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Knowledge of the Use and Benefits of Applying Biotechnology and Cell Based Therapy in Orthopaedics in Jordan: Questionnaire Survey and Regulation Assessment

Loay A. Al-Zu'be[1,*], Thakir D. Al-Momani[1], Bilal M. Al-Trabsheh[1]and Modhafar Z. Al-Zoubi [2]

[1]*Biomedical Engineering Department, The Hashemite University, P.O.Box 330207, Zarqa 13133;*

[2]*Al-Yamama Company for Health and Environmental Projects, P. O. Box: 961162, (11196), Amman, Jordan*

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Abstract

New techniques have been developed, many derived from biotechnology that enhance and expand the use of human cells and tissues as therapeutic products. These new techniques hold the promise that some day they will provide therapies for many serious medical conditions. With the increasing numbers of trauma, cancer cases and diabetes mellitus cases every year in The Hashemite Kingdom of Jordan (Jordan), it is important to explore and introduce the use of new therapeutic technologies in the Jordanian health care system, i.e., biotechnology, tissue engineering, and cell based therapy. Before introducing these therapy modalities to the Jordanian market, assessing the knowledge of these new therapeutic modalities is worth performing. The current study aimed to assess the knowledge of biological growth factors and mesenchymal stem cells (MSCs) use and benefits in orthopaedics in Jordan. The assessment was made by analyzing questionnaire results filled by a sample of Jordanian orthopaedics surgeons and senior medical school students from the Hashemite University, Zarqa, Jordan. The questionnaire results reflected good knowledge and appreciation of the use and benefits of biological growth factors and MSCs in orthopaedics applications and treatments among participants. Surprisingly, higher percentages of positive answers were reported about the knowledge of mesenchymal stem cells benefits compared to biological growth factors in the year 2012. The results also showed statistically significant lower percentages of positive answers to the question of thinking that using these new technologies will reduce the treatment cost (≤36%), compared to the percentages of positive answers to the other questionnaire questions. Still, higher percentages of positive answers were reported to whether participants will agree to use biological growth factors to accelerate the healing process on themselves (82% in 2009 & 74% in 2012). The current study also presented an assessment of the Jordanian regulations and their ability to define and regulate the use of these new therapeutic technologies and their products in Jordan. The questionnaire results and the legislations assessment highlighted the necessity to reform the Jordanian laws to build a legal framework that encourage healthcare suppliers and providers to explore and evaluate new technologies that might reduce treatment cost and hospitalization time in Jordan.

Keywords: Biotechnology, Mesenchymal Stem Cells, Medical Education, Orthopaedics, Jordanian Medical Regulations.

1. Introduction

In Jordan, orthopaedics surgeons are challenged every day to accelerate healing, reduce cost, and reduce hospitalization time. In recent years, Jordan is experiencing an increase in trauma incidents due to automobile accidents, as well as an increase in life expectancy resulting in an increase in the number of diabetes mellitus and other hormonal deficiency cases among Jordanian population. These factors resulted in a high number of orthopaedics patients with medical conditions experiencing impaired or delayed bone healing/regeneration (Brighton and Shaman *et al.*, 1995) (Stuart and Morrey, 1990; Papa *et al.*, 1993; Tisdel *et al.*, 1995; Perlman and Thordarson, 1999).

Orthopaedics patients with impaired or delayed bone healing/regeneration are stressing the healthcare system with their long hospitalization time and the extra care they need in their treatment (Cozen, 1972; Loder, 1988). All these facts require orthopaedics surgeons and healthcare professionals in Jordan to consider using new technologies, such as the use of biotechnology and cell based therapy in orthopaedics applications in Jordan to reduce treatment cost and hospitalization time.

With the advances made in molecular medicine and molecular biology, several molecules have been identified that regulate the cascade of events in a time-dependent fashion leading to repair of bone tissue (Dimitriou *et al.*, 2005). This knowledge has led to a great interest in the application of these molecules in the clinical setting, especially for treatment of impaired

* Corresponding author. e-mail: alzube@hu.edu.jo.

fracture healing. The key growth factors characterized as being present in the fracture site are TGF-β1, TGF-β2, BMP-2, BMP-3, BMP-4, and BMP-7 (OP-1), PDGF, and acidic and basic FGF (FGF-1 and FGF-2) (Bolander, 1992; Linkhart *et al.*, 1996; Einhorn, 1998).

