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Actual Practical Attitude and Knowledge of Dental Implants among Senior Dental Students and General Dentists Graduated from Some Saudi and Non-Saudi Dental Schools

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Abstract

Objective: To assess the actual practical attitude and knowledge of dental implants among senior dental students and general dentists graduated from some Saudi and Non-Saudi dental schools. **Methods:** A total of 300 senior dental students and general dentists participated in the study. Hard copies of the self-designed, multiple-choice questionnaires were distributed to all participants. The questionnaire consisted of 31 questions in five parts. Data were collected and analyzed using Chi-square test and t-test, where $p < 0.05$ was calculated to be statistically significant and $p < 0.001$ to be statistically highly significant. **Results:** There is a statistically significant relationship between the participants' answers, and their dental schools. Participants' general knowledge, training, and teaching of dental implants, as well as information about restorations retained for the dental implants, were higher among participants from Saudi dental schools than participants from non-Saudi dental schools, while the information about dental implants was higher among participants from non-Saudi dental schools than participants from Saudi dental schools. **Conclusion:** We conclude that the actual practical attitude and knowledge of dental implants among participants in the current study was insufficient. Therefore, dental implant education in the undergraduate curricula of dental schools surveyed should be updated to include teaching, laboratory training, and preclinical and clinical training.

Keywords

Knowledge, Dental Implants, Dental Schools, Non-Saudi,

Practical Attitude, Saudi

1. Introduction

Until the last decade, dental implant treatment was restricted to specialists. But recently, there has been an increase in interest in dental implants among senior dental students and general dentists to educate themselves, train and develop their skills in this type of dental treatment [1]. Furthermore, the high success rate of dental implant treatment and increased acceptance of patients undergoing dental implant treatment means that general dentists must know the maintenance of dental implants and the principles of dental implants technique [2].

As we know, dental implants are artificial roots used as a therapeutic method to replace missing teeth due to periodontal diseases, trauma, infections, developmental abnormalities, and tumors and used as support for prosthetics. In addition, this method is an acceptable and reliable treatment procedure for restoring esthetics and function in patients with partial or complete edentulous [3] [4] [5] [6]. Therefore, dental implants have helped preserve adjacent teeth and alveolar bone, increase patients acceptance and satisfaction and have developed as a rapid treatment option for oral rehabilitation, as well as being non-destructive for more than ten years [7] [8] [9] [10]. Several factors may influence the clinical success of a dental implant, such as the patient's general health, oral hygiene, smoking, occlusal loads, and the type of restorations retained on the implant [11] [12] [13].

The implant retention system can be either screw or cement-retained restorations, chosen according to the advantages and disadvantages of each system [14]. There are advantages to screw-retained restorations such as rare biological complications, ease of installation, ability to be used in poor position of implants, and in cases of minimal arch spacing (less than 4 mm) due to direct screw-on fixation [15] [16]. There are drawbacks to screw-in restorations, such as high cost, high skills requirements, and unwanted esthetic due to the screw access channel which can cause the ceramic to weaken [17] [18] [19] [20]. On the other hand, there are advantages to cement-retained restorations such as excellent esthetics, flexibility in positioning, and good occlusal contacts [17] [21] [22] [23]. But incomplete cement removal is the main drawback and causes biological complications such as periodontal tissue inflammation and bone loss [24] [25].

In the kingdom of Saudi Arabia, there are no quantitative or qualitative studies that provide a clear picture of the teaching and training dental implants in Saudi universities except two studies in 2009 G as well as 2018 G that showed that the teaching dental implants varied greatly among dental schools [24] [26]. Furthermore, there has been a decrease in the percentage of dental schools in the USA that included dental implantology in their curriculum, but there has been an increase in dental schools offering dental implantology courses as part of

their curriculum from 33% in 1974 to 86% in 2005, compared to 10% of the European dental schools that introduced dental implantology courses in their curriculum before 1990 and then rising to 80% in 2001 [27] [28]. The current study aims to evaluate the actual practical situation and knowledge of dental implants among senior dental students and general dentists who graduated from some Saudi and Non-Saudi dental schools concerning graduation schools. Thus, the primary objective of this study was to assess the effect of the participants' graduation schools on the actual practical attitude and knowledge of dental implants among senior dental students and general dentists.

2. Material and Methods

2.1. Population and Study Design

This cross-sectional study included 300 participants (150 participants from some Saudi dental schools and 150 participants from some non-Saudi dental schools, 50% male and 50% female) as follows: Eighty-eight senior dental students (5th and 6th years and interns), and 212 dentists (102 dentists who graduated less than five years ago, in addition to 110 dentists who graduated more than five years ago). This study was conducted from November 2021 AD to March 2022 AD. The participants were selected from the students and graduates of some Saudi dental schools in the kingdom of Saudi Arabia and some non-Saudi dental schools in the Republic of Yemen. Demographic details of the participants (age, gender, dental school levels of undergraduate education, and duration of graduation) were recorded.

2.2. Ethical Aspects

Informed consent was obtained from the participants, and the study proposal was registered and designed in accordance with the instructions of the Institutional Review Board (IRB), college of dentistry, King Khalid University (IRB/REG/2022-2023/52). Participants' cooperation was voluntary, and anonymity and data were secured. Study objectives were explained to all study participants.

2.3. Inclusion and Exclusion Criteria

Inclusion criteria were as follows: Senior dental students (5^{th} and 6^{th} years), dental interns, and general dentists who signed the consent form. Exclusion criteria were as follows: junior dental students (before the Fifth year) and participants who refused to sign of the consent form.

2.4. The Sample Size

The minimum sample size should be 295 participants to obtain statistically significant results with an accuracy level of 5% and a confidence level of 90%.

2.5. Questionnaire Design

An English-language questionnaire was designed to collect data in the current

study. The questionnaire content was obtained from previous studies' questionnaires with some modifications for internal reader reliability and then checked and tested by Cronbach's alpha test. A hard copy of the questionnaire was distributed to each participant. Answers to the survey questions took approximately six minutes. The questionnaire included 31 questions in five parts to assess the actual practical situations and knowledge of dental implants among senior dental students and general dentists who graduated from some Saudi and non-Saudi dental schools. The first part consisted of seven demographic questions related to age, gender, university level, date of graduation, years of experience, place of work, and place of university study.

The second part included six multiple-choice questions related to general Knowledge in the subjects of dental implants as a branch of dentistry, the distance between dental implants, the distance between the dental implant and natural teeth, the distance between the dental implant and the maxillary sinus, indications and contraindications for dental implants, and the experience in dental implants. The third part included seven questions about dental implant training and education if there were limitations in funds or supplies for the study of dental implants.

These limitations included the difficulties of teaching dental implants during the undergraduate level, workshops, seminars, and clinical training in addition to enquiring about the role of dental implant companies in dental implant training during the undergraduate level, and we asked them if they wanted to be dental implants specialists.

The fourth part asked four questions about participants' information regarding dental implants topics related to the source of this information and whether this information is sufficient and the most important factor for the success of dental implants, in addition to one question about the parts of dental implant.

The final part (seven questions) assessed the participants' Knowledge regarding the topic of dental implant retained-restorations, their types and which implant restoration are better aesthetically, fracture resistance, retention, control of periodontal complications, ease of fabrication as well as which of these factors more important in selecting retained restorations. Three hundred hard copies of the questionnaires along with cover letters containing instructions and objectives of the study were distributed to the participants in this study.

2.6. Statistical Analysis

The statistical analysis of the collected data was performed using Chi-square test and t-test. A t-test of the mean and standard deviation was used to compare an analysis of participants' ages according to their graduation schools with $p < 0.05$ statistically significant and $p < 0.001$ highly statistically significant. A Chi-square test was used to compare the percentages distribution of participants according to their graduating schools, and the answers collected for each question among participants.

3. Results

Three hundred participants returned the questionnaires. All questions have been fully answered. Distribution of participants according to graduation schools and education levels Table 1 and Figure 1. Of the total participants, 29.3% (n = 88) were senior dental students, 34% (n = 102) were graduates (<5 years), and 36.7% (n = 110) were graduates (≥5 years).

On the other hand, 40 (26.7%) of senior dental students were graduates of some Saudi dental schools, 48 (32%) were graduates of some non-Saudi dental schools, and 52 (34.7%) of general dentists (<5 years) were graduates of some Saudi dental schools and 50 (33.3%) graduates of some non-Saudi dental

Table 1. Distribution of participants according to schools of graduation and levels of education.

	Number of participants		Chi-square	
	Gs SDSs (n = 150)	Gs NSDSs (n = 150)		
Participants (n = 300)	n (%)	n (%)	Pearson Chi	P-value
SDSs (n = 88) (29.3%)	40 (26.7%)	48 (32%)	37.28	0.05*
GDs (Gs < 5 years) (n = 102) (34%)	52 (34.7%)	50 (33.3%)	43.24	0.031*
GDs (Gs ≥ 5 years) (n = 110) (36.7%)	58 (38.6)	52 (34.7%)	21.36	0.049*
Chi-square				
SDSs & Gs <5 years & Gs ≥5 years			26.18	<0.005**

Gs SDSs: Graduates of some Saudi dental schools, Gs NSDSs: Graduates of some non Saudi dental schools, SDSs: Senior dental students, Gs: Graduates, n: Number, Gs: Graduates, GDs: General dentists. *Statistically significant differences, **Highly statistically significant differences.

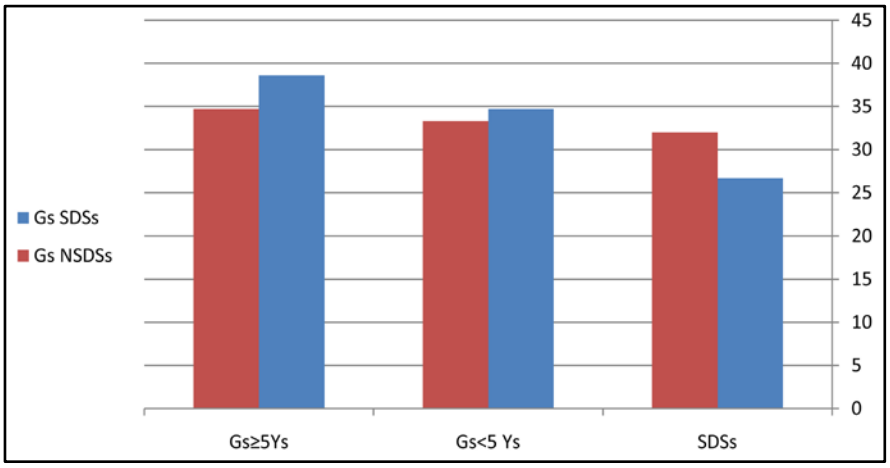

Figure 1. Distribution of participants according to schools of graduation and levels of education. Gs SDSs: Graduates of some Saudi dental schools, Gs NSDSs: Graduates of some non Saudi dental schools, Gs: Graduates, Ys: Years, SDSs: Senior dental students.

schools, as well as 58 (38.6) of general dentists (≥5 years), were graduates of some Saudi dental schools and 52 (34.7%) were graduates of some non-Saudi dental schools. Consequently, the graduates of some Saudi dental schools participating in this study were more than the graduates of some non-Saudi dental schools, except for participating senior dental students, where the graduates of some non-Saudi dental schools participating were more than the graduates of some Saudi dental schools, with a statistically significant difference ($p < 0.05$).

Table 2 and Figure 2 describe the mean and standard deviation of the participants' ages. The mean ages of graduates of some Saudi dental schools and graduates of some non-Saudi dental schools senior dental students participants were 24.22 and 24.12 years old, while the mean ages of graduates of some Saudi dental schools and graduates of some non-Saudi dental schools general dentists participants (<5 years) were 28.79 and 27.43 years old as well as the mean ages of graduates of some Saudi dental schools and graduates of some non-Saudi dental schools general dentists participants (≥5 years) were 30.72 and 29.00 years old.

Table 2. The mean and standard deviation of the participants' ages.

Participants	Mean ± SD of Age				t-test	P value
	Gs SDSs		Gs NSDSs			
	Mean	±SD	Mean	±SD		
SDSs	24.22	0.878	24.12	1.201	−2.33	0.020*
GDs (Gs <5 years.)	28.79	0.884	27.43	1.073	−2.36	0.022*
GDs (Gs ≥5 years)	30.72	1.018	29.00	1.118	−0.874	0.386

Gs SDSs: Graduates of some Saudi dental schools, Gs NSDSs: Graduates of some non Saudi dental schools, SDSs: Senior dental students, Gs: Graduates, GDs: General dentists, SD: Standard deviation.

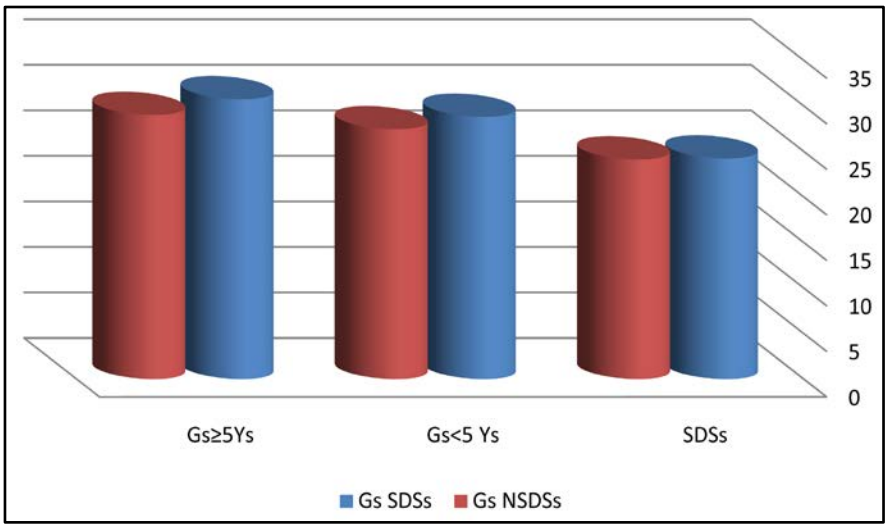

Figure 2. The mean and standard deviation of the participants' ages. Gs SDSs: Graduates of some Saudi dental schools, Gs NSDSs: Graduates of some non-Saudi dental schools, Gs: Graduates, Ys: Years, SDSs: Senior dental students.

Thus, the mean ages of general dentists participants (≥5 years) were more than general dentists participants (<5 years.) and senior dental students participants. Moreover, the mean ages of graduates of some Saudi dental schools participants were more than graduates of some non-Saudi dental schools participants with statistically significant differences ($p < 0.05$) except general dentists participants (≥5 years), where there were no statistically significant differences ($p > 0.05$).

Regarding the answers to the general Knowledge dental implants questions (Table 3). In the answers to the first question, 88.6% of graduates of some Saudi dental schools and 88% of graduates of some non-Saudi dental schools reported that they know that there is a branch of dentistry called implantology. The remaining graduates of some Saudi dental schools and graduates of some non-Saudi dental schools reported that they didn't know whether there was a branch of dentistry called implantology.

Table 3. Participants' answers to the general knowledge dental implants questions.

Questions		Gs SDSs (n = 150)	Gs NSDSs (n = 150)	Chi (P value)
		n (%)	n (%)	
Did you know that there is a branch of dentistry called implantology?	I don't know	17 (11.4%)	18 (12%)	23.7 (0.541)
	Yes	133 (88.6%)	132 (88%)	
How much distance between two implants must be present during the surgical procedure?	1 mm	7 (4.7%)	21 (14%)	8.8 (0.032*)
	2 mm	28 (18.7%)	25 (16.7%)	
	3 mm	97 (64.7%)	82 (54.7%)	
	4 mm	18 (12%)	22 (14.7%)	
How much distance between the dental implant and natural teeth must be present during the surgical procedure?	1 - 1.5 mm	54 (36%)	54 (36%)	3.9 (0.271)
	2 - 2.5 mm	42 (28%)	38 (25.3%)	
	3 - 3.5 mm	22 (14.7%)	34 (22.7%)	
	4 - 4.5 mm	32 (21.3%)	24 (16%)	
How much distance between the dental implant and the maxillary sinus must be present during the surgical procedure?	0 - 1 mm	81 (54%)	69 (46%)	16.4 (0.001**)
	1.25 - 2 mm	38 (25.3%)	50 (33.3%)	
	2.25 - 3 mm	19 (12.7%)	18 (12%)	
	3.25 - 4 mm	12 (8%)	13 (8.7%)	
Do you know the essential indications and essential contraindications of dental implants?	I don't know	43 (28.7%)	30 (20%)	13.5 (0.001**)
	No	48 (32%)	54 (36%)	
	Yes	59 (39.3%)	66 (44%)	
Do you have any experience in dental implants?	No	75 (50%)	107 (71.3%)	14.3 (<0.001**)
	Yes	75 (50%)	43 (28.7%)	

Gs SDSs: Graduates of some Saudi dental schools, Gs NSDSs: Graduates of some non Saudi dental n: Number, *Statistically significant differences, **Highly statistically significant differences.

In the answers to the second question regarding the distance between two implants that should be present during the surgical procedure, 64.7% of graduates of some Saudi dental schools and 54.7% of the graduates of some non-Saudi dental schools chose the correct answer, while the remaining the graduates of some Saudi dental schools and the graduates of some non-Saudi dental schools chose the wrong answers.

Regarding the answers to the third question about the distance between the dental implant and natural teeth, 36% of graduates of some Saudi dental schools and 36% of graduates of some non-Saudi dental schools chose the correct answer, while the remaining participants chose the wrong answers.

