following is another significant contributor to the ambiguity of the field: the so-called "Stem Cell Clinic." The disagreements amongst the scientific community regarding the nature and usefulness of orthobiologics have opened the door for direct-to-consumer marketing of these treatments. A report from 2016, for example, reported over 300 US companies selling "stem-cell" treatments, with over half of them specifically referencing the term mesenchymal stem cells in their material [58]. In 2017, this number grew to over 700 [64]. The unsubstantiated claims made by these clinics have discredited the field and have become a significant impediment to its progress [65]. The problem became so widespread that it prompted FDA commissioner Scott Gottlieb to make an official statement on the matter, stating that despite the field of regenerative medicine holding significant promise, there are unsavory characters who are attempting to "leverage the scientific promise of this field to peddle unapproved treatments that put patient's health at risk" [66].

Given the obscurity surrounding stem cells, the inherently heterogeneous and non-uniform makeup of the therapeutics, and the knock-off clinics preying on the misinformed, it is imperative that the field of orthobiologics take a large step towards legitimacy. The field is still very much in its infancy and has a long way to go to develop consensus regarding the types of procedures to perform for specific patients and conditions [16] [67]. Presently, there is significant progress being made toward achieving these goals.

4. A Push for Standardization

There have been many strides made in standardizing the field of orthobiologics [68] [69]. These have come from scientists and clinicians alike, who desire to translate these biologics into evidence-based medicine [70] [71]. In 2013, the International Cellular Medical Society asserted that there needs to be a standard

for PRP preparation, technical use, and outcome tracking [72] [73] [74]. In 2016, the 21st Century Cures Act was passed, which supported and encouraged development in the realm of regenerative medicine [71]. Advances in several basic science areas, such as cell biology, genomics, and biomaterials are leading to improved understanding of tissue degeneration, repair, and regeneration [74].

In 2015 at the AAOS/ORS Biologic Treatments for Orthopaedic Injuries Symposium, as well as the AOSSM Biologic Treatments for Sports Injuries II Think Tank in 2015, experts were given the task of identifying a consensus for the "minimum reporting requirements" for clinical studies evaluating these biologic therapeutics [73]. The PAWS method has been suggested as a simple way of algorithmically systemizing the use of PRP [75] [76] [77]. The DOSES protocol has been suggested as a means of categorizing the use of cell-based therapies [64]. Studies looking at the ideal techniques to be used during orthobiologic procedures are now being conducted [78] [79]. In February of 2018, the AAOS hosted a think tank with the goal of optimizing the clinical use of biologic therapeutics both presently and for the future. Some of the main takeaway points from the summit included the need for improved minimum information standards for studies reporting on biologics (MIBO) and commitments by physicians and institutions alike to establish high-quality patient and biorepository-linked registries that can be used for post-market surveillance and quality assessment [78]. There is growing agreement that a "renewed and comprehensive approach" to our scientific understanding of these biologics is required to "guide the appropriate and effective use of these therapies in the future" [44].

For example, in 2018, the Biologic Association (BA) was created in collaboration with the leadership of several orthopedic societies. The organization was developed to mend the knowledge gaps and foster a collaborative and unified atmosphere in the musculoskeletal biologics environment. Its goal is to promote improved understanding of the safe, ethical, and efficacious use of biologics across a variety of musculoskeletal conditions. In 2020 the BA held a summit to discuss future goals for orthobiologics, which included improved education and best practices, a more robust biologic data repository, the establishment of operational standards, and enhanced orthobiologics advocacy [80]. The BA mission statement, which sums up nicely the goals of future developments in the field of orthobiologics, reads as follows:

"The Biologic Association's mission is to foster and convene a collaboration for shared and coordinated efforts to speak with a unified voice in the musculoskeletal biologics environment, advocating for the responsible use of biologics in clinical practice, spearheading standards development, and assessing and reporting on the safety and efficacy of biologic interventions." [81].

Though these steps represent significant advances in the right direction for the field of orthobiologics, there are still challenges that must be overcome before it can be cemented as a guideline-driven, protocol-based, and research-backed

specialty. And the aforementioned information is proof of the clear progression toward this objective. Given the continuous scientific and clinical advancement, in combination with the growth of the field, an updated definition of the term orthobiologics is warranted.

5. An Updated Definition

Many societies and physicians alike have offered their own attempt at a definition of the term "Orthobiologics". These include:

"… the use of biological substances to help musculoskeletal injuries heal quicker." [7].

"... the injection of a small volume of solution into multiple sites of painful ligament and tendon insertions and adjacent joint spaces, with the goal of reducing pain and ostensibly promoting tissue repair and growth." [16].

"... a variety of injectable substances, including isolated growth factors, platelet-rich plasma (PRP) and other autologous blood formulations, and cell therapy approaches using cells derived from bone marrow, properly prepared and preserved amniotic sources, or adipose tissue." [34].

"... any treatment that utilizes the body's native cellular components to promote healing of damaged or diseased tissues." [6].

".... biological substances found naturally in the body that help injuries heal more quickly." [74].

Given the similarities yet subtle differences amongst the various proposed meanings, it is incumbent that a simple, overarching definition imbued with relevant topical additions be suggested. We propose the following definition:

Orthobiologics is a field which focuses on the use of naturally occurring biological substances to enhance healing of injured or diseased tissues of the musculoskeletal system. These substances can be either autologous or allogeneic, cellular, or acellular. They can be derived from multiple sources including blood, bone marrow, adipose, synovium and amniotic material, and are manipulatable to varying degrees to bring about the desired therapeutic properties.

This definition, though lengthier than the others, provides a clear overview as to the foundation of the field in a simple manner. And as the field continues to evolve, it can easily be adapted and built upon to encompass new discoveries that are realized.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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