Several approaches have been utilized to elicit the formation of bone in segmental defects and facilitate the healing process (Flemming, 2002). These approaches have included the implantation of osteoconductive extracellular scaffolds (Holmes, 1987; Martin, 1989; Zardiackas, 1994; Johnson, 1996; Hollinger *et al.*, 2008) and the implantation of bone morphogenetic proteins in various matrices (Brighton and Hunt, 1991; Gehart, 1993; Cook, 1994; Stevenson, 1994; Wolff, 1994; Nurminskaya and Linsenmayer, 1996; Schmitz *et al.*, 1999; Haynesworth *et al.*, 2002). Another concept is based upon *ex vivo* expansion of pluripotent mesenchymal stem cells (MSC) loaded onto a carrier system.

The MSC are self renewing pluripotent progenitor cells that have been isolated from the whole marrow of chicks, mice, rats, rabbits, goats, and humans (Goshima, 1991; Haynesworth, 1992; Haynesworth *et al.*, 2002). These cells have the capability of differentiating into osteoblasts, chondrocytes, adipocytes, tenocytes, and myoblasts. Potential advantages of this strategy consist of decreased need for massive cellular proliferation and osteoblast progenitor cell chemotaxis into the defect as well as development of appropriate signaling for early bone formation in the graft site. This osteogenic potential of marrow derived MSC has been well defined *in vivo* (Mardon, 1987; Owens, 1988; Ohgishi, 1989; Goshima, 1991).

The role of MSC in bone regeneration and formation continues to be defined, and manipulation of MSC has resulted in new therapeutic strategies (Goshima *et al.*, 1991; Lennon *et al.*, 2001; Khan, 2005; Kraus, 2006). While this concept (application of MSC) has demonstrated its potential role for surgical reconstruction and arthrodesis procedures, significant questions exist regarding the use of this technology in developing countries including Jordan. This project aimed to assess the knowledge of biological growth factors and mesenchymal stem cells use and benefits in orthopaedics applications among a selected sample of Jordan's orthopaedics surgeons and senior medical school students.

We hypothesized that orthopaedics surgeons and the senior medical school students in Jordan are aware of the benefits, cost, applicability, and the advantages over the classical treatment modalities of using biotechnology and cell based therapy in orthopaedics applications and treatments in Jordan. Furthermore, it is hypothesized that orthopaedics surgeons and the senior medical school students in Jordan are willing to use this cutting edge technologies on themselves to accelerate the bone healing process.

2. Materials and Methods

2.1. The Questionnaire

The questionnaire was prepared by the investigation team and it was designed to investigate if the doctors and students participating had the knowledge about the use and benefits of biological growth factors (BGF) and mesenchymal stem cells (MSCs) in orthopaedics. The questionnaire consisted of two parts; the first part was designed to investigate the knowledge of BGF use and benefits in orthopaedics in Jordan, and it consisted of nine "Yes/No/I don't know" questions asking the participants [*(1) Do you have any information or any idea about using the biological growth factors in orthopaedics applications and treatments? ; (2) Do you know the benefits of its use?; (3) Do you recommend using it?; (4) Do you think that it will reduce the treatment cost?; (5) Do you think that it will reduce hospitalization time?; (6) If you are to choose between the available "old" technology and using the biological growth factors technology, will you use the biological growth factors technology?; (7) Do you think it is an expensive technology?; (8) Do you believe that it can be used in Jordan?; and, (9) If you got an injury in your bone, do you agree to use this technology to accelerate the healing process?*], successively.

The second part intended to investigate the knowledge of MSCs use and benefits in orthopaedics in Jordan, and it consisted of nine "Yes/No/I don't know" questions asking the participants [*(1) Do you have any information or any idea about using mesenchymal stem cells in orthopaedics applications and treatments? ; (2)Do you know the benefits of its use? ; (3)Do you recommend using it? ; (4) Do you think that it will reduce the treatment cost? ; (5) Do you think that it will reduce hospitalization time? ; (6) If you are to choose between the available "old" technology and using mesenchymal stem cells, will you use mesenchymal stem cells? ; (7) Do you think it is an expensive technology? ; (8) Do you believe that it can be used in Jordan? ; and (9) If you got an injury in your bone, do you agree to use this technology to accelerate the healing process?*].

The questionnaire was circulated to be filled at two different time points, the first time was in October 2009 and the second time was in March 2012. In 2009, the questionnaire was given to a sample of orthopaedics surgeons (n=19), whereas, in 2012, the questionnaire was given to another sample of orthopaedics surgeons (n=24) and to a sample of fourth year-senior medical school students (n=29). The questionnaire was written in English, then it was translated to Arabic by the investigation team. The questionnaire was presented to the participants in its Arabic version to be answered.