In the answers to the fourth question regarding the distance between the dental implant and the maxillary sinus, 54% of the graduates of some Saudi dental schools and 46% of the graduates of some non-Saudi dental schools chose the correct answer, while the remaining participants chose the wrong answers.

In the answers to the fifth question, 39.3% of the graduates of some Saudi dental schools and 44% of the graduates of some non-Saudi dental schools reported that they know the indications and essential contraindications of dental implants. In contrast, 50% of graduates of some Saudi dental schools and 28.7% of graduates of some non-Saudi dental schools said that they had experience in dental implants in the answers to the sixth question.

There are significant differences in the answers to the second question ($p < 0.05$) and highly significant differences in the answers to the fourth, fifth, and sixth questions ($p < 0.001$), while there are no significant differences in the answers to the other remaining questions ($p > 0.05$).

The academic education of dental implant training among the participants in the current study is summarized in Table 4.

59.3% of the graduates of some Saudi dental schools and 72.7% of the graduates of some non-Saudi dental schools think there are limitations on funding or supplies for studying dental implants. Moreover, 79.3% of graduates of some Saudi dental schools and 83.3% of graduates of some non-Saudi dental schools in this study reported that they did not take dental implants training during their undergraduate studies, except dental implants lectures in some courses (35.3% and 30.7%). Therefore, most participants reported that they want to participate in workshops and seminars on dental implants (79.3% and 74.6%).

On the other hand, regarding the question of implant companies supporting implant training during undergraduate studies, the participants reported that it included the implants (30.7% and 25.3%), the simulated models (26.7% and 32%), the components restorative (20% and 21.3%), the lab training funding (16.6% and 16%) and clinical training funding (6% and 5.4%).

Regarding the questions about implant procedures, 20.7% of graduates of some Saudi dental schools and 16.7% of graduates of some non-Saudi dental schools reported that they carried out implant procedures. Moreover, more than half of the participants confirmed that they want to be specialists in dental implants (74% and 63.4%).

Table 4. Participants' answers regarding dental implant training and education.

Questions		Gs SDSs (n = 150)	Gs NSDSs (n = 150)	Chi (P value)
		n (%)	n (%)	
Do you think there are limitations in funding or supplies to study dental implants?	No	61 (40.7%)	41 (27.3%)	31.3 (<0.001**)
	Yes	89 (59.3%)	109 (72.7%)	
Did you receive training in dental implants during your undergraduate studies at your college?	No	119 (79.3%)	125 (83.3%)	0.79 (0.374)
	Yes	31 (20.7%)	25 (16.7%)	
Which of the following teaching methods were used during the dental implant program in your college?	Lectures	53 (35.3%)	46 (30.7)	9.15 (<0.001**)
	Symposiums	25 (16.7%)	30 (20%)	
	PLT	50 (33.3)	45 (30%)	
	CT	22 (14.7)	29 (19.3%)	
Do you want to participate in workshops and seminars on dental implants?	Yes	119 (79.3%)	112 (74.6%)	11.1 (0.004*)
	No	31 (20.7%)	38 (25.4%)	
Which of the following support did you receive from implant companies for dental implant training during your undergraduate studies?	SM	40 (26.7%)	48 (32%)	7.31 (0.001**)
	IS	46 (30.7%)	38 (25.3%)	
	RC	30 (20%)	32 (21.3%)	
	LTF	25 (16.6%)	24 (16%)	
	CTF	9 (6%)	8 (5.4)	
Did you do dental implant procedures?	Yes	31 (20.7%)	25 (16.7%)	0.79 (0.374)
	No	119 (79.3%)	125 (83.3%)	
Do you want to be a dental implant specialist?	Yes	111 (74%)	95 (63.4%)	9.4 (0.009*)
	NO	39 (26 %)	55 (36.6%)	

Gs SDSs: Graduates of some Saudi dental schools, Gs NSDSs: Graduates of some non Saudi dental PLT: Phantom lab training, CT: Clinical training SM: Simulated models supplying, IS: Implants supplying, RC: Restorative components supplying, LTF: Lab training funding, CTF: Clinical training funding, n: Number. **Highly statistically significant differences, *Statistically significant differences.

There were highly significant differences between the answers to the first, third, fourth, fifth, and seventh questions ($p < 0.001$), while there were no significant differences in the answers to the second and sixth questions ($p > 0.05$).

Regarding participants' information about dental implants (Table 5). In the participants' answers to the first question, 32% of graduates of some Saudi dental schools and 22.7% of graduates of some non-Saudi dental schools said that they obtained their information about dental implants from the internet, while 37.3% of graduates of some Saudi dental schools and 48.7% of graduates of some non-Saudi dental schools said that they do not have accurate information about dental implants. The remaining participants reported that they obtained their

Table 5. Participants' information about dental implants.

Questions		Gs SDSs (n = 150)	Gs NSDSs (n = 150)	Chi (P value)
		n (%)	n (%)	
What is the source of your information about dental implants?	Texts	11 (7.3%)	10 (6.7%)	7.4 (0.385)
	I don't H K	56 (37.3%)	73 (48.7%)	
	Internet	48 (32%)	34 (22.7%)	
	PG	2 (1.3%)	2 (1.3%)	
	SA	9 (6%)	11 (7.3%)	
	Seminars	3 (2%)	4 (2.7%)	
	UG	15 (10%)	8 (5.3%)	
	Workshops	6 (4%)	8 (5.3%)	
Is your information about dental implant sufficient?	No	127 (84.3%)	124 (82.7%)	20.1 (<0.001**)
	Yes	23 (15.3%)	26 (17.3%)	
How many parts are there in a dental implant?	One	21 (14%)	22 (14.7%)	14.6 (0.001**)
	Two	51 (34%)	23 (15.3%)	
	Three	78(52%)	105 (70%)	
What is the most factor for the success of dental implants?	CS	98 (65.3%)	62 (41.3%)	21.8 (0.001**)
	PP	11 (7.3%)	19 (12.7%)	
	T & DIM	12 (8%)	28 (18.7%)	
	Skills of clinician	10 (6.7%)	14 (9.3%)	
	Surgical technique	9 (6%)	6 (4%)	

Gs SDSs: Graduates of some Saudi dental schools, Gs NSDSs: Graduates of some non Saudi dental HK: Have Knowledge, PG: Postgraduate, UG: Undergraduate, T & DIM: Type and material of dental implant. PP: Patient preference, CS: Case selection, SA: Scientific articles/journals, n: Number, **Highly statistically significant differences, *Statistically significant differences.

information about dental implants from texts (7.30% and 6.70%), postgraduate studies (1.30% of all participants), scientific articles/journals (6% and 7.3%), seminars (2% and 2.7%), undergraduate studies (10% and 5.3%) and workshops (4% and 5.3%).

Answers to the second question for most of the participants (84.3% of graduates of some Saudi dental schools and 82.7% of graduates of some non-Saudi dental schools) revealed that the participants' information about dental implants is insufficient, compared to 15.3% and 17.3% of them have sufficient information about dental implants.

Regarding the third question about the number of parts number dental implants, 52% of graduates of some Saudi dental schools and 70% of graduates of

some non-Saudi dental schools chose the correct answer, while the remaining participants chose the wrong answers.

In the answers to the fourth question about the most factor for the success of dental implants, 65.3% of graduates of some Saudi dental schools and 41.3% of graduates of some non-Saudi dental schools answered that case selection is the most factor for the success of dental implants, compared to the remaining of the participants who reported that the type and material of dental implant (8% and 18.7%), the patient preference (7.3% and 12.7%), the skills of the clinician (6.7% and 9.3%) and the surgical technique (6% and 4%) are the most the success factor for dental implants. There were highly significant differences in the answers to all questions ($p < 0.001$), whereas there were no significant differences in the answers to the first question ($p > 0.05$).

Participants' answers to questions about the dental implant retained-restoration are summarized in Table 6. Regarding the answers to the first question, 56.7% of graduates of some Saudi dental schools and 58.7% of graduates of some non-Saudi dental schools answered that they have an idea about dental implant-retained restorations systems, while the remaining reported that they have no idea about dental implant-retained restorations systems.

Regarding the best aesthetic appearance of retained restorations systems (answers to the second question), 54.7% of graduates of some Saudi dental schools and 48.7% of graduates of some non-Saudi dental schools chose cement retained-restoration (CRR), versus 36% and 38% of the participants chose screw retained-restoration (SRR), while the remaining reported that they didn't know.

In the third question answers about fracture resistance, 59.3% of graduates of some Saudi dental schools and 72.7% of graduates of some non-Saudi dental schools showed predilection to use screw-retained restoration (SRR), compared to 40.7% and 27.3% of participants showed predilection to use cement-retained restoration (CRR). In the fourth question about the factor influencing the selection of implant-retained restorations, 22.7% of graduates of some Saudi dental schools and 21.3% of graduates of some non-Saudi dental schools reported that aesthetics is the factor influencing to choice of implant-retained restorations. The remaining answers of participants varied, where some of the participants chose soft tissue health (20% and 20.7%), cost-effectiveness (11.3% and 13.3%), retention (13.3% and 14%), ease of fabrication (16% and 14.7%) and the expertise required are important factors influencing the selection of implant-retained restorations.

In the answers to the fifth question, 62.7% of graduates of some Saudi dental schools and 68.7% of graduates of some non-Saudi dental schools reported that screw-retained restoration is desirable when implant retention is most needed. In contrast, 37.3% and 31.3% of participants reported that cement-retained restoration is desired when implant retention is required most.

In the answers to the sixth question about controlling complications of peri-implant diseases, 47.3% of graduates of some Saudi dental schools and 56% of

Table 6. Participants' answers to questions about the dental implant retained-restoration.

Questions		Gs SDSs	Gs NSDSs	Chi (P value)
		n (%)	n (%)	
Do you have an idea of retained restorative systems in dental implants?	Yes	85 (56.7%)	88 (58.7%)	0.123 (0.726)
	No	65 (43.3%)	62 (41.3%)	
What are the best aesthetically retained restorations in dental implants?	SRR	54 (36%)	57 (38%)	8.4 (0.015*)
	CRR	82 (54.7%)	73 (48.7%)	
	I don't know	14 (9.3%)	20 (13.3%)	
When the fracture resistance of an implant is necessary, which of the following retained restorations will be used?	SRR	89 (59.3%)	109 (72.7%)	31.3 (<0.001**)
	CRR	61 (40.7%)	41 (27.3%)	
Which of the following is an important factor influencing the choice of implant-retaining restorations?	Aesthetics	34 (22.7%)	32 (21.3%)	0.54 (0.462)
	STH	30 (20%)	31 (20.7%)	
	CE	17 (11.3%)	20 (13.3%)	
	Retention	20 (13.3%)	21 (14%)	
	EF	24 (16%)	22 (14.7%)	
	RE	25 (16.7%)	24 (16%)	
When implant retention is most required, what retained restoration is desirable?	SRR	94 (62.7%)	103 (68.7%)	29.6 (<0.001**)
	CRR	56 (37.3%)	47 (31.3%)	
If we want to control the complications of peri-implant diseases, which of the following retained restoration should be used?	SRR	71 (47.3%)	84 (56%)	14.2 (0.001**)
	CRR	79 (52.7%)	66 (44%)	
Which of the following implant-retained restoration is preferred, when ease of fabrication is important?	SRR	67 (44.7%)	41 (27.3%)	9.8 (0.002*)
	CRR	83 (55.3%)	109 (72.7%)	

Gs SDSs: Graduates of some Saudi dental schools, Gs NSDSs: Graduates of some non Saudi dental STH: Soft tissue health, CE: Cost-effectiveness, EF: Ease of Fabrication, RE: Required Expertise, CRR: Cement retained restoration, SRR: Screw retained restoration, n: Number, **Highly statistically significant differences, *statistically significant differences.

graduates of some non-Saudi dental schools chose screw-retained restoration, while the remaining chose cement-retained restoration. On the other hand, In the answers to the seventh question about the importance of ease of fabrication, 55.3% of graduates of some Saudi dental schools and 72.7% of graduates of some non-Saudi dental schools preferred cement-retained restoration, while the remaining preferred screw-retained restoration.

There are statistically significant differences in answers to the second question ($p < 0.05$) and highly significant differences in the third, fifth, sixth, and seventh

questions answers ($p < 0.001$), while there were no statistically significant differences in the first and fourth questions answers ($p > 0.05$).

After evaluating the answers to the questions on the questionnaire parts of the current study, there was a significant correlation between the participants' answers and the participants' graduation schools. The participants' general Knowledge, training, and teaching of dental implants, as well as retained restoration of the dental implant, were higher among graduates of some Saudi dental schools, as compared to graduates of some non-Saudi dental schools, while information about dental implants was higher among graduates of some non-Saudi dental schools, as compared to graduates of some Saudi dental schools.

Table 7 shows the frequency of correct and wrong participants' answers about actual practical attitudes toward dental implants. There was an increase in the frequency of wrong answers more than correct answers without statistically

Table 7. Frequency of participants' correct and incorrect answers regarding actual practical attitude towards dental implants.

Some information from the participants about dental implants	Correct	Incorrect
	n (%)	n (%)
The space between two implants during the surgical procedure.	179 (59.7%)	121 (40.3%)
The distance between the dental implant and natural teeth during the surgical procedure.	108 (36%)	192 (64%)
The distance between the dental implant and the maxillary sinus during the surgical procedure.	150 (50%)	150 (50%)
The number of parts in a dental implant.	183 (61%)	117 (39%)
The most important factor for the success of dental implants.	160 (53.3%)	140 (46.7%)
The best aesthetically retained restorations in dental implants.	139 (46.3%)	161 (53.7%)
The retained restorations for fracture resistance in dental implant.	102 (34%)	198 (66%)
The main factor in selecting retained restorations in dental implants.	65 (21.7%)	235 (78.3%)
The retained restorations to retain the implant.	159 (53%)	141 (47%)
The retained restorations to control complications of peri-implant diseases.	111 (37%)	189 (63%)
The easy fabrication retained restorations in dental implants.	192 (64%)	108 (36%)
Chi-square test		
The average	141 (46.9%)	159 (53.1)
Chi (P value)	0.369 (0.252)	

n: Number.

significant differences ($p > 0.05$).

4. Discussion

The dental implant procedure is an elective treatment method, and patients depend on dentists to give them details about this procedure and other treatment options to make the right decision, as several studies revealed that dentists represent the source for their patients about dental implants information [29] [30]. Thus, assessing the knowledge and actual practical attitude of senior dental students and general dentists plays an essential role in determining whether they can help their patients. To our knowledge, there is a lack of studies conducted in the college of dentistry at King Khalid University and the faculty of dentistry at Sana'a University to assess the practice and understanding of undergraduate students and dentists who graduated from Saudi dental schools as well as non-Saudi dental schools towards dental implants.

Furthermore, seniors dental students and general dentists represent the future dental specialists providing oral and dental treatment, therefore should be adequately educated regarding dental implants. This study aimed to assess the practice and knowledge of dental implants among senior dental students and general dentists who graduated from Saudi dental schools and non-Saudi dental schools less than five ago and more than five years ago .Several studies have evaluated levels of knowledge and attitudes about dental implants among dental students and dentists as in a previous study in Nepal, 67.14% of the participants revealed that they had received enough knowledge about dental implants during their undergraduate studies [31] [32].

In the 1990s, the American Association of Dental Schools determined guidelines for undergraduate training in implant dentistry of curriculum. Thus, the implant theory and clinical training in undergraduate dental studies should be increased [33]. The results of the current study confirmed this need, where 84.3% of graduates of some Saudi dental schools and 82.7% of graduates of some non-Saudi dental schools reported that they did not obtain sufficient information about dental implants during their undergraduate studies. These findings are consistent with the results of another study which revealed that about 40% of the participants reported that they did not receive sufficient information about dental implants during their undergraduate education [34].

An American study reported that 84% of students completed an implant dentistry course as undergraduate training [35]. In contrast with the results of the current study, it was revealed that 79.3% of graduates of some Saudi dental schools and 83.3% of graduates of some non-Saudi dental schools in this study reported that they did not take dental implants training during their undergraduate studies except dental implants lectures in some courses. These results agree with the results of another Saudi study that displayed that most students (78.8%) did not obtain enough lectures and training about dental implants during undergraduate studies [26]. Therefore, the dental implant should be involved in the

undergraduate curriculum as an essential part, and revision curriculums in these dental schools by the current standards of dental education in Europe and America [27] [36].

On the other hand, more than half of the participants in this study (65.3% of graduates of some Saudi dental schools and 41.3% of some non-Saudi dental schools) also reported that case selection is the most significant standard for the success of dental implants procedure which is lower than those participants revealed in a previous Saudi study [37].

Another Saudi survey of five dental schools revealed that in only one school, the students should be finished dental implant cases as a compulsory requirement in the fourth or fifth year [1]. These results are similar to the results in the present study, where 20.7% of graduates of some Saudi dental schools and 16.7% of graduates of some non-Saudi dental schools reported that they carried out implant procedures. Furthermore, no preclinical training in dental implants was offered in the dental schools surveyed, except one school that conducted workshops for students [1]. These results are Identical to the results of this study, where only 4% and 5.3% of participants reported that they attended workshops. All these results confirm the need for more preclinical and clinical training in the dental implant for undergraduate students [28] [38] [39].