2.2. Statistical Analysis

Statistical analyses were performed using SigmaStat 3.0 (SPSS Inc., Chicago, Illinois). The amount of "yes" answers to each question in each questionnaire was analyzed. Analysis of variance (ANOVA) was performed followed by Holm-Sidak post hoc tests to identify differences between the percentages of positive "yes" answers among the questionnaire questions and the

differences between the overall additive percentages of the positive answers of the nine questions among the different groups of participants in all time points selected. *P* values less than 0.05 were considered statistically significant.

2.3. Evaluating Jordanian Regulations Related to Biotechnology and Cell Based Therapy Products

To investigate the Jordanian regulations regarding biotechnology and cell based therapy use, a review of the Jordanian regulations governing the definition, manufacturing, and circulation was made for those therapy modalities and their products.

3. Results

3.1. (2009) Questionnaire

In 2009, nineteen questionnaires in total were filled by orthopaedics surgeons; eight were filled by orthopaedics surgeons from the city of Amman in their private clinics, five were filled by orthopaedics surgeons from King Hussain medical city in Amman, two were filled by orthopaedics surgeons from the city of Zarqa in their private clinics, and four were filled by orthopaedics surgeons from the city of Irbid in King Abdullah-I hospital.

The percentages of positive "Yes" answers were determined for each question of the questionnaire, according to the medical institution they were filled in (Tables 1 & 2). There were no statistically significant differences among the percentages of positive answers in the MSCs part (Table 2).

Table 1. 2009 Orthopaedics surgeons knowledge of biological growth factors use and benefits questionnaire results according to each health care institution:

Question #	% of Positive answers of the knowledge of the biological growth factors use and benefits in orthopaedics				
	Amman private clinics (n=8)	King Hussain medical city (n=5)	Zarqa private clinics (n=2)	King Abdullah-I hospital (n=4)	Mean ± SD
1	87.5	100	100	75	90.6 ± 12
2	50	100	100	75	81.3 ± 24
3	87.5	60	50	100	74.4 ± 23
4	50	60	0	25	33.8 ± 27 [a]
5	62.5	80	100	50	73.1 ± 22
6	100	80	50	75	76.2 ± 21
7	75	100	50	50	68.8 ± 24
8	75	60	100	100	83.8 ± 20
9	75	80	100	75	82.5 ± 12

[a] : $P < 0.03$ versus all questions

Table 2. 2009 Orthopaedics surgeons knowledge of mesenchymal stem cells use and benefits questionnaire results according to each health care institution:

Question #	% of Positive answers of the knowledge of mesenchymal stem cells use and benefits in orthopaedics				
	Amman private clinics (n=8)	King Hussain medical city (n=5)	Zarqa private clinics (n=2)	King Abdullah-I hospital (n=4)	Mean ± SD
1	75	100	0	75	62.5 ± 43
2	75	100	50	100	81.3 ± 24
3	75	80	100	25	70 ± 32
4	62.5	60	0	25	36.9 ± 30
5	75	100	50	25	62.5 ± 32
6	87.5	80	100	75	85.6 ± 11
7	62.5	100	50	50	65.6 ± 24
8	62.5	80	100	50	73.1 ± 22
9	62.5	80	100	75	79.4 ± 16

However, in the BGF part, the percentages of the positive answers were significantly lower for the fourth question "*Do you think that it will reduce the treatment cost?*" as compared to all other questions in BGF part of the questionnaire (33.8 % with $P < 0.03$) (Table 1).

No differences in the percentage of the negative "No" answers nor in the percentages of the "I don't know" answers among the nine questions in both parts of the questionnaire (Data not shown).

3.2. (2012) Questionnaire

In 2012, fifty three questionnaires in total were filled; twenty four by orthopaedics surgeons from six different medical institutions and twenty nine by fourth year-senior medical school students (MD students) from The Hashemite University, Zarqa, Jordan. The twenty four orthopaedics surgeons' questionnaires were filled in the following medical institutions; King Hussain medical city in Amman (n=4), Jordan University Hospital in Amman (n=3), AlBasheer Hospital in Amman (n=5), Prince Hamza Hospital in Amman (n=3), the city of Salt public hospital (n=3), AlIsraa Private Hospital in Amman (n=6).

The percentages of positive "Yes" answers were determined for each question according to the medical institution they were filled in (Surgeons n=24), and for the senior medical school students (MD students n=29) (**Tables 3 & 4**). Furthermore, the percentages of positive "Yes" answers were determined for the entire sample participated of both the orthopaedics surgeons and the medical school students (Total n=53) (Table 5).

In the BGF part of the questionnaire, the percentages of the positive answers for the entire sample of participants (Total n=53) were significantly lower for the fourth question "*Do you think that it will reduce the treatment cost?*" as compared to the six other questions (18% with $P < 0.02$), and strongly trending lower as compared to the remaining two questions ($P = 0.078$).

Furthermore, the BGF results showed significantly lower percentages of the positive answers for the fifth question "*Do you think that it will reduce hospitalization time?*" as compared to three questions (35% with $P < 0.05$). On the other hand, the percentages of the positive "Yes" answer for the ninth question "*If you got an injury in your bone, do you agree to use this technology to accelerate the healing process?*" were significantly greater (74% with $P < 0.02$) as compared to two other questions (Table 3).

In the MSCs part of the questionnaire, the percentages of the positive answers for the entire sample of participants (Total n=53) were significantly lower for the fourth question "*Do you think that it will reduce the treatment cost?*" as compared all other questions (17 % with $P < 0.03$). Furthermore, the percentages of the positive answers of the sixth "*If you are to choose between the available "old" technology and using the biological growth factors technology, will you use the biological growth factors technology?"* and eighth "*Do you believe that it can be used in Jordan?*" questions were significantly lower as compared to the percentages of questions one and two (46% & 47% respectively with $P < 0.05$) (Table 4).

In the BGF part of the questionnaire, the overall percentage of the positive answers for the nine questions answered by the orthopaedics surgeons (Surgeons n=24) (54%) was significantly greater ($P < 0.01$) than the overall percentage of the positive answers for the nine questions answered by the senior medical school students (MD students n=29) (32%). A similar trend was found in the MSCs part of the questionnaire, where the overall percentage of the positive answers orthopaedics surgeons was significantly greater as compared to senior medical school students' answers.

The overall additive percentages of positive "Yes" answers in the 2009 questionnaire were significantly higher as compared to all groups of participants in the year 2012. Furthermore, the overall additive percentages of the 2012 questionnaire filled by the orthopaedics surgeons group results showed significantly higher positive "Yes" answers percentages in its both parts (BGF & MSCs) (54% & 57%) as compared to the 2012 questionnaire filled by the 4th year medical school students group results (32% & 31%) (Table 5).

3.3. Jordanian Regulations Related to Biotechnology and Cell Based Therapy Products

Drugs are regulated in Jordan by the Drug and Pharmacy Provisional Law No. (80) of the year 2001. In this law the term "drug" was defined as "*any substance or group of substances used to diagnose the diseases affecting human being or cure the same, lessen the pain or protect human body from diseases, or a group of substances other than foodstuff which has certain effect on human body or any of its functions*."

Moreover, section (B) of article (3) of this law states "It shall be prohibited to circulate any infant milk formula and its special formula, and supplementary food, medical plants, natural products, disinfectant and detergents, medical equipment and supplies, pharmaceutical preparations containing vitamins and minerals, cosmetic preparations and any other substances related to treatment or cure of human beings from disease, unless they are licensed according to the Minister's Directions and Coordinating with the concerned official authorities".

Two committees were formed according to the Drug and Pharmacy Provisional Law No. (80) of the year 2001. The first is The Higher Committee for Medicine & Pharmacy, with one of its responsibilities stated as "*Controlling of any substances or preparations related to treatment of diseases, or any other substances the Minister may deem necessary to have them under control*" according to bulletin (14) of Section (A) of Article (4). The second committee is the Technical Committee for Registration of New Drugs, with one of its responsibilities stated as "*Study the new developments related to drugs, and their precautions and side effects, and take any proper decisions in that regard*" according to bulletin (3) of section (C) of Article (9).

Table 3: 2012 Knowledge of biological growth factors use and benefits questionnaire results according to each health care institution.