In the present study, regarding the best aesthetic appearance 54.7% of graduates of some Saudi dental schools and 48.7% of graduates of some non-Saudi dental schools chose cement retained-restoration (CRR) more than screw retained-restoration (SRR). These results agree with the results of another study exhibited that the senior dental students considered CRR to be superior to SRR with regards to aesthetics [34]. Moreover, most of the participants in this study (59.3% of graduates of some Saudi dental schools and 72.7% of graduates of some non-Saudi dental schools) showed a predilection to use screw-retained restoration (SRR) as fracture resistance more than cement retained-restoration (CRR). These results correspond with standards of dental implants regarding aesthetics due to the possibility of the presence of a screw access hole in screw-retained restoration (SRR) if the positioning of dental implants improperly and are not corresponding with standards of dental implants regarding the resistance of fracture due to presence of unsupported ceramic in SRR, resulting in an increased fractures incidence [15] [20] [40].

On the other hand, newly graduated dentists in another study said that they want to provide dental implant treatment to their patients, similar to the current study, where more than half of the participants confirmed that they want to be specialists in dental implants (74% and 63.4%) [38].

Furthermore, In the present study, there were significant differences between CRR and SRR in graduates of some Saudi dental schools and graduates of some non-Saudi dental schools answers where the correct answers included the preponderance of CRR on SRR except for the third question and fifth question answers where SRR preponderance on CRR among graduates of some Saudi dental schools more than graduates of some non-Saudi dental schools except the se-

venth question answers where the correct answers included the preponderance of CRR on SRR among graduates of some non-Saudi dental schools more than graduates of some Saudi dental schools. These results are dissimilar to the other studies' results which found that there were slight or insignificant significant differences between CRR and SRR in the participants' answers [41].

The significant result in this study was that 50% of graduates of some Saudi dental schools and 71.3% of some non-Saudi dental schools did not have any experience in dental implants, which may be due to the lack of clinical training in dental implants for students during the undergraduate teaching [35].

The present study was a survey study, so it may not reflect the updated curriculum in dental schools surveyed in the current study. But it revealed a defect in the curricula of dental schools surveyed in teaching dental implants due to the lack of clear guidelines for curricula as well as differences in teaching methods applied in these schools. Thus, curriculum guidelines and teaching methods applied in these schools should be the same, in addition to providing an adequate faculty-to-student ratio for dental implant teaching.

5. Conclusion

There is a need for more academic teaching and laboratory as well as clinical training in dental implants for senior dental students and the general dentists who graduated from dental schools surveyed in the current study by offering the lowest mandatory clinical requirements for the cases that students must attend during the undergraduate studies. Moreover, adding more information about dental implants into the curricula of dental schools surveyed.

6. Strength and Limitations

The results of this study may help policymakers and program directors in different institutions in Saudi Arabia and the Republic of Yemen to identify points of improvement in teaching dental implants to undergraduate students. There were limitations during the current study, including the low number of dental schools surveyed in limited areas, in addition to the difficulties during data collections. Therefore, there is a need for an increase in the number of dental schools surveyed and the sample size in more regions to popularize the results.

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Conflicts of Interest

There is no conflict of interest.

References

[1] Al Kindi, M., Ramalingam, S., Abuhaimed, A. and Alkharan, H. (2018) Undergra-

duate Implant Dentistry Training in Saudi Dental Schools. *Journal of Ayub Medical College Abbottabad*, **30**, 217-222.

[2] Young, M.P., Carter, D.H., Sloan, P. and Quayle, A.A. (1999) A Survey of Oral Implantology Teaching in the University Dental Hospitals and Schools of the United Kingdom and Eire. *British Dental Journal*, **187**, 671-675. https://doi.org/10.1038/sj.bdj.4800364

[3] Brunski, J.B. (1999) In Vivo Bone Response to Biomechanical Loading at the Bone/Dental-Implant Interface. *Advances in Dental Research*, **13**, 99-119. https://doi.org/10.1177/08959374990130012301

[4] Feine, J.S., Carlsson, G.E., Awad, M.A., *et al*. (2002) The McGill Consensus Statement on Overdentures, Montreal, Quebec, Canada, May 24-25, 2002. *International Journal of Prosthodontics*, **15**, 413-414.

[5] Wang, H.-L., Shotwell, J.L., Itose, T. and Neiva, R.F. (2005) Multidisciplinary Treatment Approach for Enhancement of Implant Esthetics. *Implant Dentistry*, **14**, 21-29. https://doi.org/10.1097/01.id.0000154802.20125.b9

[6] Palmer, R. (1999) Introduction to Dental Implants. *British Dental Journal*, **187**, 127-132. https://doi.org/10.1038/sj.bdj.4800222a

[7] Zarb, G.A. (1983) The Edentulous Milieu. *Journal of Prosthetic Dentistry*, **49**, 825-831. https://doi.org/10.1016/0022-3913(83)90358-X

[8] Jivraj, S. and Chee, W. (2006) Rationale for Dental Implants. *British Dental Journal*, **200**, 661-665. https://doi.org/10.1038/sj.bdj.4813718

[9] Tsirlis, A. (2005) Clinical Evaluation of Immediate Loaded Upper Anterior Single Implants. *Implant Dentistry*, **14**, 94-103. https://doi.org/10.1097/01.id.0000156386.27897.7d

[10] Derks, J., Schaller, D., Håkansson, J., Wennström, J.L., Tomasi, C. and Berglundh, T. (2016) Effectiveness of Implant Therapy Analyzed in a Swedish Population: Prevalence of Peri-Implantitis. *Journal of Dental Research*, **95**, 43-49. https://doi.org/10.1177/0022034515608832

[11] Geckili, O., Bilhan, H., Geckili, E., Cilingir, A., Mumcu, E. and Bural, C. (2014) Evaluation of Possible Prognostic Factors for the Success, Survival, and Failure of Dental Implants. *Implant Dentistry*, **23**, 44-50. https://doi.org/10.1097/ID.0b013e3182a5d430

[12] Vohra, F., Al-Rifaiy, M.Q., Almas, K. and Javed, F. (2014) Efficacy of Systemic Bisphosphonate Delivery on Osseointegration of Implants under Osteoporotic Conditions: Lessons from Animal Studies. *Archives of Oral Biology*, **59**, 912-920. https://doi.org/10.1016/j.archoralbio.2014.05.016

[13] Diz, P., Scully, C. and Sanz, M. (2013) Dental Implants in the Medically Compromised Patient. *Journal of Dentistry*, **41**, 195-206. https://doi.org/10.1016/j.jdent.2012.12.008

[14] da Rocha, P.V.B., Freitas, M.A. and de Morais Alves da Cunha, T. (2013) Influence of Screw Access on the Retention of Cementretained Implant Prostheses. *The Journal of Prosthetic Dentistry*, **109**, 264-268. https://doi.org/10.1016/S0022-3913(13)60055-4

[15] Michalakis, K.X., Hirayama, H. and Garefis, P.D. (2003) Cement-Retained Versus-screw-Retained Implant Restorations: A Critical Review. *International Journal of Oral & Maxillofacial Implants*, **18**, 719-728.

[16] Korsch, M., Obst, U. and Walther, W. (2014) Cement-Associated Peri-Implantitis: A Retrospective Clinical Observational Study of Fixed Implant-Supported Restora-

tions Using a Methacrylate Cement. *Clinical Oral Implants Research*, **25**, 797-802. https://doi.org/10.1111/clr.12173

[17] Hebel, K.S. and Gajjar, R.C. (1997) Cement-Retained versus Screw-Retained Implant Restorations: Achieving Optimal Occlusion and Esthetics in Implant Dentistry. *Journal of Prosthetic Dentistry*, **77**, 28-35. https://doi.org/10.1016/S0022-3913(97)70203-8

[18] Pietrabissa, R., Gionso, L., Quaglini, V., Di Martino, E. and Simion, M. (2000) An *in Vitro* Study on Compensation of Mismatch of Screw versus Cement-Retained Implant Supported Fixed Prostheses. *Clinical Oral Implants Research*, **11**, 448-457. https://doi.org/10.1034/j.1600-0501.2000.011005448.x

[19] McGlumphy, E.A., Mendel, D.A. and Holloway, J.A. (1998) Implant Screw Mechanics. *Dental Clinics of North America*, **42**, 71-89. https://doi.org/10.1016/S0011-8532(22)00606-1

[20] Zarone, F., Sorrentino, R., Traini, T., Di lorio, D. and Caputi, S. (2007) Fracture Resistance of Implant-Supported Screw-versus Cement-Retained Porcelain Fused to Metal Single Crowns: SEM Fractographic Analysis. *Dental Materials*, **23**, 296-301. https://doi.org/10.1016/j.dental.2005.10.013

[21] Misch, C.E. (1995) Screw-Retained versus Cement-Retained Implant-Supported Prostheses. *Practical Periodontics and Aesthetic Dentistry*, **7**, 15-18.

[22] Guichet, D.L., Caputo, A.A., Choi, H. and Sorensen, J.A. (2000) Passivity of Fit and Marginal Opening in Screw-or Cement-Retained Implant Fixed Partial Denture Designs. *International Journal of Oral & Maxillofacial Implants*, **15**, 239-246.

[23] Taylor, T.D. and Agar, J.R. (2002) Twenty Years of Progress in Implant Prosthodontics. *Journal of Prosthetic Dentistry*, **88**, 89-95. https://doi.org/10.1067/mpr.2002.126818

[24] Chee, W.W., Duncan, J., Afshar, M. and Moshaverinia, A. (2013) Evaluation of the Amount of Excess Cement around the Margins of Cement-Retained Dental Implant Restorations: The Effect of the Cement Application Method. *Journal of Prosthetic Dentistry*, **109**, 216-221. https://doi.org/10.1016/S0022-3913(13)60047-5

[25] Agar, J.R., Cameron, S.M., Hughbanks, J.C. and Parker, M.H. (1997) Cement Removal from Restorations Luted to Titanium Abutments with Simulated Subgingival Margins. *Journal of Prosthetic Dentistry*, **78**, 43-47. https://doi.org/10.1016/S0022-3913(97)70086-6

[26] Aljohani, H.A. and Alghamdi, A.S.T. (2009) Predoctoral Dental Implant Education at King Abdulaziz University. *The Saudi Dental Journal*, **21**, 135-138. https://doi.org/10.1016/j.sdentj.2009.10.005

[27] Lim, M.V., Afsharzand, Z., Rashedi, B. and Petropoulos, V.C. (2005) Predoctoral Implant Education in U.S. Dental Schools. *Journal of Prosthodontics*, **14**, 46-56. https://doi.org/10.1111/j.1532-849X.2004.04047.x

[28] Atashrazm, P., Vallaie, N., Rahnema, R., Ansari, H. and Shahab, M.P. (2011) Worldwide Predoctoral Dental Implant Curriculum Survey. *Journal of Dentistry of Tehran University of Medical Sciences*, **8**, 12-18.

[29] Sharma, A., Shrestha, B., Chaudhari, B.K., Suwal, P. and Singh, R.K. (2018) Knowledge, Awareness, and Attitude Regarding Dental Implants among Dental Interns. *Journal of Nepal Medical Association*, **56**, 607-615. https://doi.org/10.31729/jnma.3440

[30] Vohra, F. and Habib, R. (2015) Knowledge and Attitude of Dentists toward Implant Retained Restorations in Saudi Arabia. *Nigerian Journal of Clinical Practice*, **18**, 312-317. https://doi.org/10.4103/1119-3077.151788

[31] Dhami, B., Shrestha, P., Lamichhane, B., Sharma, A.K. and Gupta, S. (2017) Dental Implants and General Dental Practitioners of Nepal: A Study of Existing Knowledge and Need for Further Education. *Journal of College of Medical Sciences-Nepal*, **13**, 212-215. https://doi.org/10.3126/jcmsn.v13i1.16668

[32] Nagpal, D., Prakash, S., Kalra, D.D. and Singh, G. (2018) Knowledge, Attitude, and Practice of Dental Implants among Dental Postgraduates and Practitioners in Davangere City, Karnataka: A Cross-Sectional Study. *Indian Journal of Dental Research*, **29**, 575-582. https://doi.org/10.4103/ijdr.IJDR_500_15

[33] Slavkin, H.C. (1998) Science, Technology and Health Literacy for the 21st Century: A Future for Dentistry. *New York State Dental Journal*, **64**, 25-28.

[34] Vohra, F., Shah, A.H., Zafar, M.S. and Kola, Z. (2015) Knowledge and Practice of Implant-Retained Restorations among Dental Students in Saudi Arabia. *Pakistan Journal of Medical Sciences*, **31**, 848-853. https://doi.org/10.12669/pjms.314.7384

[35] Petropoulos, V.C., Arbree, N.S., Tarnow, D., Rethman, M., Malmquist, J., Valachovic, R., *et al*. (2006) Teaching implant Dentistry in the Predoctoral Curriculum: A Report from the ADEA Implant Workshop's Survey of Deans. *Journal of Dental Education*, **70**, 580-588. https://doi.org/10.1002/j.0022-0337.2006.70.5.tb04114.x

[36] Mattheos, N., Albrektsson, T., Buser, D., De Bruyn, H., Donos, N., Hjorting Hansen, E., *et al*. (2009) Teaching and Assessment of Implant Dentistry in Undergraduate and Postgraduate Education: A European Consensus. *European Journal of Dental Education*, **13**, 11-17. https://doi.org/10.1111/j.1600-0579.2008.00556.x

[37] Alghamdi, M., Aboalshamat, K., Alghamdi, D., Abed, S., Almahlawi, H., AlKathiri, S., Abu Thiraa, A., Alsulami, A. and Alzughaibi, M. (2020) Knowledge and Attitudes of Dental Interns and Dentists on Implants and Implant-Retained Restorations in Jeddah, Saudi Arabia. *The Open Dentistry Journal*, **14**, 329-336 https://doi.org/10.2174/1874210602014010329

[38] Maalhagh-Fard, A., Nimmo, A., Lepczyk, J.W. and Pink, F.E. (2002) Implant Dentistry in Predoctoral Education: The Elective Approach. *Journal of Prosthodontics*, **11**, 202-207. https://doi.org/10.1053/jopr.2002.126726

[39] Afsharzand, Z., Lim, M.V., Rashedi, B. and Petropoulos, V.C. (2005) Predoctoral Implant Dentistry Curriculum Survey: European Dental Schools. *European Journal of Dental Education*, **9**, 37-45. https://doi.org/10.1111/j.1600-0579.2004.00363.x

[40] Chee, W., Felton, D.A., Johnson, P.F. and Sullivan, D.Y. (1999) Cemented versus Screw-Retained Implant Prostheses: Which Is Better? *International Journal of Oral & Maxillofacial Implants*, **14**, 137-141.

[41] Heckmann, S.M., Karl, M., Wichmann, M.G., Winter, W., Graef, F. and Taylor, T.D. (2004) Cement Fixation and Screw Retention: Parameters of Passive Fit: An *in Vitro* Study of Three-Unit Implant-Supported Fixed Partial Dentures. *Clinical Oral Implants Research*, **15**, 466-473. https://doi.org/10.1111/j.1600-0501.2004.01027.x

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Current Problems of the Diagnostics and Treatment of Sepsis and Burn Injuries: The Modified Pathogenetic Concept

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Abstract

Background: The deep understanding of pathogenesis is a key moment in the formation of the modern strategy of modern medicine. We conducted the thorough analysis of the microscopic processes occurring in the bodies of patients with purulent-septic complications. The modified pathogenetic concept of the diagnostic and treatment model of diseases with septic complications is presented. The obtained information about the mechanisms of origin and development of these diseases is fundamentally important for finding the modern effective methods of treating patients. The aim of the research is to modify treatment tactics for patients with sepsis and burn injuries based on the modified pathogenetic concept using modern diagnostics, *i.e.* the method of fluorescence spectroscopy (MFS) and biomarkers. Materials and Methods: The proposed modified pathogenetic concept of the diagnostic and treatment model of diseases with purulent-septic complications along with standard methods was used successfully for effective treatment of 15 patients with sepsis and 25 with burn injuries. Results: 3 main scenarios of behaviour of spectral-fluorescence characteristics of patients with sepsis are illustrated. Spectral-fluorescence markers of sepsis were studied, which are informative 24 to 48 hours before the appearance of obvious clinical and laboratory signs of significant changes in the general somatic status of patients. Conclusions: The proposed diagnostic and therapeutic approach is new and fundamentally important for diagnostics and monitoring of the process of treatment of patients with purulent-septic diseases and burn injuries. An in-depth understanding of the dynamics of septic complications and the corresponding changes of the main markers of these diseases during treatment is especially relevant. The use of infusion therapy with solutions of donor albumin as an effective pathogenetic treatment is scientifically justified.

Keywords

Purulent-Inflammatory Diseases, Sepsis, Modified Pathogenetic Diagnostic and Treatment Model, Method of Fluorescent Spectroscopy, Biomarkers, Albumin Infusion

1. Introduction

For more than thirty years, special attention has been paid to the diagnosis and treatment of sepsis. The international protocol for its intensive therapy was updated periodically with the participation of dozens of leading organizations, well-known scientists and experts [1]. Unsatisfactory results of treating sepsis were related directly to the lack of the effective methods of its express diagnosis, especially early [1] [2] [3]. When treating patients with severe pathology, insufficient attention was mostly paid to the microscopic processes that occur in the patients' bodies, and especially in their blood. Thus, it did not always lead to the discussion from the first principles and the significant improvement of traditional treatment schemes. In particular, when conducting biochemical blood analysis with determination of protein fractions and albumin level, it was impossible to detect the real changes in the structure of albumin molecules in septic complications. In this regard, it was fundamentally important to develop the pathogenetic concept for the significant improvement of diagnostic tactics, especially at the early stage of the development of purulent-inflammatory diseases and sepsis. The particular attention should be focused on the problems of diagnosis, treatment tactics and the effective monitoring of the condition of patients and correction of the treatment process.