Question #	% of Positive answers of the knowledge of the biological growth factors use and benefits in orthopaedics									
	King Hussain (n=4)	Jordan Univ (n=3)	AlBasheer (n=5)	Prince Hamza (n=3)	Salt Hospital (n=3)	AlIsraa Hospoital (n=6)	4th year MD students (n=29)	Surgeons (n=24) Mean ± SD	Total (n=53) Mean ± SD
1	50	33	100	67	100	83	31	72 ± 27	66 ± 29
2	100	33	60	67	67	83	24	68 ± 23	62 ± 27
3	50	0	60	33	33	83	27	43 ± 28	41 ± 27
4	0	0	40	33	0	33	17	18 ± 20[a]	18 ± 18 *
5	50	0	40	33	33	50	41	34 ± 19[b]	35 ± 17 **
6	50	33	60	67	33	67	38	52 ± 16	50 ± 15
7	25	100	60	33	67	33	38	53 ± 28	51 ± 27
8	100	33	40	100	67	67	31	68 ± 29	63 ± 30
9	100	33	60	100	100	83	45	79 ± 28[c]	74 ± 28***

[a , *] : P< 0.02 versus questions (1,2,6,7,8,9) ; [b] : $P < 0.03$ versus questions (1,2,8, 9) ; [**] : $P < 0.05$ versus questions (1,2,8) , [c , ***] : $P < 0.02$ vs questions (3,5)

Table 4 : 2012 knowledge of MSC use and benefits questionnaire results according to each health care institution

Question #	% of Positive answers of the knowledge of mesenchymal stem cells use and benefits in orthopaedics								
	King Hussain (n=4)	Jordan Univ (n=3)	AlBasheer (n=5)	Prince Hamza (n=3)	Salt Hospital (n=3)	AlIsraa Hospoital (n=6)	4th year MD students (n=29)	Mean ± SD Surgeons (n=24)	Mean ± SD Total (n=53)
1	50	67	80	100	100	83	28	80 ± 19	72 ± 26
2	50	67	80	100	100	83	31	80 ± 19	73 ± 26
3	50	33	60	67	67	50	31	55 ± 13	51 ± 15
4	0	33	20	33	0	16	17	17 ± 15[a]	17 ± 14[*]
5	50	33	40	100	33	50	31	51 ± 25[b]	48 ± 24
6	50	33	60	33	67	50	28	49 ± 14[c]	46 ± 15 [**]
7	0	100	60	100	100	50	48	68 ± 40	65 ± 38
8	50	33	20	67	100	33	24	51 ± 29[d]	47 ± 29 [***]
9	75	33	60	67	67	67	45	62 ± 15	59 ± 15

[a ,*]: $P < 0.03$ versus all questions ; [b , c , d , **] : $P < 0.04$ versus questions (1,2) ; [***] : $P < 0.05$ versus questions (1,2)

Table 5: The overall additive percentages of the positive answers among all groups of participants in all time points selected:

Group #	Group Name	# of Participants (n)	Over all additive % of Positive answers (Mean ± SD)
1	2009 Orthopaedics Surgeons Biological growth factors Questionnaire Results	19	74 ± 16[a]
2	2009 Orthopaedics Surgeons Mesenchymal Stem Cells Questionnaire Results	19	69 ± 15[b]
3	2012 Orthopaedics Surgeons Biological growth factors Questionnaire Results	24	54 ± 20[c]
4	2012 Orthopaedics Surgeons Mesenchymal Stem Cells Questionnaire Results	24	57 ± 20[d]
5	2012 Medical School Students Biological growth factors Questionnaire Results	29	32 ± 9
6	2012 Medical School Students Mesenchymal Stem Cells Questionnaire Results	29	31 ± 10
7	2012 Total Number of Participants Biological growth factors Questionnaire Results	53	51 ± 18
8	2012 Total Number of Participants Mesenchymal Stem Cells Questionnaire Results	53	53 ± 17

[a] : $P < 0.03$ versus groups (4, 5, 6, 7, & 8); [b] : $P < 0.05$ versus groups (5, 6, 7, & 8); [c & d]: $P < 0.005$ versus groups (5 & 6)

4. Discussion

Using a simple questionnaire, this study assessed the knowledge of biological growth factors and mesenchymal stem cells use and benefits in orthopaedics among a sample of Jordanian orthopaedics surgeons and 4th year senior medical school students. The assessment aimed to test the hypothesis that Jordanian orthopaedics surgeons and the senior medical school students in Jordan are aware of the benefits, cost, applicability, and the advantages over the classical treatment modalities of using biotechnology and cell based therapy in orthopaedics applications and treatments.

When assessing the knowledge of biological growth factors (BGF) use and benefits among orthopaedics

surgeons, the questionnaire results showed that the percentages of the positive "Yes" answers to knowing the use and benefits of this technology (first & second questions) were notably high among participants in the year 2009 (90% & 81%) and moderate among participant in the year 2012 (72% & 68%) (Tables 1 & 3). The differences in percentages between the two time points might be attributed to the differences in sample size of participants, which was bigger in the 2012 time point, or due to the fact that participants were from different health care institutions at each time point. Still, the elevated positive percentage of knowledge indicates high level of education and interest in BGF and its applications among Jordanian orthopaedics surgeons.

In contrast, the BGF questionnaire part results showed that the percentages of the positive "Yes" answers to the forth question "*Do you think that it will reduce the treatment cost?*" were significantly lower compared to the other questions in the year 2009 (33% with $P<0.03$), and significantly lower compared to questions (1, 2, 6, 7, 8, & 9) in the year 2012 (18% with $P<0.02$). These findings reflect a negative view of inefficiency in cost reduction of using this treatment modality in orthopaedics applications in Jordan among the participants.

The negative view of inefficiency in cost reduction might be attributed to the lack of an exact estimate of the cost of these new technologies, especially that these technologies and their components are not frequently employed in Jordan's health care system providers and suppliers are considered emerging technology yet to be characterized and evaluated.

In the 2012 questionnaire, the BGF questionnaire part results of the orthopaedics surgeons group (n=24) showed lower percentages of positive "Yes" answers to the fifth question "*Do you think that it will reduce hospitalization time?*" as compared to the first, second, eighth, and ninth questions (%34 with P<0.03) (Table 3). This is consistent with the view of inefficiency among orthopaedics surgeons participated in the questionnaire, which was seen in the results of question four. Interestingly, the data showed that despite the negative view of inefficiency of the cost and hospitalization time reductions, the orthopaedics surgeons agreed on using this technology to accelerate the healing process on themselves in case they got injured (79%) (Table 3). This interesting finding might suggest that the participants are in favor of using this new technology on themselves but not on others, especially that the percentages of positive answers of question three "*Do you recommend using it?*" were low and comparable to the results of question four and five (Table 3).

When assessing the knowledge of mesenchymal stem cells (MSCs) use and benefits among orthopaedics surgeons, the questionnaire results obtained in the year 2009 showed no statistical significance among the percentages of positive "Yes" answers among the nine questions, reflecting no specific point of views adopted among the orthopaedics surgeons group (n=19) that participated about the use and benefits of this modality in orthopaedics in Jordan at that time point (Table 2).

On the other hand, when investigating the 2012 questionnaire results of the MSCs part filled by the orthopaedics surgeons group (n=24), the questionnaire results showed that the percentages of the positive "Yes" answers to knowing the use and benefits of this technology (First & Second questions) were significantly higher than the answers to questions (4, 5, 6, & 8) (80% with $P< 0.04$) (Table 4). Furthermore, questions one and two results were comparable to the results obtained in the year 2009 (Table 2) and relatively higher than the results reported in the BGF part in the year 2012 (Table 3). The high positive percentage of knowledge indicates high level of education and interest in mesenchymal stem cells and its applications among Jordanian orthopaedics surgeons, and it can be noticed in a higher extent when compared to the biological growth factors.

When investigating the 2012 questionnaire results for both BGF and MSCs filled by the 4th year medical school students group (n=29), the percentages of positive "Yes" answers were significantly lower as compared to the orthopaedics surgeons group in the year 2012 (n=24), except for question four where both percentages were low and comparable (Tables 3 & 4). A similar argument can be made when comparing the overall additive percentages of the positive "Yes" answers among the participated groups, where the 2012 orthopaedics surgeons group overall percentages were significantly higher compared to the medical school students percentages in both parts of the questionnaire (BGF & MSCs) ($P< 0.005$) Table (5).

These findings might raise concerns of the educational curricula presented to medical students which might be lacking the necessary material that explains new modalities and technologies and practices in medicine. It is considered vital to expose medical students to new modalities and technologies while they are attending their basic biomedical courses and before they start their clinical education, in order to avoid the elevated uncertainty and ignorance levels that were notably present in the medical students "I don't know" answers to the questions (Figure 3) as compared to the results obtained from the orthopaedics surgeons answers (Figures 1 & 2).