2. Literature Review

Cytokines (interleukins: IL-1, IL-6, IL-8, IL-10, IL-12), presepsin, factor platelet activation (PAF), transforming growth factor-β (TGF-β), C-reactive protein (CRP), lactate and procalcitonin (PCT) are the sensitive biomarkers of endotoxicosis and systemic inflammatory reaction in the severe condition [2]. The considerable attention was paid to their research. We will dwell briefly on the most important information about these biomarkers and discuss the problem of their use for the diagnosis of purulent-septic complications in the medical practice. We shall make the extensive use of the information presented in the papers [1] [2] [3] [4].

The primary model of sepsis is the immune response to endotoxin, LPS, which was found in the cell walls of gram-negative bacteria. LPS is an excellent example of the pathogen-associated molecular pattern (PAMP) [3]. Innate immune cells, such as macrophages, have receptors that recognize different types of PAMPs. When interacting with bacterial ligands, these receptors stimulate macrophages to produce TNF-α, IL-1β та IL-6. These pro-inflammatory cytokines

cause the systemic inflammatory response characteristic of early sepsis. For many years doctors believed that sepsis was an overreaction of the innate immune system to a bacterial infection. The 1991 consensus conference defined "sepsis" as the combination of infection with two or more signs of SIRS.

Roger C. Bone is now believed to have recognized that sepsis is more than severe hyperinflammatory SIRS [5]. The importance of CARS (compensatory anti-inflammatory response syndrome), which often follows a hyperinflammatory phase, has also been highlighted, especially in patients who develop sepsis [6]. In patients with sepsis, there are also signs of severe organ dysfunction. This can include lung, liver and/or kidney damage, as well as the cognitive impairment. The terminal stage of sepsis is septic shock, in which patients develop cardiovascular collapse and are unresponsive to infusion and vasopressor therapy. In the dynamics of the course of sepsis, two phases should be distinguished. With the development of SIRS, the hyperinflammatory phase occurs at first. Pro-inflammatory and anti-inflammatory cytokines are produced in the body at the same time, but when their imbalance is disturbed, signs of CARS with immunosuppression and multiple organ dysfunction appear. At this stage, it is fundamentally important to carry out the effective treatment before the development of irreversible processes.

As the sepsis paradigm has evolved over time, various approaches to its diagnosis and treatment have been tested, including various biomarkers. The main focus, starting in 1980, was directed on the early phase with hyperergic inflammatory response, for which high doses of corticosteroids were used, which were considered an important component of its treatment. The subsequent research and advances in the treatment of major sepsis problems have been closely linked to the use of pro-inflammatory cytokines, particularly TNF-α, IL-1β and IL-6, which cause SIRS [3]. At the same time, CRP also appears, the synthesis of which is activated in the liver with the help of IL-6, as well as PCT. CRP and PCT have become new potential biomarkers since 2003.

At the end of the last decade, lactate was used as a biomarker for the diagnosis and treatment of septic complications. Later, when the therapy was aimed at the anti-inflammatory phase of sepsis, the new scientific research continued and new biomarkers were studied successfully. After recognizing the importance of CARS, biomarkers of the immunosuppressive phase of sepsis deserve considerable attention. There is the sufficient convincing evidence that adaptive immunity is impaired in patients with severe sepsis. The earliest sign of weakening of the immune response both in patients with sepsis and in people after trauma is the decrease in the expression of proteins of the major histocompatibility complex (MHC) class II (HLA-DR) - human leukocyte antigen on the surface of macrophages and other antigen-representing cells.

The clinical studies have focused on monocyte HLA-DR expression, which was markedly suppressed in most patients with sepsis initially, but recovered within ten days in surviving patients [7]. Similar depression may occur after severe trauma, and failure to recover within the first week of hospital stay in sur-

viving patients is a real predictor of developing sepsis in these patients. The low levels of HLA-DR expression predict, accordingly, a low percentage of patient survival, as well as an increased risk of nosocomial infection. The clinical utility of measuring IL-10, which inhibits the expression of MHC class II, and TGF-β, which suppresses the proliferation of T cells, has been proven. The elevated levels of IL-10 predict the mortality of patients with severe sepsis. It has also been disclosed that they correlate with inhibition of HLA-DR monocyte expression. IL-10 is a reliable biomarker of neonatal sepsis [8]. In addition, it was also shown that at early and late onset of sepsis, rather a rapid increase in the level of IL-10 was practically not noticed. TGF-β has been shown to promote tissue repair, but its role is not as important as that of IL-10.

None of the biomarkers discussed in the above publications are perfect, but in principle they can be useful. In order to study the possible change in the health status of patients during treatment more deeply and to direct this process in the right direction, it would be very important to know the dynamic picture of changes of biomarkers and to understand which of them reflect most globally and affect the change in the health status of patients. Over time, much attention is paid to the search for new biomarkers of septic complications in the field from SIRS to CARS.

3. Data and Methodology

3.1. Data Source

When conducting the biochemical blood analysis with determination of protein fractions and albumin level, it was impossible to detect the real changes in its structure during septic complications. In this regard, it was fundamentally important to develop the pathogenetic concept in order to improve the diagnostic tactics significantly for patients with purulent-septic diseases.

Modern clinical studies of the level of HSA have proven its important diagnostic value for assessing the condition of patients and predicting the course of their diseases [9]. The basis for this is the ability of albumin to form complexes with the products of bacterial life - toxins, which provide its detoxification function and are important for detecting of pathologies. The reverse side of the sorption of toxins by albumins is inhibition of the transport function of proteins. It has been established that the release of toxins from the local pathological focus leads to the syndrome of endogenous intoxication (EI). The body's protection against toxic compounds is carried out by the immune system, but it ensures the elimination of only high-molecular foreign substances with a molecular weight of at least 5000 Da. The elimination of low molecular weight toxins is provided by blood transport proteins.

3.2. Research Results

3.2.1. The Modified Diagnostic and Treatment Model of Purulent-Inflammatory Diseases and Sepsis

Over the past twenty years, some authors [10] [11] have demonstrated the diag-

nostic value of MFS, which was illustrated specifically on the disease models "in vitro" [12], as well as specifically "*in vivo*" and confirmed in clinical practice for patients with obstetric [13] and surgical [14] pathologies and with burn injury [15] [16]. Considerable attention was paid to the understanding of the essence of the pathological processes that occur in the bodies of patients with purulent-septic diseases at the molecular level. It is based on the fact that in diseases accompanied by EI, part of the albumin molecules are blocked by toxins. As a result, there are two types of albumin molecules in their blood: normal and blocked by toxins. At the same time, pathological molecules lose their ability to perform their main functions, namely transport and detoxification. So, the pathogenetic concept of the diagnostic and treatment model of purulent-inflammatory diseases and sepsis was proposed [12]. Since part of the albumin molecules in the blood of patients are blocked by toxins, there are two types of albumin molecules in their blood: normal concentration (X) and blocked (concentration (1-X)). Blocked albumin molecules lose their ability to perform their main functions, namely transport and detoxification. This allows us to understand better the processes of genesis during the course of sepsis in patients' bodies.

Taking into account the above-discussed features of the protection of patients with purulent-septic diseases from toxic compounds, the modified concept of the diagnostic and therapeutic approach of purulent-inflammatory diseases and sepsis is proposed. The proposed concept consists in determining X^o—the limit minimum concentration of normal albumin in the blood of the patient with sepsis. In the case of $X > X^o$, albumin molecules eliminate successfully toxins. The problem of sepsis is complex, and its solution must be comprehensive. The diagnosis and control of the process of its treatment can also be carried out within the framework of MFS and with the use of biomarkers. The most important role of biomarkers is to obtain information about X^o (SIRS). As a result, we can get information about I_F and λ_{max} of precisely at the time of SIRS. At the same time, the approach proposed by us within the framework of the MFS will continue to be relevant. It will allow us to study the BS samples of patients and analyze changes in dynamics of I_F and λ_{max} in details. In the future, it is necessary to measure the dynamics of IL-6 and other biomarkers that appear when the patient's condition worsens (after the transition to the CARS state). At the same time, there is a change of I_F and λ_{max} in this state, information about which we will receive within the framework of the MFS. But I_F and λ_{max} can also provide the information about how they are affected by donor albumin infusions. We shall see that donor albumin infusions will also reduce biomarkers that appear when a patient's condition deteriorates (for example, IL-6 if albumin infusions are used in treatment after biomarkers appear). The fundamental role in the diagnostic approach has the information obtained within the MFS regarding I_F and λ_{max}, but we do not know how they behave in SIRS, and even more so between SIRS and CARS, because no one has done this.

3.2.2. Study of Spectral-Fluorescent Characteristics of BS of Patients with Sepsis

Now consider, for example, the results of the examination within the framework of the MFS of several patients with sepsis and with burn injuries.

Figure 1, Table 1 present the results of the study of spectral-fluorescence characteristics of two patients with sepsis. Both of them had sepsis-epiduritis. The first patient was young (33 years old), she had no concomitant diseases, but there was a late application for medical help. The second patient was older (60 years old), but he addressed timely for medical help. Bacteremia was diagnosed in both patients. A thorough clinical and laboratory examination was conducted for them. Antibiotic and infusion therapy in significant volumes were prescribed. Patient 1 was admitted to the hospital due to the manifestation of a septic condition. MFS helped to identify the septic peak in the long-wave region (Figure 1, curve 1) and to decide the further rational choice of treatment tactics. Further studies of the FS of BS of this patient (Figure 1, curves 3, 4) proved that bacteremia was not overcome completely in her body, although the long-wave septic peak disappeared. However, the competitive struggle between bacteremia and compensatory capabilities of the patient's body in combination with complex medical measures continued. Only the subsequent long treatment process of this patient led to the final suppression of endotoxemia and recovery of this patient (Figure 1, curve 5). Curve 1 is very interesting from the point of view of

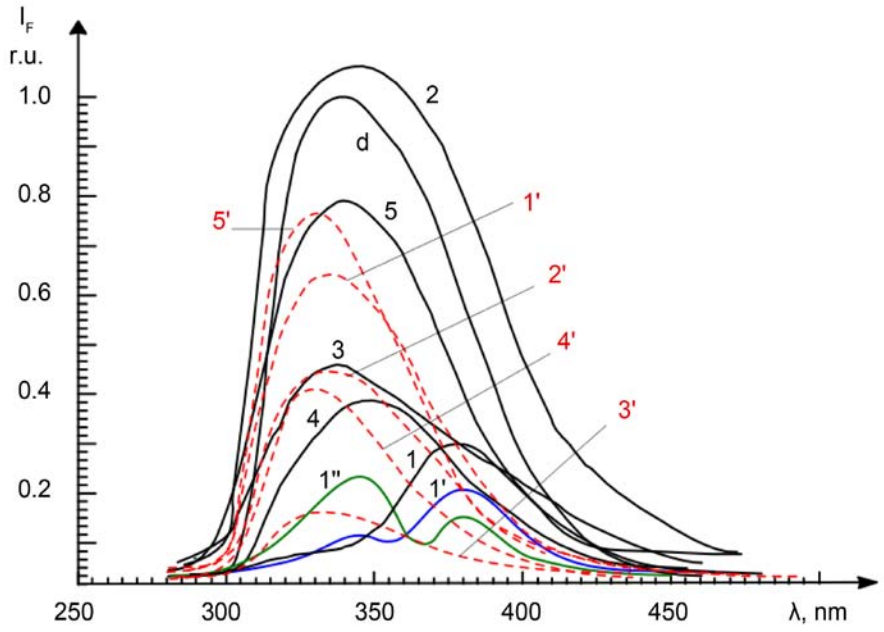

Figure 1. Fluorescence spectra of the blood serum of a person with sepsis-epiduritis who was treated in Emergency hospital in 2001-2002: 1—28.12.2001; 1'—30.12., 1"—02.01.2002; 2—04.01.2002; 3—12.02.2002 p.; 4—19.03.2002 p.; 5—04.06.2002 p. and a patient with sepsis-epiduritis, who was treated in 2002 in Emergency hospital: 1'—03.06; 2'—05.06; 3'—06.06; 4'—07.06; 5'—10.06 and blood serum of the donor (d). λex = 280 nm, donor blood serum (d). λex = 250 nm (340 nm—"normal peak", 380 nm—"septic peak").

Table 1. Changes of the spectral-fluorescence characteristics of the blood serum of two patients with sepsis-epiduritis.

N	d	1	1'	1'	1''	1''	2	3	4	5	1'	2'	3'	4'	5'
Date	28.12	28.12	30.12	30.12	02.01	02.01	04.01	12.02	19.03	04.06	03.06	05.06	06.06	07.06	10.06
λ_{max}, nm	340	380	380	345	380	345	345	337	349	340	336	334	333	330	331
I_F, r.u.	1.0	0.3	0.21	0.12	0.15	0.23	1.07	0.46	0.39	0.79	0.64	0.44	0.16	0.41	0.76

the ideology of biomarkers. The main contribution to FS here is given by blocked albumin molecules, and a minor contribution at λ = 345 nm indicated that she was in the CARS state. This confirms that in this condition, even a small amount of normal albumin molecules ensured the survival of this patient in the severe septic condition.

In the case of the second patient (**Figure 1**, dashed curves), the source of infection in his body was removed surgically at the beginning of the treatment process. The detailed monitoring of the treatment process within the framework of the MFS showed that the behaviour of the fluorescence curves during the recovery of this patient was qualitatively consistent with the behaviour of the recovery of the previous patient. Unfortunately, during the treatment of the above-mentioned patients, whose monitoring was followed within the framework of MFS, no pathogenetic concept was proposed, and infusion of donor albumin solutions was not used. However, both patients recovered and were discharged successfully from the hospital.

The third scenario studied by us within the framework of the MFS demonstrates clearly the behaviour of the FS of BS of the patient with sepsis caused by multiple soft tissue foci of infection on the basis of diabetes (**Figure 2(a)**, **Table 2**). This person was admitted to the hospital at the beginning of the formation of the septic state in her body. So, no two-peak structure was detected during the study of the FS of her BS. After the surgical intervention, against the background of intensive antibacterial and anti-inflammatory therapy, there was a gradual decrease in the fluorescence intensity of her BS, but the patient's condition did not change practically for three days. Unfortunately, this scenario was not so optimistic. According to the pathogenetic concept, in this case, complete albumin molecules were also blocked by sugar residues.

In this case, there were actually two types of pathological albumin molecules: blocked by toxins and an increased number of glycolyzed ones. This patient's condition worsened suddenly within one day against the background of intensive antibiotic therapy, which can be explained by the presence of a number of serious concomitant diseases and her advanced age. Glycolization of albumin molecules also contributed to this, due to the presence of diabetes in the patient. The patient died as a result of generalization of the infection and multiple organ failure.

However, despite such a difficult scenario of the course of the disease, presented in **Figure 2(a)**, MFS gives us the opportunity to discuss theoretically

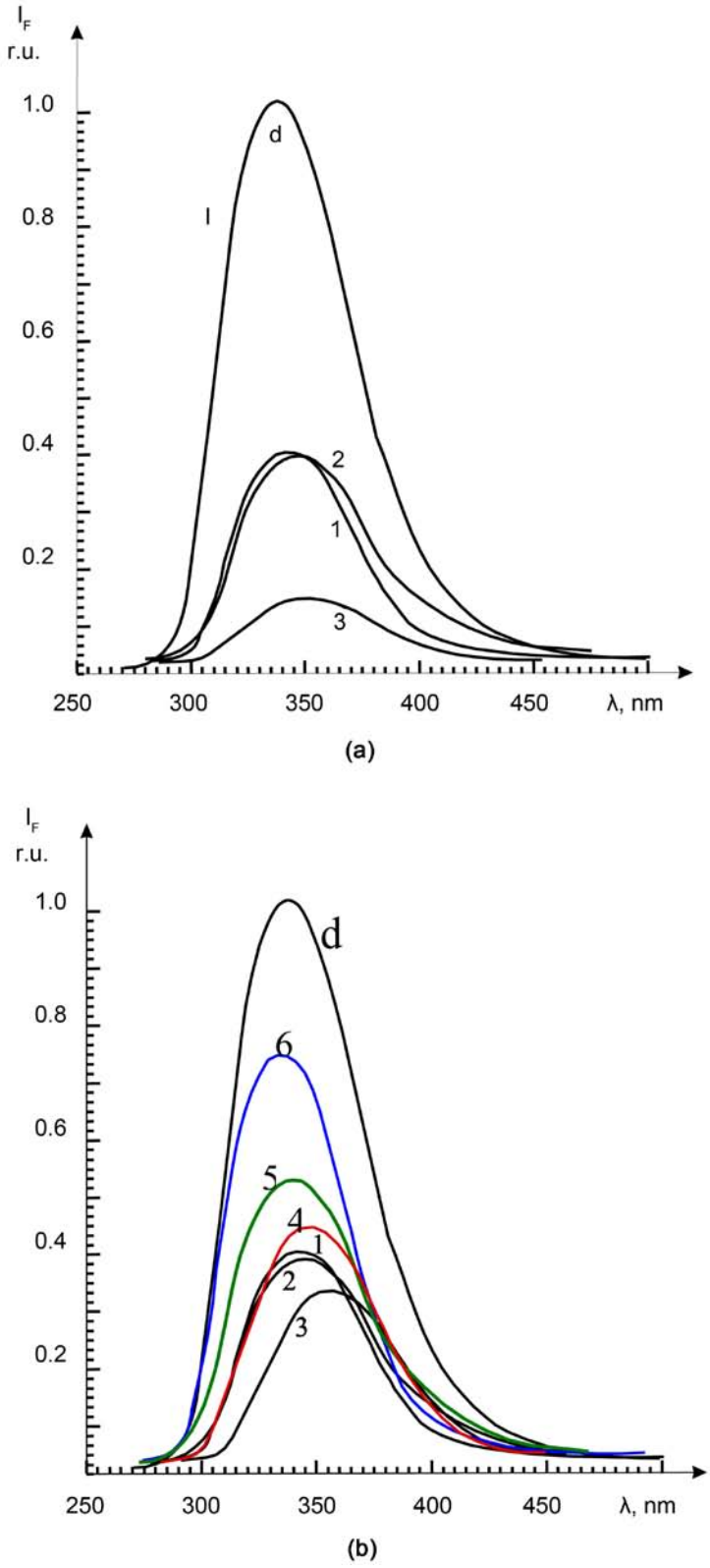

Figure 2. (a) Fluorescence spectra of blood serum of the patient with sepsis and diabetes, who was treated in 2002 in Emergency hospital and blood serum of a donor (d). λ_{ex} = 280 nm. (b) Fluorescence spectra of blood serum of the patient with sepsis and diabetes, who was treated in 2002 at Emergency hospital and blood serum of a donor (d). λ_{ex} = 280 nm.

Table 2. (a) Changes in the spectral-fluorescence characteristics of the blood serum of person 3, a patient with sepsis and diabetes. (b) Changes in the spectral-fluorescence characteristics of the blood serum of person 3, a patient with sepsis and diabetes.

(a)

N	d	1	2	3
Date	03.06	03.06	05.06	06.06
λ_{max}, nm	338	342	347	351
I_F, r.u.	1.0	0.41	0.40	0.15

(b)

N	d	1	2	3	4	5	6
Date	03.06	03.06	05.06	07.06	09.06	11.06	14.06
λ_{max}, nm	338	342	347	355	345	338	334
I_F, r.u.	1.0	0.41	0.40	0.33	0.45	0.53	0.75

another possible scenario for the treatment of this patient, starting from 03.06, which, unfortunately, was not implemented. It could have been implemented if the pathogenetic concept of the development of purulent-inflammatory diseases and sepsis had been proposed at that time. According to this scenario, the patient should be injected with 150 - 200 ml of 20% donor albumin and continue to monitor within the framework of the MFS FS of BS and perform albumin infusions after 2 - 3 days until complete recovery. The scenario of such a possible variant of the treatment process for this patient is presented in **Figure 2(a)** and in **Table 2(b)**.

At the same time, it would be necessary to adjust the tactics of diabetes treatment as well. Although this did not give a full guarantee of the recovery of this patient, the mentioned procedure should be performed, giving the patient the last chance to survive. It is obvious that these results could be obtained only within the framework of MFS. The final result of treatment also depends on the presence of concomitant diseases that require the additional treatment. The actual treatment of this patient should be carried out immediately according to a different scenario, using infusions of donor albumin and adjusting the treatment of diabetes.

The particular attention should be paid to the relevance of this problem for high-income countries due to the increase of the number of people, including pregnant women, with obesity and diabetes, which contributes to the increased risk of developing of purulent-septic complications. Obesity can affect negatively a woman's health, causing insulin resistance, dyslipidemia, hormonal and psychological problems, along with sexual problems during menopause [17]. About 6% of albumin molecules in BS of healthy donors are glycosylated. At the same time, 9% - 12% of patients with diabetes are in a glycosylated state due to the presence of hyperglycemia [12]. So, the sum of pathological and glycosylated albumin molecules should be considered pathological. Glycated hemoglobin

(HbA1c) is an early prognostic marker for the diagnosis of diabetes, which enables us to detect this disease at the early stages, and also allows us to prescribe the appropriate treatment in order to prevent its development. Normally, this indicator is 4% - 5.6%. A level of A1c (HbA1c) between 5.7% - 6.4% means that a person has prediabetes. As a result, her chances of developing diabetes are high. The closer the HbA1c level is to 6.4%, the higher the risk of developing diabetes. An indicator of 6.5% and above indicates that a person already has diabetes. In 1977, it was proposed to determine HbA1c, which is a stable connection of hemoglobin with glucose, formed as a result of non-enzymatic glycosylation of hemoglobin for the assessment of glycemia. The use of HbA1c for the diagnosis of the diabetes has been approved by the WHO since 2011. According to the recent data, it is believed that HbA1c underestimates glycemic control in patients with diabetes. At the same time, glycosylated albumin is a more reliable indicator of glycemic control. The role of HbA1c in patients with chronic renal failure requires further research. Logically, patients with diabetes are prone to the occurrence of purulent-septic complications in the body and their long course. The logical hypothesis is that "albumin overloaded with sugar residues" is not able to bind completely and eliminate toxic products from the body, which leads to the deepening of endogenous intoxication. Pregnant women with diabetes are a risk group for the formation of postpartum purulent-inflammatory diseases. If the medical institution does not have the possibility to monitor the treatment process within the framework of MFS, it is necessary to carry out the detailed monitoring of the state of health of patients, in particular, to carry out clear monitoring of the level of glycemia in the BS. When the level of glycemia increases, it is advisable to correct the therapeutic tactics of diabetes and use infusions of a 20% solution of donor albumin.

The dynamics of changes of the spectral-fluorescence characteristics of the BS of patients with sepsis reflects objectively the clinical features of the course of this disease, which depends significantly on the quality of diagnosis and correlates with the effectiveness of treatment tactics.

3.2.3. The Study of Spectral-Fluorescent Characteristics of BS of Patient with Burn Injury

Figure 3(a) presents the results of research in the dynamics of FS, and in **Table 3(b)**—data for spectral-fluorescence characteristics of the patient with a burn injury (28% burn surface area), who obtained the inpatient treatment at St. Luke Hospital in February 2017. He was prescribed immediately the appropriate treatment, including the antibiotic therapy and infusion therapy with a volume of up to 3 litres daily, as well as infusions of 10% donor albumin (06.02, 10.02 100 ml each day). The condition of this patient was serious. Despite the intensive treatment, his condition deteriorated significantly during the first 5 days. This is evidenced by a decrease in fluorescence intensity (Curves 1, 2). He had a fairly significant EI. Thus, the treatment process was corrected, including additional infusions of a 10% solution of donor albumin (February 15, 18, 26, and March 2,

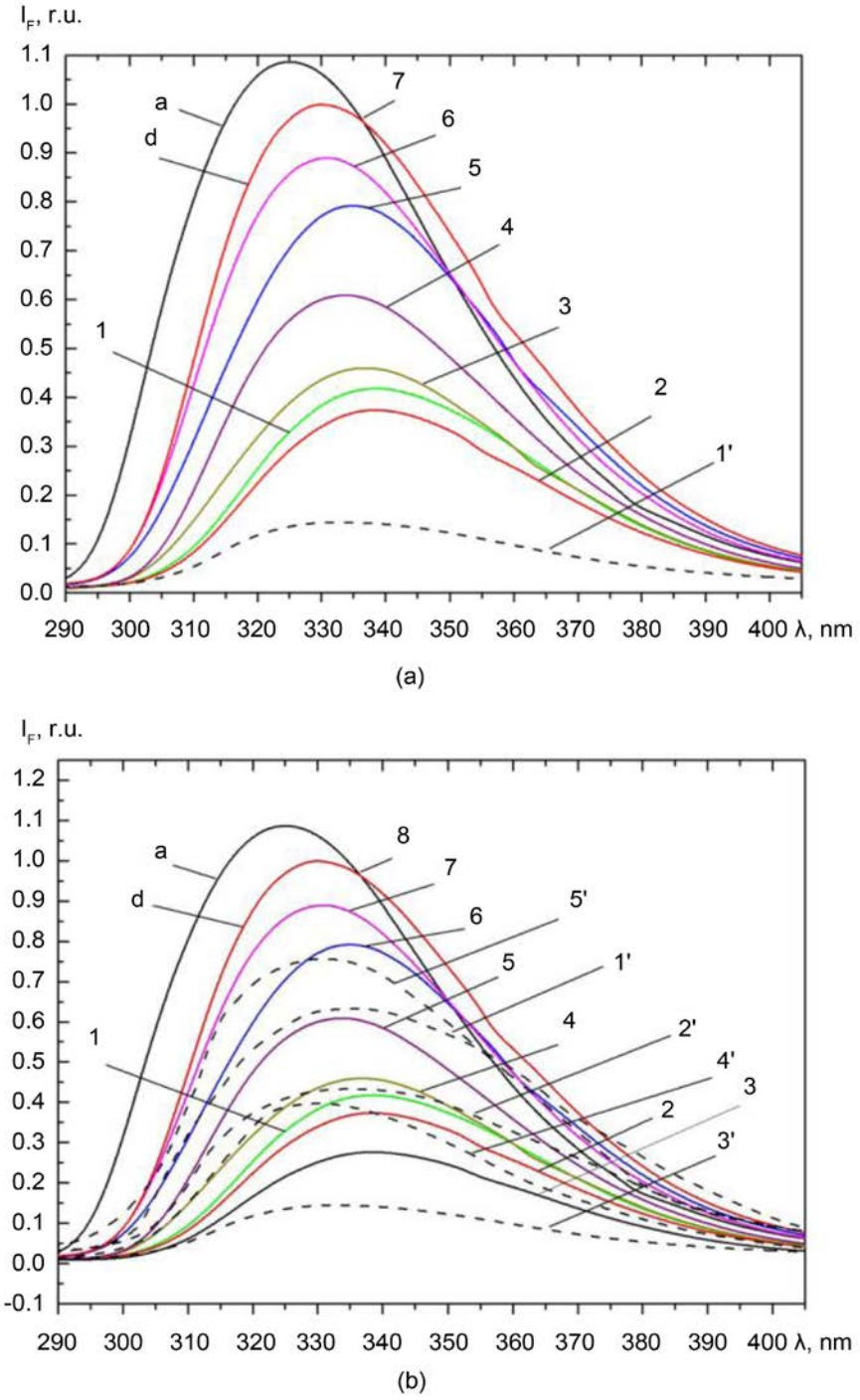

Figure 3. (a) Fluorescence spectra of the blood serum of the patient with a burn injury who was hospitalized in 2017 in the dynamics of treatment, a patient with sepsis (1') who was treated in 2002, a donor (d) and a 20% solution albumin (a). λ_{ex} = 280 nm. (b) FS of BS of the patient with a burn injury who was hospitalized in 2017 in dynamics during treatment, a patient with sepsis (1'-5') who was treated in 2002, a donor (d) and 20% donor albumin (a). λ_{ex} = 280 nm.

100 - 150 ml each day). These infusions made it possible to improve significantly the functioning of the body's detoxification systems with the gradual normalization

Table 3. Changes in the spectral-fluorescence characteristics of the blood serum of the patient with a burn injury. (b) Changes in the spectral-fluorescence characteristics of the blood serum of the patient with a burn injury.

(a)

N	A	D	1'	1	2	3	4	5	6	7
Date	06.06	06.06	06.06	9.02	14.02	22.02	27.02	03.03	10.03	31.03
λ_{max} nm	330.1	333.1	333	335.1	339.1	337	334	335.1	331.1	332.0
I_F, r.u.	1	1	0.16	0.41	0.37	0.46	0.61	0.79	0.89	0.95

(b)

№	1	2	3	4	5	6	7	8	1'	2'	3'	4'
Date	9.02	14.02	22.02	25.02	28.02	03.03	10.03	31.03	3.06	5.06	6.06	7.06
λ_{max} nm	335.1	339.1	337	337	334	335.1	331.1	332.0	335.2	335.2	334.1	331.6
I_F, r.u.	0.41	0.37	0.27	0.46	0.61	0.79	0.89	0.95	0.63	0.43	0.14	0.40

of endogenous albumin synthesis by the liver. As a result, the fluorescence intensity of the BS of the patient increased markedly, and the long-wavelength shift of FS leveled off (Curves 3 - 7). After that, the patient was discharged from the hospital in the satisfactory condition.

Figure 3(a) (Curve 2) and **Table 3(a)** demonstrate a decrease in the fluorescence intensity of FS. If we do not take this fact into account and do not prescribe an infusion of donor albumin, there will be an increase in EI and we will get curve 3 within the framework of MFS 22.02 (see **Figure 3(b)**). It can be seen from this figure that the patient's condition has approached septic (Curves 3 and 3' are close to each other). Thanks to the monitoring of the treatment process within the framework of the MFS, it was possible to identify a threatening situation for this patient. He should be given several sessions of infusion therapy with a solution of donor albumin until the possible improvement of his health and his recovery. The scenario of his treatment at the final stage took place under the supervision of the MFS and is illustrated in **Figure 3(b)** and **Table 3(b)**. If the infusion of donor albumin had not been prescribed on 22.02, his health could have deteriorated significantly. In this case, treatment should be continued using infusion therapy with a solution of donor albumin, although there was no absolute guarantee of successful completion of the treatment process in this case. It is fundamentally important to be able to monitor the treatment process within the framework of the MFS. At the same time, it is very important to carry out the detailed monitoring of the patient's condition during the treatment process, adjusting the treatment process if possible. Summarizing, we note that the dynamics of changes in the spectral-fluorescence characteristics of patients with sepsis and burn injury during the treatment reflects properly the clinical features of the

course of these diseases.

4. Conclusions

1) The method of diagnostics of purulent-inflammatory diseases and sepsis was proposed within the framework of the MFS.

2) It has been established that the structure of FS of BS in the patients with these diseases is an effective marker of its severity.

3) At the same time, in patients with severe sepsis, the structure of FS of BS is double-peaked, which reflects the presence of two types of albumin molecules in the blood of patients.

4) Spectral-fluorescence characteristics obtained within the framework of MFS have a pre-manifest nature. These changes are usually registered 24 - 48 hours before the appearance of obvious clinical and laboratory signs of the patients' condition.

5) The modified pathogenetic concept of the diagnostic and therapeutic approach to purulent-inflammatory diseases and sepsis is proposed and presented.

6) A modern approach for diagnosis and effective control of the treatment process within the framework of MFS and biomarkers using infusions of donor albumin solutions was proposed.

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Conflicts of Interest

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

References

[1] Finnerty, C.C., Herndon, D.N., *et al*. (2006) Cytokine Expression Profile over Time in Severely Burnes Pediatric Patients. *Shock*, **26**, 13-19. https://doi.org/10.1097/01.shk.0000223120.26394.7d

[2] Finnerty, C.C., Herndon, D.N., Chinkes, D.L. and Jeschke, M.G. (2007) Serum Cytokine Differences in Severely Burned Children with and without Sepsis. *Shock*, **27**, 4-9. https://doi.org/10.1097/01.shk.0000235138.20775.36

[3] Faix, J.D. (2013) Biomarkers of Sepsis. *Critical Reviews in Clinical Laboratory Sciences*, **50**, 23-26. https://doi.org/10.3109/10408363.2013.764490

[4] Lopez, O.N., Cambiaso-Daniel, J., Branski, L.K., *et al*. (2017) Predicting and Managing Sepsis in Burn Patients: Current Perspectives. *Therapeutics and Clinical Risk Management*, **13**, 1107-1117. https://doi.org/10.2147/TCRM.S119938

[5] Balk, R. (2011) Roger C. Bone, MD and the Evolving Paradigms of Sepsis. *Contributions to Microbiology*, **17**, 1-11. https://doi.org/10.1159/000323970

[6] Bone, R.C., Grodzin, C.J. and Balk, R.A. (1997) Sepsis: A New Hypothesis for Pathogenesis of the Disease Process. *Chest*, **112**, 235-243.

https://doi.org/10.1378/chest.112.1.235

[7] Tschaikowsky, K., Hedwig-Geissing, M., Schiele, A., *et al*. (2002) Coincidence of Pro- and Anti-Inflammatory Responses in the Early Phase of Sepsis: Longitudinal Study of Mononuclear Histocompatibility Leukocyte Antigen-DR Expression, Procalcitonin, C-Reactive Protein, and Changes in T-Cell Subsets in Septic and Postoperative Patients. *Critical Care Medicine*, **30**, 1015-1023. https://doi.org/10.1097/00003246-200205000-00010

[8] Zeitoun, A.A.H., Gad, S.S., Attia, F.M., *et al*. (2010) Evaluation of Neutrophilic CD64, Interleukin 10 and Procalcitonin as Diagnostic Markers of Early- and Late-Onset Neonatal Sepsis. *Scandinavian Journal of Infectious Diseases*, **42**, 299-305. https://doi.org/10.3109/00365540903449832

[9] Gryzunova, Yu.A. and Dobretsova, G.E. (1998) Dobretsov Albumin Serum Albumin in Clinical Medicine. GEOTAR, Moscow, 440 p.

[10] Gerych, I.D., Bulavenko, O.V. and Ostapyuk, L.R. (2015) Fluorescence Spectroscopy: Possibilities of Application in Medical Practice. Liga-Press, Lviv, 366 p.