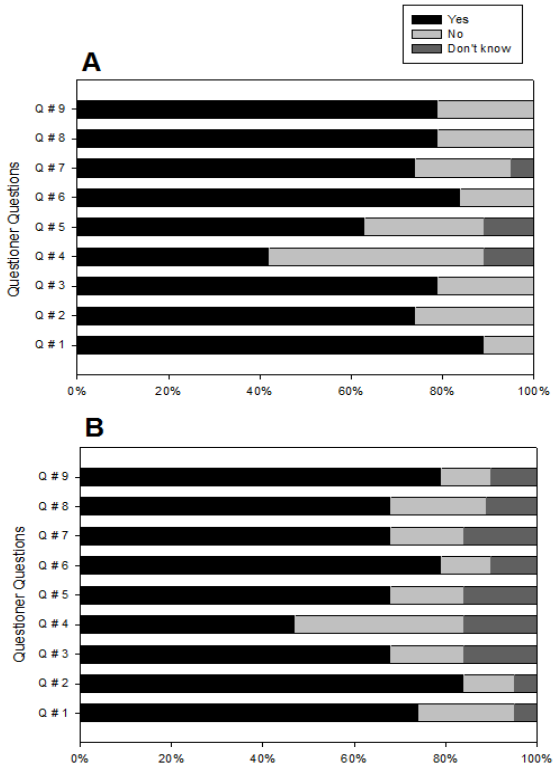

Figure 1: 2009 Questionnaire results obtained from orthopaedics surgeons. (A) Knowledge of biological growth factors use and benefits questionnaire results, (B) Knowledge of mesenchymal stem cells use and benefits questionnaire results. Values are Presented as percentages of the total sample obtained (n= 19).

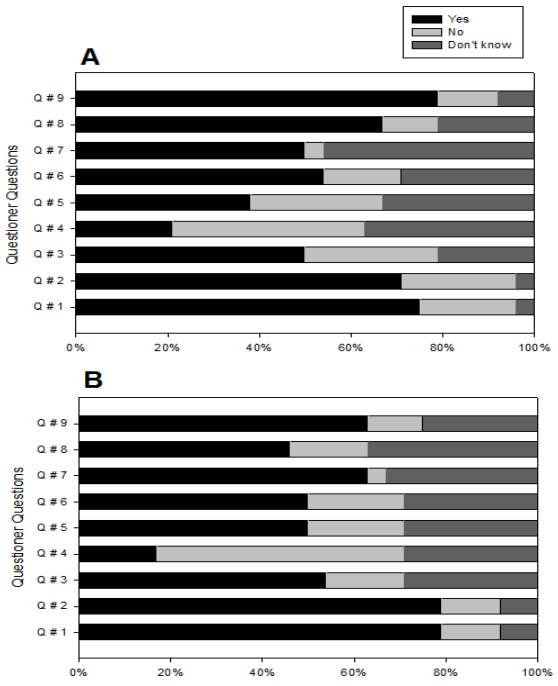

Figure 2: 2012 Questionnaire results obtained from orthopaedics surgeons. (A) Knowledge of biological growth factors use and benefits questionnaire results, (B) Knowledge of mesenchymal stem cells use and benefits questionnaire results. Values are presented as percentages of the total sample obtained (n= 24).

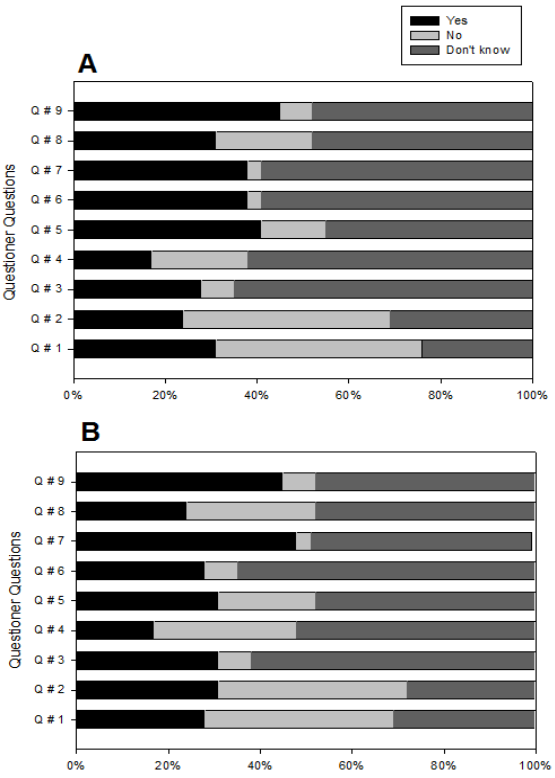

Figure 3: 2012 Questionnaire results obtained from 4th year medical school students. (A) Knowledge of biological growth factors use and benefits questionnaire results, (B) Knowledge of mesenchymal stem cells use and benefits questionnaire results. Values are presented as percentages of the total sample obtained (n= 29).