[11] Ostapiuk, L. (2019) Diagnostic and Therapeutic Model of Sepsis and Purulent-Inflammatory Diseases. *International Journal of Clinical Medicine*, **10**, 577-595. https://doi.org/10.4236/ijcm.2019.1011047

[12] Bulavenko, O.V., Gerych, I.D., Ostapiuk, L.R., *et al*. (2013) Modeling of Blood Serum Changes in Patients with Various Diseases and Treatment Measures. *Biomedical and Biosocial Anthropology*, **20**, 8-14.

[13] Bulavenko, O., Ostapiuk, L., Rud, V., *et al*. (2021) Problems and Challenges to Women's Reproductive Health in the 21st Century. *Acta Scientific Women's Health*, No. 3, 70-87. https://doi.org/10.31080/ASWH.2021.SI.03.0012

[14] Ostapiuk, L. (2022) The Pathogenetic Concept of the Diagnostic-Treatment Approach for Patients with Purulent-Septic Complications. *International Journal of Clinical Medicine*, **13**, 1-21. https://doi.org/10.4236/ijcm.2022.131001

[15] Zaporozhan, S., Savchyn, V., Ostapiuk, L., Voloshinovskii, A., Tuziuk, N. and Malyi, T. (2020) The New Approach to the Diagnostics and Treatment of Endogenous Intoxication in Patients with Burn Injury. *International Journal of Clinical Medicine*, **11**, 375-388. https://doi.org/10.4236/ijcm.2020.116033

[16] Ostapiuk, L., Voloshinovskii, A., Savchyn, V., Tuziyk, N. and Malui, T. (2021) Current Problems of Diagnostics and Treatment of Purulent-Inflammatory Diseases and Sepsis in Medical Practice. *International Journal of Clinical Medicine*, **12**, 87-107. https://doi.org/10.4236/ijcm.2021.123011

[17] Trischitta, V. (2003) Relationship between Obesity-Related Metabolic Abnormalities and Sexual Function. *Journal of Endocrinological Investigation*, **26**, 62-64.

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Postmenopausal Osteoporosis and Osteopenia Management with a Combination of Once-Monthly Oral Ibandronate and Cholecalciferol—A Systematic Review

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Abstract

Postmenopausal osteoporosis and osteopenia are chronic and uncurable conditions that invariably lead to an increased risk of vertebral, hip, and femoral neck fracture if left untreated. Clinical guidelines establish, in general, pharmacological combinations allied to lifestyle changes as the mainstay of their management, and also increasing bone marrow density, lowering fracture risk, and improving quality of life are their main therapeutic goals. The objective of this systematic review was to analyze the available data in the scientific medical literature regarding the role of the ibandronate and cholecalciferol combination in postmenopausal osteoporosis and osteopenia management. Based on our results, we concluded that the above combination is safe and feasible for the clinical control of both conditions.

Keywords

Ibandronate, Cholecalciferol, Postmenopausal Osteoporosis, Postmenopausal Osteopenia, Systematic Review

1. Introduction

Postmenopausal osteoporosis imposes an enormous human and economic burden on healthcare systems all over the world. Bound to compromise all women after their reproductive years (even though in varying degrees), this condition drives huge efforts in all research levels at international, public administration, pharmaceuticals, and university settings to elucidate its natural history, as well as finding either novel or repositioned therapeutic modalities. Ibandronate is a substance of the bisphosphonates class, able to decrease osteoclast activity, reduce bone crystalized inorganic mineral matrix solubility, and downregulate proosteoclasts signaling, with an overall effect of slowing down, preserving, or increasing bone mineral density (BMD) [1] [2] [3] [4] [5]. Cholecalciferol is the most widely used substance of the vitamin D class, universally indicated for postmenopausal osteoporosis and osteopenia prevention and treatment due to its ability to make calcium and phosphate available to the bone remodeling process. Assuming pharmacological combination therapy for postmenopausal osteoporosis management has a consensus status for most clinical situations, the association of ibandronate and cholecalciferol presents itself as a feasible resource for increasing patient adherence, as well as assuring therapeutic efficacy. Therefore, we aimed to retrieve through a systematic review of the available evidence in the scientific clinical literature detailing the safety and efficacy of the ibandronate and cholecalciferol combination in the setting of postmenopausal osteoporosis and osteopenia management. To the best of our knowledge, ours is the first initiative of performing a grouped analysis of previously published papers with the above combination.

2. Methodology—Primary Studies Search and Selection

The study was performed by two independent "searchers" (MS and LHS) who worked in parallel and blindly, both according to the following parameters: 1) epidemiological studies, observational studies, randomized clinical trials (RCT), non-RCT, systematic reviews and meta-analyses as study types; 2) no language or year of publication restrictions; 3) the names of the authors of the primary studies were not regarded (even though personal consulting was permissible); 4) the following sources were scrutinized, with respective parameters:

- Pubmed: "ibandronate" in the title and "cholecalciferol" or "vitamin D" anywhere in the text
- *Literatura Latino-Americana e do Caribe em Ciências da Saúde* (LILACS): "*ibandronato*" in the title and "*colecalciferol*" or "*vitamina D*" anywhere in the text
- Google Scholar: 1) "ibandronate" in the title and "cholecalciferol" or "vitamin D" anywhere in the text; 2) up to three search pages
- Networked Digital Library of Theses and Dissertations (NDLTD): "ibandronate" in the title and "cholecalciferol" or "vitamin D" anywhere in the text
- *Biblioteca Digital Brasileira de Teses e Dissertações* (BBTD): "*ibandronato*"

in the title and "*colecalciferol*" or "*vitamina D*" anywhere in the text

- World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (WCOOMD): "ibandronate" in the title and "cholecalciferol" or "vitamin D" anywhere in the text (Google and Pubmed platforms)
- European Congress on Osteoporosis and Osteoarthritis (ECOO): "ibandronate" in the title and "cholecalciferol" or "vitamin D" anywhere in the text (Google and Pubmed platforms)
- National Osteoporosis Foundation (NOF): "ibandronate" in the title and "cholecalciferol" or "vitamin D" anywhere in the text (Google and Pubmed platforms)
- American Academy of Orthopaedic Surgeons (AAOS): "ibandronate" in the title and "cholecalciferol" or "vitamin D" anywhere in the text (Google e Pubmed platforms)
- Bibliographic references from the selected publications

Support literature, such as textbooks, basic science papers, and pharmacological compendiums, was consulted when deemed necessary (not accounted for systematic review purposes). The studies search was performed according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [6]. Flowchart is depicted in **Figure 1**.

Results of the "searchers" were crossed by a reviewer for validation, who reported no conflicts between the body of findings of the former two. Studies were selected through respective titles and abstracts, according to the following parameters of interest: BMD maintenance at medium and long term, bone fracture risk reduction, comparison with other bisphosphonates, influence on patients' quality of life, effects on blood levels of markers linked to bone metabolism, influence on bone tissue and tolerability. Text search was extended from the title/abstract to the body of the text when searchers felt necessary. No personal contact with the studies' authors was necessary. A comprehensive literature on the general pharmacology of ibandronate and cholecalciferol was also retrieved.

3. Postmenopausal Osteoporosis

3.1. Definition and Pathophysiology

Osteoporosis is a bone degenerative condition characterized by low cortical and/or trabecular density of the hip, vertebrae, femoral neck, and/or distal forearm, expressed as a T-score ≤2.5 standard deviations (SD) as measured by bone densitometry (DXA). Postmenopausal osteoporosis occurs in the context of the physiological lowering of estrogen secretion, typical of this phase of life (biomechanical defects and aging are co-mechanisms) [1] [3]. Bone remodeling is accelerated, leading to a net loss of bone tissue with each cycle. Since trabecular bone is more susceptible to this phenomenon than cortical bone, one can assume that osteoporosis might be more common in bones where the former prevails such as the hip, vertebrae, and femoral neck. Subsequent deterioration of bone architecture and strength loss predispose either to fracture due to trauma

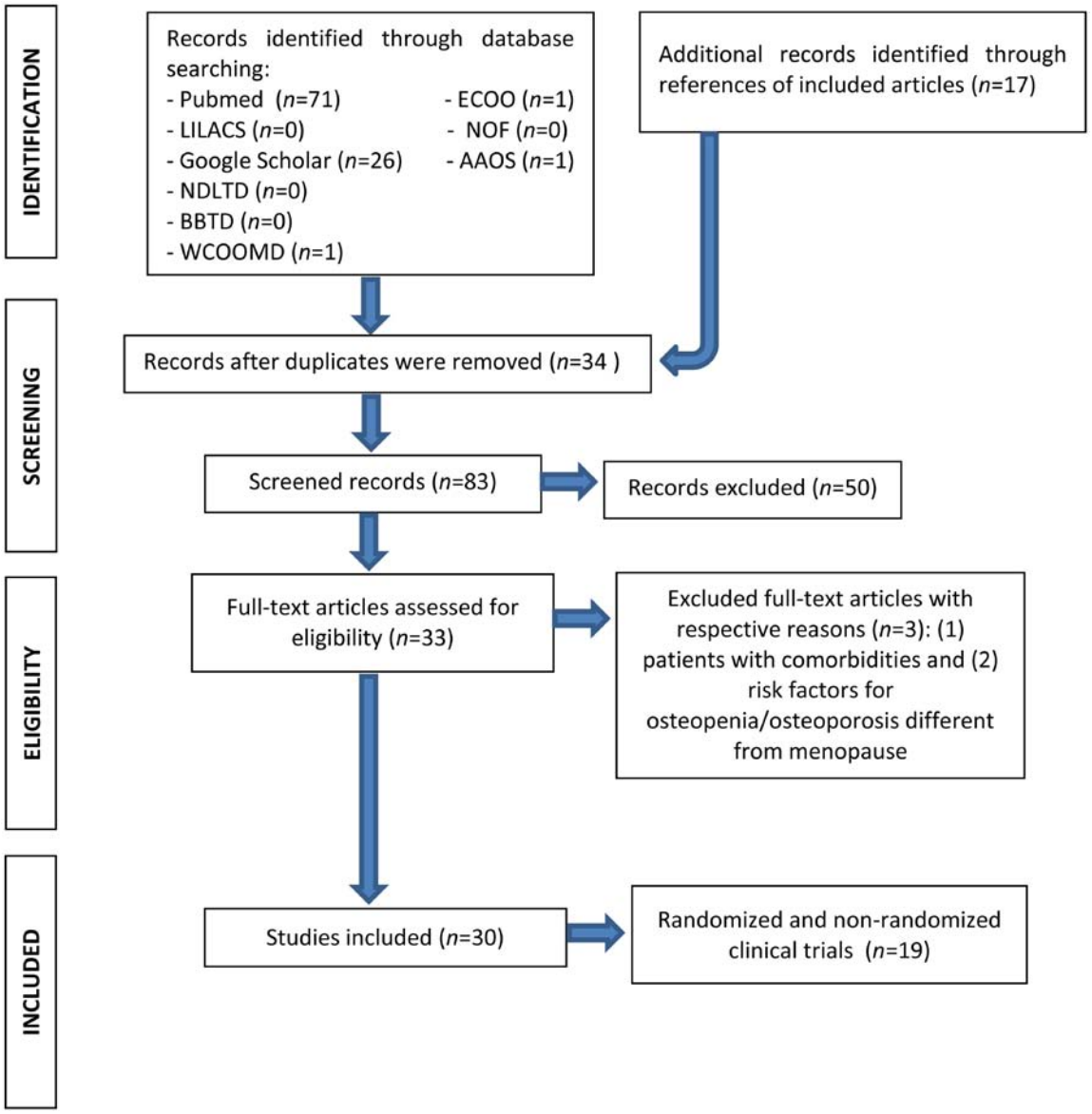

Figure 1. Diagram for study selection as applied in the current systematic review.

of lesser magnitude or to atypical fractures. It is a subclinical condition until complicated with bone fracture [2] [4].

3.2. Epidemiology

Women in their 6th decade of life present a 40% risk of experiencing an osteoporotic fracture, with the vertebrae being the most commonly affected bones. The latter type of fracture is associated with the following rates: 1) two-thirds occur in women >75 years of age, 2) there is a 5-fold increased risk for additional vertebral fractures, and 3) there is 2- to 3-fold increased risk for hip, proximal femur or distal forearm fractures [3]. Despite their greater frequency, vertebral fractures can be asymptomatic [1] [7]. Hip fractures result in greater morbidity, mortality, and costs than all other osteoporotic fracture types combined, as 60%

of patients do not regain their pre-fracture independence [1] [3].

3.3. Radiological Diagnosis

DXA of the total hip, femoral neck, or lumbar spine is considered the gold standard for osteoporosis diagnosis, therapeutic follow-up, and therapeutic change assessment [3]. Known limitations of this technique are:

- Poor precision for changes of <3% to 6% and <2% to 4% in BMD of hip and spine, respectively [3].
- Measurement of crystalized inorganic mineral matrix density, disregarding osseous connective tissue (collagen fibers, osteocalcin, and other non-collagen proteins).

Based on this limitation, one can suppose that a T-score increase might not forcibly reflect a clinically significant bone microarchitectural improvement. In fact, even when BMD measurements have not significantly increased, fracture risk can decrease disproportionately, suggesting that other factors of bone strength different than the crystalized inorganic mineral matrix might play a role [3] [4].

3.4. Laboratory Diagnosis

Even though biochemical markers of bone turnover (s-CTx, urinary N-telopeptide, propeptide type 1 procollagen, bone-specific alkaline phosphatase, and osteocalcin) are not recommended for postmenopausal osteoporosis diagnosis, they can be useful in predicting rapidity of bone loss, as a tool for estimating the magnitude of BMD post-therapeutic increases and to point out the timing for medication resumption during a "bisphosphonates holiday" (see further) [3].

3.5. Pharmacological Prophylaxis

Indications for postmenopausal osteoporosis prophylaxis are [3]:

- primary fracture prevention: 1) T-score ≤2.5 at the femoral neck and total hip and 2) osteopenia (T-score between −1.0 and −2.5) at the femoral neck or hip *plus* either 10-year hip fracture risk ≥3% or a 10-year major osteoporosis-related fracture risk ≥20% (based on FRAX model*).
- secondary fracture prevention: 1) fracture of hip or vertebra (regardless of BMD) and 2) fracture of the proximal humerus, pelvis, or distal forearm under a T-score between −1.0 and −2.5.

Therapeutic classes and drugs approved for the prevention and/or treatment of postmenopausal osteoporosis are bisphosphonates, selective estrogen-receptor modulators (e.g., raloxifene), human monoclonal antibodies to sclerotin (e.g., romosozumab), strontium ranelate, recombinant parathyroid hormone (PTH analogs) (e.g., teriparatide), tissue-selective estrogen complex, receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitors (denosumab), calcitonin

*FRAX model is an assessment tool for estimating 10-year bone fracture risk in treatment-naïve individuals, based on parameters such as a history of fractures, BMD, and parental history.

and estrogen therapy [1]. Parameters for the best modality choice are fracture prevention efficacy, site of optimal fracture prevention (spine vs. hip), and the onset of effect [3]. Assuming that postmenopausal osteoporosis is an uncurable and inexorably evolving condition, treatment can never be stopped (even though "holidays" can be considered) and the achieved benefits can only be maintained as long as the therapy endures [3].

4. Bisphosphonates Class

4.1. Pharmacology

Bisphosphonates represent a class of drugs that increases bone strength by inhibiting tissue resorption during its physiological remodeling process. They are mainly indicated as first-line therapy for postmenopausal osteoporosis prevention and management [4]. The following mechanisms of action are described for this class of drugs [1] [2] [3] [4] [5].

- inhibition of osteocyte farnesyl diphosphate synthase (mevalonate pathway).

Osteocyte enzyme farnesyl diphosphate synthase (FDS) yields farnesyl pyrophosphate, which promotes prenylation (addition of hydrophobic molecules) of small GTPase signaling proteins, a phenomenon involved in osteoclast activation. By inhibiting FDS, bisphosphonates stop the prenylation of these GTPase signaling proteins, either preventing osteoclasts activation or leading to cell apoptosis [8].

- hydroxyapatite crystals' solubility decrease.

Bisphosphonates are chemically composed of two phosphate groups that allow binding to hydroxyapatite crystals composing the crystalized inorganic mineral matrix, decreasing the solubility of the latter and slowing down bone resorption.

- proosteoclasts signaling downregulation.

Reduced hydroxyapatite crystals solubility, as described above, prevents osteocyte cytokines from reaching proosteoclasts, stopping their differentiation into osteoclasts.

Bisphosphonates' nadir effect on osteoclast activity is expected to be attained within 3 months of therapy and will inevitably lead to inhibition of osteoblasts activation and therefore bone remodeling. Nevertheless, within 3 additional months, an equilibrium is expected to take place, leading to a net result of either BMD preservation or gain. After this term, a clinically significant reduction of fracture risk is expected to be reached [4]. Bisphosphonates take longer to bring BMD and fracture risk to baseline levels than non-bisphosphonates, but their effect stands longer after interruption (this characteristic can be advantageous during the so-called "bisphosphonates holiday") [3].

4.2. Safety

Bisphosphonates' immediate side effects are limited to the digestive system (esophageal irritation, dysphagia, and gastrointestinal symptoms) [4]. The drugs of this class are potentially nephrotoxic and therefore are contraindicated in pa-

tients with a glomerular filtration rate <30 mL/min. Inhibition of osteoclast activity caused by bisphosphonates is expected to lower calcium efflux to the blood, leading to one-week duration hypocalcemia, which is clinically unimportant in most cases. Nevertheless, bisphosphonates are contraindicated in patients with preexisting hypocalcemia or under other associated risky conditions, such as hypoparathyroidism [4] [5]. Prolonged suppression of bone resorption and its subsequent formation can lead to tissue microdamage accumulation and bone frailty [4].

Bisphosphonates-related osteonecrosis of the jaw is a side effect that belongs to the broader group of medication-related osteonecrosis of the jaw (MRONJ) and it can occur under the following circumstances: 1) cancer patients undergoing odontological procedures reaching periodontal tissues; 2) poor fitting of dental appliances or poor oral health; 3) parenteral bisphosphonates used for prevention of bone complications due to cancer; 4) bisphosphonates use for longer than 3 to 5 years; 5) concomitant diabetes mellitus or corticosteroids use. It is not possible to grade individual risk for this side effect. There are no reports of such an adverse event during clinical trials [1] [3] [4]. Atypical femur fractures are a complication associated with bilateral chronic bone stress and triggered by minor trauma. They occur under the following circumstances, when associated with bisphosphonates use: a) patients with Asian ethnicity; b) coexistence with lateral bowing of the femur, autoimmune diseases, corticosteroids use; c) bisphosphonates use for longer than 3 years. Their rate declines with the discontinuation of the substances of the class [3]. The risk for jaw osteonecrosis as well as atypical femur fractures is expected to decrease during the "bisphosphonates holiday".

4.3. Usage

"Bisphosphonates holiday" is feasible, based on the premise that these drugs are retained by the skeleton, extending anti-fracture benefits. The "holiday" can be considered either after 5 years or after 10 years of oral therapy (if T score ≤ −2.5 and/or there is a report of a recent fracture) of oral therapy. The effects of a "bisphosphonates holiday" on the risk of bone fracture are unknown [3] [4]. Concomitant supplementation with vitamin D and calcium is recommended, not only for bone health in general but also to reduce the risk of hypocalcemia [5].

5. Ibandronate

5.1. Pharmacology

Ibandronate is a nitrogen-containing bisphosphonate with enough potency and skeletal binding capacity to enable a once-monthly interval dosage [1] [7]. Its pharmacological effect is a cumulative-dependent decrease of bone turnover biochemical markers, as it maintains tissue quality, strength, and architecture, without affecting mineralization and repair properties [1]. An ibandronate struc-

tural formula is depicted in Figure 2.

Clinical effects associated with ibandronate use are: 1) increased lumbar spine and proximal femur BMD and mechanical strength, 2) sustained decrease of bone absorption biochemical markers after three months, and 3) risk reduction of osteoporotic vertebral fractures. Ibandronate consolidated pharmacokinetics parameters are listed below [1] [5]:

- bioavailability: 0.63% (relative to IV administration; reduced by ~90% with food).
- intestinal absorption: impaired by food and beverages (other than plain water).
- Cmax: 49.7 ng/mL (10% of this value is attained after 8 h, due to bone binding, when a slower clearance phase starts as ibandronate returns to the blood to ongoing renal excretion).
- tmax: 0.5 to 2 h.
- bone sequestration rate: 40% to 50% (the remainder being excreted in the urine 24 hours after administration).
- Vd: 90 to 160 L.
- protein binding: 84% to 86% (steady under clinically relevant blood concentration).
- increases in plasma concentration (dose >50 mg): disproportionally greater than dosing.
- half-life: ~1.3 h.
- terminal half-life: 10 to 72 h.
- estimated bone half-life: years.
- renal clearance: 56.9 mL/min (urine excretion linearly related to creatinine clearance).
- fecal excretion: trace amounts.

Ibandronate is not biotransformed [1].

5.2. Indication

In addition to prevention and first-line treatment of postmenopausal osteoporosis, ibandronate is used off-label for the reduction of skeletal events during glucocorticoid chronic use and malignancy hypercalcemia prevention (pathological bone resorption due to bone metastases) [5] [9].

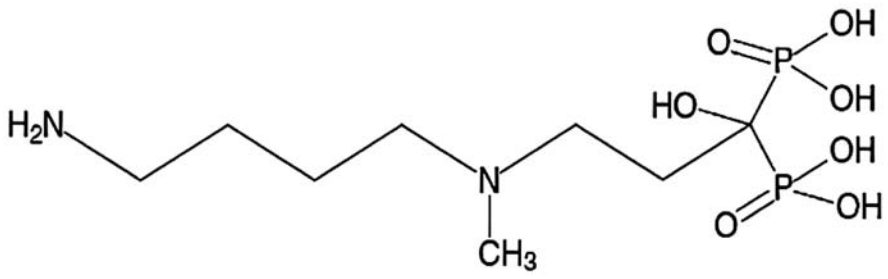

Figure 2. Ibandronate structural formula (adapted from [7]).

5.3. Adherence

Postmenopausal osteoporosis is more common among elderly women and consequently, there is a higher likelihood of concurrent diseases requiring concomitant medication, increasing interactions risk as well as predisposing to adherence and safety concerns. The once-monthly dosage interval, feasible with ibandronate, could minimize these issues among treated patients [7].

5.4. Safety

The most commonly reported adverse reactions with ibandronate are: 1) upper gastrointestinal ulcerations, 2) flu-like symptoms, 3) musculoskeletal symptoms, and 4) nervous system disorders [1] [7]. Immediate adverse events associated with ibandronate share the following characteristics: a) mild to moderate in intensity, b) last 1 to 4 days, and c) did not lead to withdrawal during clinical trials [1]. Once-monthly interval dosage can minimize oesophageal irritation, given the reduced administration frequency [7]. Ibandronate is contraindicated in the following circumstances: i) preexisting gastrointestinal symptoms and disorders (dysphagia, epigastralgia, gastroesophageal reflux disease, gastritis, hiatal hernia), ii) an inability to sit or stand upright for longer than 1 h after administration and iii) creatinine clearance <30 mL/min [1] [3] [4] [5]. No episodes of jaw osteonecrosis were reported with ibandronate [1]. No dose adjustment is necessary during hepatic failure or under a creatinine clearance >30 mL/min [1]. Intestinal absorption is impaired by multivalent cations such as calcium, aluminum, and iron. No pharmacokinetic interactions were demonstrated between ibandronate and other drugs commonly prescribed to postmenopausal women (e.g., tamoxifen and estrogen). Ibandronate interacts with bone-imaging agents used in bone scintigraphy [1] [5].

5.5. Dosage

A recommended regimen is 150 mg once monthly for 3 years [1]. Ibandronate should be taken after 6 hours of fasting (preferentially in the morning) and longer than 1 hour before a meal (with plain water and without any other medications). Patients should not lie down for 60 minutes afterward [1] [3] [5].

6. Cholecalciferol

6.1. Vitamin D Physiology

Cholecalciferol (vitamin D3) is the major form of vitamin D in nature. It is attainable from the following sources: 1) corneocyte membrane 7-dehydrocolesterol, destined for photobiological transformation; 2) regular diet (cod liver oil, mackerel, salmon); 3) as the major form of vitamin D in pharmacological supplements. It can be considered simultaneously as a pre-hormone and a vitamin. Whatever its origin, cholecalciferol is destined to be converted to 25-hydroxyvitamin-D (calcidiol) in the liver by the action of vitamin D-25-hydroxylase. 25-hydroxyvitamin-D is destined to be converted to the biologically active

1,25-dihydroxy vitamin D (calcitriol) by the action of renal vitamin D-1-alpha-hydroxylase. Calcitriol stimulates the synthesis of 25-hydroxyvitamin D-24-hydroxylase, an enzyme that catalyzes the former to inactive calcitroic acid in peripheral cells, the latter destined to be excreted in the bile. Cholecalciferol to calcidiol enzymatic transformation obeys first-order kinetics, *i.e.*, the conversion rate is proportional to the concentration of the former. Nevertheless, 1,25-dihydroxy vitamin D blood levels are strictly controlled through a balance of vitamin D-1-alpha-hydroxylase activity and 25-hydroxyvitamin D-24-hydroxylase catabolic rate in peripheral tissues [10]. On average, the skin releases 250 mcg of cholecalciferol daily, most of it destined either to be excreted in the bile or to be degraded to calcitroic acid, with only 2 mcg converted to bioavailable calcitriol. Physiological actions of calcitriol are: a) to facilitate the active absorption of calcium and phosphate in the small intestine and of calcium in the renal tubules to allow bone mineralization; b) to modulate parathyroid hormone secretion; c) to increase bone reabsorption of calcium and phosphate by increasing RANKL synthesis (a ligand to receptor activator of nuclear factor kappa-B), with subsequent nuclear factor kappa-light chain stimulation and proosteoclast to osteoclast differentiation (under hypocalcemia) [5] [10] [11].

If vitamin D is abruptly interrupted and there is no sun exposure, calcitriol blood levels would still be maintained by two subsequent mechanisms: a) routine calcidiol to calcitriol conversion, the former having a terminal half-life of 2 months; b) cholecalciferol muscle and fat-storage retrieval by the organism [10]. Assuming its biological origin, it is possible to predict the physiological availability of cholecalciferol according to the following factors: 1) skin weight (by inference 7-dehydrocholesterol quantity, inversely proportional to age); 2) skin integrity (the dermal structure is compromised by aging); 3) UVB exposure ("vitamin D winter", earth latitude, weather); 4) fish in the diet; 5) skin melanin quantity (a UVB absorbing molecule); 6) sunscreen use; 7) clothing; 8) glass shielding (a UVB absorbing material). Given the above factors, it is no wonder to verify that vitamin D deficiency is a highly prevalent condition in the western world and, by inference, bone metabolism complications associated with calcitriol decrease, especially among postmenopausal women [11].

6.2. Cholecalciferol Pharmacokinetics

Cholecalciferol absorption takes place in the small intestine, it is fat-dependent and occurs readily. From the former, it is transported inside chylomicrons via the lymphatic system into the bloodstream, and linked to vitamin D binding protein (DBP) thereon. Cholecalciferol consolidated pharmacokinetics parameters are listed below [3] [5] [10]:

- time to conversion to 25-hydroxyvitamin-D3: 10 to 24 hours.
- protein binding rate: 50% to 80%.
- circulating half-life: 2 days.
- functional half-life: 2 to 3 months (influenced by DBP concentration and genetic polymorphisms).

- minimum serum levels for optimal calcium absorption: 30 ng/mL.

Oral cholecalciferol increases intestinal calcium and phosphate absorption in the range of 10% - 15% to 30% - 40% and 60% - 80% rates, respectively [5]. Vitamin D3 pharmacokinetics is unaltered by ibandronate under single dosages of 24,000 IU and 150 mg, respectively [12].

6.3. Safety

Cholecalciferol side effects are generally associated with excessive doses and consist of hypercalcemia, nephrocalcinosis, osteoporosis, non-skeletal calcification, and pancreatitis [5]. According to the American Geriatric Society, 25-hydroxyvitamin D blood levels up to 100 ng/mL can be considered safe. Daily vitamin D dosage can be increased up to 10,000 IU in obese patients, due to fat distribution. Safety of doses ≥400 IU daily during pregnancy is not established. Maternal hypercalcemia may lead to supravalvular aortic stenosis syndrome and suppression of PTH release in the neonate. Excessive amounts of vitamin D in nursing mothers may result in hypercalcemia in infants [5].

6.4. Dosage

The Institutes of Medicine recommends 1500 to 2000 IU of vitamin D daily to treat and prevent postmenopausal osteoporosis [11]. Even though vitamin D and calcium supplementation are universally suggested, there is no consensus on the ideal daily regimens which vary from 600 IU to 1200 IU and 2000 to 2500 mg, respectively, depending on age and institutional recommendations. To attain calcidiol blood levels >30 ng/mL in vitamin D deficient adults in a 5 to 8 weeks term, vitamin D 50,000 IU once a week (or 7000 daily) regimen is suggested [3].

7. Rationale for Ibandronate and Cholecalciferol Combination

The rationale for ibandronate and cholecalciferol fixed-dose combination in the postmenopausal osteoporosis setting is supported by the following aspects.

7.1. Additive Effect

Postmenopausal osteoporosis presents a complex pathophysiology, hinting the indication for different therapeutic modalities. Ibandronate and cholecalciferol fixed-dose combination can be considered clinically feasible for the following reasons: 1) both ibandronate and vitamin D influence at least two important pathophysiological elements related to osteoporosis, *i.e.*, bone unbalanced resorption and low vitamin D availability, respectively; 2) both belong to first-line pharmacological classes recommended for this condition; 3) there is no know interaction between the two.

7.2. Synergistic Effect

Ibandronate decreases the uptake of calcium from bone into the blood, an effect potentially associated with hypocalcemia. By increasing intestinal and renal cal-

cium absorption, cholecalciferol could decrease this risk.

7.3. Therapeutic Adherence

Combining both substances in the same pharmaceutical formulation can simplify the daily medical routine, especially in the setting of a chronic incurable condition, as well as improve adherence.

8. Results

We retrieved a total of 10 general studies and 19 clinical trials on ibandronate and cholecalciferol (16 RCT and 3 non-RCT), the latter ones comprehending a total of 11,218 patients (no epidemiological studies, observational studies, systematic reviews, or meta-analyses were found). Reported research parameters were: 1) comparative tolerability in women previously using weekly bisphosphonates; 2) satisfaction or preference of women in transitioning from weekly bisphosphonate to the studied combination; 3) effect on bone microarchitecture in women with osteopenia; 4) 25-hydroxyvitamin D and bone markers levels; 5) comparative efficacy with weekly alendronate regarding the lumbar spine and total hip BMD; 6) regional distribution of lumbar vertebrae and hip BMD changes; 7) tolerability in general; 8) bone strength, bone metabolism and muscle strength; 9) prevention of bone loss; 10) BMD mantainence after 3 years and 5 years of use. Studies' conclusions reported the combination as a) effective, 8 trials; b) safe and effective, 2 trials; c) safe and non-inferior, 1 trial, d) well tolerated, preferred or satisfying, 4 trials; e) comparable or non-inferior, 2 trials; f) ineffective, 1 trial (2 of 4 endpoints). The studied combination was regarded as safe in 12 trials (non-comparative results, not informed or not applicable, 5 trials). Concentrations of ibandronate and vitamin D varied from 2.5 mg daily/20 mg to 150 mg monthly and 200 IU daily to 24,000 IU monthly, respectively. The findings related to the clinical trials are summarized in **Appendix**.

9. Discussion

Postmenopausal osteoporosis is a chronic and uncurable condition that might compromise all women after their reproductive years. This syndrome's complex pathophysiology makes a multi-target therapeutic approach warranted, with an association of drug combinations and lifestyle changes, as the best possible modality. Ibandronate and cholecalciferol had their individual roles on postomenopausal osteoporosis and osteopenia management already evidenced. Their combination in postmenopausal osteoporosis and osteopenia setting is bound to provide pharmacological additive and synergistic effects as well as comfort to the patient, consistently with the combination management recommended for the condition. One limitation of our study was the uneven regimens of ibandronate and vitamin D used in selected clinical trials. Nevertheless, Cho *et al*. and Yoon *et al*. studies regimens [13] [14] outstood for combining ibandronate and vitamin D, the latter under a 24,000 IU monthly dosage (consistently with therapeu-

tic adherence policies, as well as with the daily dosage range recommended for maintaining sufficient vitamin D levels - 800 to 1000 IU -, as detailed by a recent osteoporosis consensus [3]). Another limitation of our systematic review was the impossibility of providing an overall statistical expression to our findings due to the primary studies' methodological heterogeneity. Notwithstanding, we consider that the grouped analysis of retrieved publications, as well as the combination rationale detailed above, allows us to suggest considering the ibandronate and cholecalciferol combination for postmenopausal osteoporosis and osteopenia management.

10. Conclusion

Based on the results of analyzed clinical trials, we concluded that the combination of ibandronate and cholecalciferol for postmenopausal osteoporosis and osteopenia management is safe and feasible, as well as consistent with the pharmacological combination and adherence approach recommended for the condition.