As of 2005, the value of the collective cell therapy market was estimated to be $26.6 billion. For 2010 and 2015 projections predicted the number to be $56.2 billion and $96.3 billion respectively (*Cell Therapy-Technologies, Markets, and Companies)*. Considering the vast amount of resources invested in this market, it is clear from the questionnaire results obtained from this report, that accepting these technologies in Jordan requires clarifications to Jordan's healthcare providers of the financial efficiency of using biotechnology and cell based therapy products in orthopaedics treatments and applications. Furthermore, enhancements in Jordan's medical educational system are required to integrate biotechnology and cell based therapy sciences in Jordan's medical schools curriculum to improve the knowledge of these new technologies among medical school students and to build confidence in the efficacy and efficiency of using these therapy modalities in their future practices.

A vital aspect of accepting, acquiring, and using new biotechnologies and cell based therapy is having a clear unambiguous legal framework that governs manufacturing, importing, processing, and use of these new therapeutic products. The lack of such framework will prevent healthcare suppliers from manufacturing or importing the components of these new technologies,

preventing the healthcare providers from exposing themselves and their patients to these technologies to be able to evaluate its efficiency in reducing treatment cost and time.

In Jordan, the registration procedure for growth factors, cytokines, and their carriers is clear since it is well described in the "Jordanian Criteria of Registration of Drugs". On the other hand and to the best of our knowledge, there are no explicit regulations or rules that govern the manufacturing, circulation, inspection, or registration of biotechnology or cell based therapy products in Jordan.

In the term "Drug" definition, at the Drug and Pharmacy Provisional Law No. (80) of the year 2001, Some can argue that the last part of the definition, i.e. "or a group of substances other than foodstuff which has certain effect on human body or any of its functions.", might implicitly included biotechnology and cell based therapy in it. The argument will be mistaken because engineered-living cells are not considered "substances". Moreover, in section (B) of article (3) of the same law, the statement "and any other substances related to treatment or cure of human beings from disease" does not include engineered tissue and/or cell based therapy products, because again tissues and cells are not substances.

Despite the lack of proper definition that include engineered tissue and cell based therapy, the Drug and Pharmacy Provisional Law formed a committee with the name "The Higher Committee for Medicine & Pharmacy", which according to its responsibility listed in bulletin (14) of Section (A) of Article (4), one might consider engineered tissue and cell based therapy products under "*preparation related to treatment of disease*", however, it is more appropriate to have an explicit bulletin that aims to control tissue engineering and cell based therapy products.

The Drug and Pharmacy Provisional Law formed a committee called "The Technical Committee for Registration of New Drugs", which according to its responsibility listed in bulletin (3) of Section (C) of Article (9), this committee can study engineered tissue and cell based therapy products as "*new developments related to drugs*", however, the term "drug" need to include engineered tissue and cell based therapy products in its definition.

The Jordanian regulations need to be modified with explicit laws that regulate manufacturing, importing, and use of biotechnology and cell based therapy products to reduce bureaucratic committees' procedures, and to cope with the international standards and with the advances made in molecular medicine and molecular biology. These legal modifications will encourage healthcare suppliers and providers in Jordan to explore and evaluate new technologies in medicine that might reduce treatment cost and hospitalization time in Jordan, which will also lead to increasing the relatively low level of awareness of the use, benefits, and applications of biotechnology and cell based therapy products in orthopaedics in Jordan (Table 5).

The sample of orthopaedic surgeons who participated in questionnaire has not been classified according to specialty or experience in order to get a general assessment of the sample participating in the questionnaire, however, a classification of the participants specialty or experience is required in future studies to get a comprehensive and precise assessment. Moreover, the sample of fourth year medical school students is not a representative sample of all medical school students in Jordan; still it was selected to acquire a general assessment for later investigations among medical school and related field's students. The fourth year medical school students were selected to participate in the questionnaire due to the fact that they have just finished their basic biomedical course work and are just about to start their clinical education.

To the best of our knowledge this is the first study investigating the knowledge of growth factors and MSC use and benefits among a sample of Jordanian orthopaedics surgeons and senior medical school students. The investigation team realizes that the participating sample is far from being a representative sample, however, the scientific value lies in having a general assessment as a base line that will trigger further investigations aiming to enhance the educational practices in medical schools as well as the clinical practices in Jordan's health care centers and institutions.

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