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Conflicts of Interest

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

References

[1] Frampton, J.E. and Perry, C.M. (2008) Ibandronate: A Review of Its Use in the Management of Postmenopausal Osteoporosis. *Drugs*, **68**, 2683-2707. https://doi.org/10.2165/0003495-200868180-00011

[2] Hasan, W.N.W., Chin, K.Y., Jolly, J.J., *et al.* (2018) Identifying Potential Therapeutics for Osteoporosis by Exploiting the Relationship between Mevalonate Pathway and Bone Metabolism. *Endocrine, Metabolic and Immune Disorders—Drug Targets*, **18**, 450-457. https://doi.org/10.2174/1871530318666180423122409

[3] LeBoff, M.S., Greenspan, S.L., Insogna, K.L., *et al.* (2022) The Clinician's Guide to Prevention and Treatment of Osteoporosis. *Osteoporosis International*, **33**, 2049-2102. https://doi.org/10.1007/s00198-021-05900-y

[4] Maraka, S. and Kennel, K.A. (2015) Bisphosphonates for the Prevention and Treatment of Osteoporosis. *BMJ*, **351**, h3783. https://doi.org/10.1136/bmj.h3783

[5] pdr.net (2022) Ibandronate. https://www.pdr.net/drug-summary/Boniva-Injection-ibandronate-2109.3350

[6] Selçuk, A.A. (2019) A Guide for Systematic Reviews: PRISMA. *Turkish Archives of Otorhinolaryngology*, **57**, 57-58. https://doi.org/10.5152/tao.2019.4058

[7] Chesnut III, C.H. (2006) Treating Osteoporosis with Bisphosphonates and Addressing Adherence: A Review of Oral Ibandronate. *Drugs*, **66**, 1351-1359.

https://doi.org/10.2165/00003495-200666100-00004

[8] Ali, N., Jurczyluk, J., Shay, G., *et al*. (2015) A Highly Sensitive Prenylation Assay Reveals *in Vivo* Effects of Bisphosphonate Drug on the Rab Prenylome of Macrophages outside the Skeleton. *Small GTPases*, **6**, 202-211. https://doi.org/10.1080/21541248.2015.1085485

[9] drugbank.com (2022) Vitamin D3: Uses, Interactions, Mechanism of Action. https://go.drugbank.com/drugs/DB00169

[10] Vieth, R. (2020) Vitamin D Supplementation: Cholecalciferol, Calcifediol, and Calcitriol. *The European Journal of Clinical Nutrition*, **74**, 1493-1497. https://doi.org/10.1038/s41430-020-0697-1

[11] Holick, M.F. (2017) The Vitamin D Deficiency Pandemic: Approaches for Diagnosis, Treatment and Prevention. *Reviews in Endocrine and Metabolic Disorders*, **18**, 153-165. https://doi.org/10.1007/s11154-017-9424-1

[12] Jeon, J.-Y., Lee, S.Y., Im, Y.-J., *et al*. (2014) Comparison of the Pharmacokinetics, Safety, and Tolerability of Vitamin D3 in DP-R206 (150-mg Ibandronate/24,000-IU Vitamin D3 Tablet) and as Monotherapy (24,000 IU) in Healthy Male Korean Adults. *Clinical Therapeutics*, **36**, 48-57. https://doi.org/10.1016/j.clinthera.2013.12.001

[13] Cho, I.J., Chung, H.Y., Kim, S.W., *et al*. (2015) Efficacy of a Once-Monthly Pill Containing Ibandronate and Cholecalciferol on the Levels of 25-Hydroxyvitamin D and Bone Markers in Postmenopausal Women with Osteoporosis. *Endocrinology and Metabolism* (*Seoul*), **30**, 272-279. https://doi.org/10.3803/EnM.2015.30.3.272

[14] Yoon, S.H. (2017) A Monthly Combined Agent of Ibandronate and Cholecalciferol Is Effective in Bone Metabolism but Not in Muscle Strength and Bone Mineral Density in Korean Postmenopausal Women with Osteoporosis. *Maturitas*, **100**, 158. https://doi.org/10.1016/j.maturitas.2017.03.142

[15] Binkley, N., Silverman, S.L., Simonelli, C., *et al*. (2009) Monthly Ibandronate Suppresses Serum CTX-I within 3 Days and Maintains a Monthly Fluctuating Pattern of Suppression. *Osteoporosis International*, **20**, 1595-1601. https://doi.org/10.1007/s00198-008-0827-4

[16] Binkley, N., Martens, M.G., Silverman, S.L., *et al*. (2009) Improved GI Tolerability with Monthly Ibandronate in Women Previously Using Weekly Bisphosphonates. *Southern Medical Journal*, **102**, 486-492. https://doi.org/10.1097/SMJ.0b013e31819ed0dd

[17] Bock, O., Börst, H., Beller, G., *et al*. (2012) Impact of Oral Ibandronate 150 mg Once Monthly on Bone Structure and Density in Postmenopausal Osteoporosis or Osteopenia Derived from *in Vivo* μCT. *Bone*, **50**, 317-324. https://doi.org/10.1016/j.bone.2011.10.027

[18] Bonnick, S.L., Silverman, S., Tanner, S.B., *et al*. (2009) Patient Satisfaction in Postmenopausal Women Treated with a Weekly Bisphosphonate Transitioned to Once-Monthly Ibandronate. *Journal of Women's Health* (*Larchmt*), **18**, 935-943. https://doi.org/10.1089/jwh.2008.1064

[19] Chapurlat, R.D., Laroche, M., Thomas, T., *et al*. (2013) Effect of Oral Monthly Ibandronate on Bone Microarchitecture in Women with Osteopenia—A Randomized Placebo-Controlled Trial. *Osteoporosis International*, **24**, 311-320. https://doi.org/10.1007/s00198-012-1947-4

[20] Emkey, R., Koltun, W., Beusterien, K., *et al*. (2005) Patient Preference for Once-Monthly Ibandronate versus Once-Weekly Alendronate in a Randomized, Open-Label, Cross-Over Trial: The Boniva Alendronate Trial in Osteoporosis (BALTO).

Current Medical Research and Opinion, **21**, 1895-1903.
https://doi.org/10.1185/030079905X74862

[21] Emkey, R., Delmas, P.D., Bolognese, M., *et al*. (2009) Efficacy and Tolerability of Once-Monthly Oral Ibandronate (150 mg) and Once-Weekly Oral Alendronate (70 mg): Additional Results from the Monthly Oral Therapy with Ibandronate for Osteoporosis Intervention (MOTION) Study. *Clinical Therapeutics*, **31**, 751-761.
https://doi.org/10.1016/j.clinthera.2009.04.018

[22] Engelke, K., Fuerst, T., Enslin, M.B., *et al*. (2009) Regional Differences of Spinal BMD Changes after One Year Once-Monthly Ibandronate as Measured by 3D QCT. *Journal of Clinical Densitometry*, **12**, 120. https://doi.org/10.1016/j.jocd.2008.07.076

[23] Engelke, K., Fuerst, T., Dasic, G., *et al*. (2010) Regional Distribution of Spine and Hip QCT BMD Responses after One Year of Once-Monthly Ibandronate in Postmenopausal Osteoporosis. *Bone*, **46**, 1626-1632.
https://doi.org/10.1016/j.bone.2010.03.003

[24] Lewiecki, E.M., Keaveny, T.M., Kopperdahl, D.L., *et al*. (2009) Once-Monthly Oral Ibandronate Improves Biomechanical Determinants of Bone Strength in Women with Postmenopausal Osteoporosis. *The Journal of Clinical Endocrinology & Metabolism*, **94**, 171-180. https://doi.org/10.1210/jc.2008-1807

[25] McClung, M.R., Bolognese, M.A., Sedarati, F., *et al*. (2009) Efficacy and Safety of Monthly Oral Ibandronate in the Prevention of Postmenopausal Bone Loss. *Bone*, **44**, 418-422. https://doi.org/10.1016/j.bone.2008.09.011

[26] Miller, P.D., McClung, M.R., Macovei, L., *et al*. (2005) Monthly Oral Ibandronate Therapy in Postmenopausal Osteoporosis: 1-Year Results from the MOBILE Study. *Journal of Bone and Mineral Research*, **20**, 1315-1322.
https://doi.org/10.1359/JBMR.050313

[27] Miller, P.D., Epstein, S., Sedarati, F., *et al*. (2008) Once-Monthly Oral Ibandronate Compared with Weekly Oral Alendronate in Postmenopausal Osteoporosis: Results from the Head-to-Head MOTION Study. *Current Medical Research and Opinion*, **24**, 207-213. https://doi.org/10.1185/030079908X253889

[28] Miller, P.D., Recker, R.R., Reginster, J.-Y., *et al*. (2012) Efficacy of Monthly Oral Ibandronate Is Sustained over 5 Years: The MOBILE Long-Term Extension Study. *Osteoporosis International*, **23**, 1747-1756.
https://doi.org/10.1007/s00198-011-1773-0

[29] Nakamura, T., Mizunuma, H., Itabashi, A., *et al*. (2007) Monthly Oral Ibandronate Is Well Tolerated and Efficacious in Japanese Osteoporotic Subjects. *Journal of Bone and Mineral Research*, **22**, S333.

[30] Reginster, J.-Y., Adami, S., Lakatos, P., *et al*. (2006) Efficacy and Tolerability of Once-Monthly Oral Ibandronate in Postmenopausal Osteoporosis: 2 Year Results from the MOBILE Study. *Annals of Rheumatic Diseases*, **65**, 654-661.
https://doi.org/10.1136/ard.2005.044958

[31] Stakkestad, J.A., Lakatos, P., Lorenc, R., *et al*. (2008) Monthly Oral Ibandronate Is Effective and Well Tolerated after 3 Years: The MOBILE Long-Term Extension. *Clinical Rheumatology*, **27**, 955-960. https://doi.org/10.1007/s10067-007-0824-6

Acronyms

Cmax: maximal concentration; **CTx:** C-telopeptide of type 1 collagen; **BMD:** bone mineral density; **DBP:** vitamin D binding protein; **DXA:** bone densitometry; **FDS:** farnesyl diphosphate synthase; **FEA:** finite element analysis; **GI:** gastrointestinal; **HSA:** hip structural analysis; **NA:** not applicable; **NI:** not informed; **OPSAT-Q:** Osteoporosis Patient Satisfaction Questionnaire; **QCT:** quantitative computed tomography; **RANKL:** receptor activator of nuclear factor kappa-B ligand; **RCT:** randomized clinical trial; s**CTx:** serum C-telopeptide of type 1 collagen; **tmax:** maximal time; **Vd:** volume of distribution.

Appendix. Selected RCT and Non-RCT with the Combination of Ibandronate and Vitamin D in Osteoporosis and Osteopenia Management

AUTHORS	STUDY OBJECTIVES	REGIMENS	STUDY TYPE	*n*	RESULTS	SAFETY	CONCLUSION
Binkley 2009 (a) [15]	To assess serum CTX levels in postmenopausal women with osteoporosis after 3 days of therapy	Group A: ibandronate 150 mg once-monthly Group B: placebo Both regimens: (1) included vitamin D 400 IU daily and (2) lasted 6 months	Randomized double-blind	$n_A = 49$ $n_B = 17$	Median reductions of serum CTX-1 were: (1) Group A, 70.2% and (2) Group B, 6.0% ($p < 0.0001$) (levels remained consistently below baseline over 6 months)	Ibandronate was well tolerated	Serum CTX-1 was decreased in Group A and remained suppressed below baseline over 6 months
Binkley 2009 (b) [16]	To assess GI tolerability with once-monthly ibandronate in postmenopausal women previously using weekly bisphosphonates	Ibandronate 150 mg once-monthly plus vitamin D (dosage NI), for 6 months	Self-paired	89	Regarding once-monthly ibandronate: (1) >60% of patients reported an improvement in heartburn or acid reflux, (2) >70% reported improvements in stomach upset, and (3) of those patients who complained of stomach upset within 48 h of taking their last weekly bisphosphonate, >80% reported improved overall satisfaction (statistical significance NI for any of the above parameters)	The tested regimen was well tolerated	A majority of women who experienced GI tolerability issues with weekly bisphosphonates reported improvements after transitioning from a weekly bisphosphonate to the tested regimen
Bock 2012 [17]	To assess the impact of monthly ibandronate on bone structure and density in post-menopausal osteoporosis or osteopenia, derived from in vivo microCT	Group A: ibandronate 150 mg once-monthly Group B: placebo Both regimens: (1) included vitamin D 400 IU daily and (2) lasted 12 months	Randomized	$n_A = 36$ $n_B = 34$	Group A: (1) performed better than Group B ($p = 0.045$) (multiple regression analysis of primary endpoints) and (2) reduction in bone turnover ($p < 0.001$) Secondary endpoints (Group A): (1) greater increases in distal tibia cortical thickness, cortical density and total density ($p \leq 0.043$) and (2) greater increases of hip and lumbar DXA-BMD ($p \leq 0.017$)	NI	While there was a greater mineralization in Group A, this effect differed among body regions

Continued

Bonnick 2009 [18]	To assess postmenopausal women's satisfaction with a weekly bisphosphonate transitioned to once-monthly ibandronate in the setting of prevention and treatment of osteoporosis and osteopenia	Ibandronate 150 mg once-monthly plus vitamin D (dosage NI), for 6 months	Self-paired	1678	OPSAT-Q: (1) composite satisfaction score was changed ($p < 0.0001$) and (2) there was improvement in domain scores (convenience, quality of life and overall satisfaction) (all $p < 0.0001$)	Improvement in OPSAT-Q side effects domain score ($p = 0.02$)	Patients previously using weekly bisphosphonates reported improved satisfaction with the tested regimen
Chapurlat 2013 [19]	To assess the effect of once-monthly ibandronate on bone microarchitecture among women with osteopenia	Group A: ibandronate 150 mg once-monthly Group B: placebo Both regimens: (1) included vitamin D 400 IU daily and (2) lasted 24 months	Randomized double-blind	$n_A = 72$ $n_B = 77$	Tibial cortical volumetric BMD in group A was greater at 12 and 24 months (statistical significance NI), with better cortical thickness Areal BMD - group A in comparison to group B: (1) hip and spine was greater at 12 and 24 months ($p < 0.001$) and (2) radius was greater at 24 months ($p = 0.09$)	Most adverse events with group A regimen were the ones expected with bisphosphonates use in general and none were serious	Group A regimen improved tibial cortical volumetric BMD at 12 and 24 months, and preserved tibial cortical thickness
Cho 2015 [11]	To assess the efficacy of once-monthly ibandronate plus cholecalciferol on the levels of 25-hydroxyvitamin D and bone markers among postmenopausal women with osteoporosis	Group A: ibandronate 150 mg once-monthly Group B: ibandronate 150 mg once-monthly plus cholecalciferol 24,000 IU Both regimens for 16 weeks	Randomized double-blind	$n_A = 99$ $n_B = 102$	Group A in comparison to group B ($p < 0.001$) - serum levels: (1) vitamin D increased and (2) CTx decreased	Group A regimen was used without any adverse events	Group A regimen may be useful for the amelioration of vitamin D deficiency and decreasing serum levels of resorption markers in patients with postmenopausal osteoporosis

Continued

Emkey 2005 [20]	To assess the preference for once-monthly ibandronate or weekly alendronate among postmenopausal patients with osteoporosis	Sequence A: ibandronate followed by alendronate Sequence B: alendronate followed by ibandronate Both sequences: (1) ibandronate and alendronate under once-monthly 150 mg and weekly 70 mg regimens, respectively, (2) included vitamin D (dosage NI), and (3) had a 3 months duration each	Randomized, open-label and crossed-over	$n_A = 170$ $n_B = 172$	Patients showed superior preference rates for ibandronate ($p < 0.0001$)	Patients who preferred ibandronate chose "it is easier to tolerate side effects" in the questionnaire (statistical significance not calculated)	Significantly more women preferred once-monthly ibandronate than weekly alendronate
Emkey 2009 [21]	To assess the efficacy and tolerability of weekly alendronate versus once-monthly ibandronate among postmenopausal women with osteoporosis (posthoc analysis Miller 2008)	Group A: ibandronate and alendro-nate-matched placebo Group B: alendronate and ibandro-nate-matched placebo Both regimens: (1) 12 months duration, (2) ibandronate and alendronate under once-monthly 150 mg and weekly 70 mg regimens, respectively, and (3) included vitamin D 400 IU daily	Randomized double-blind	$n_A = 887$ $n_B = 873$	Groups A and B, respectively (statistical significance NI): (1) median changes in trough concentrations of sCTx, −75.5% and −81.2% and (2) percentage of responders (mean lumbar spine and hip BMD gains), 90% and 87.5%, and 92% and 90%	GI adverse events were reported in ≤30%	Group A regimen provided clinically comparable efficacy and and GI tolerability compared to group B

Continued

Engelke 2009 [22]	To assess the regional differences of lumbar vertebrae BMD changes among postmenopausal women with osteoporosis	Group A: ibandronate 150 mg once-monthly Group B: placebo Both regimens: (1) 12 months duration and (2) included vitamin D 400 IU daily	Randomized	$n_A = 41$ $n_B = 35$	Groups A and B % BMD changes, respectively ($p < 0.05$): (1) total vertebral body, 3.0 and −1.1, (2) vertebral midsection, 2.4 and −1.3, (3) trabecular total vertebral body, 1.2 and −2.8, (4) superior section of the anterior and middle trabecular vertebral body, 1.8 and −3.4 and (5) middle cortical and subcortical vertebral body, 3.5 and −0.3	NI	Group A regimen increased lumbar spine integral and trabecular BMD in comparison to group B
Engelke 2010 [23]	To assess the regional distribution of hip QCT BMD with once-monthly ibandronate among postmenopausal women with osteoporosis (posthoc analysis of Lewiecki 2009)	Group A: ibandronate 150 mg once-monthly Group B: placebo Both regimens: (1) 12 months duration and (2) included vitamin D 400 IU daily	Randomized double-blind	$n_A = 47$ $n_B = 46$	Group A BMD increases in comparison to group B: (1) vertebral superior and inferior trabecular and cortical midsection ($p = 0.032$, 0.055 and 0.014, respectively), (2) total hip (trabecular, cortical and subcortical) ($p = 0.005$, 0.047 and 0.009, respectively), (3) trochanter (trabecular and cortical) ($p = 0.007$ and 0.01, respectively) and (4) trabecular femoral neck ($p = 0.02$)	NA	Group A regimen provided improved vertebral, total hip, trochanter, and femoral neck QCT BMD, in comparison to group B
Lewiecki 2009 [24]	To assess the biomechanical determinants of bone strength among postmenopausal women with osteoporosis under ibandronate	Group A: ibandronate 150 mg once-monthly Group B: placebo Both regimens: (1) 12 months duration and (2) included vitamin D 400 IU daily	Randomized double-blind	$n_A = 47$ $n_B = 46$	Group A had increased, relatively to group B: (1) total hip QCT BMD ($p = 0.005$), (2) DXA areal BMD ($p = 0.003$), (3) FEA-derived hip strength to density ratio ($p < 0.001$), (4) femoral, peripheral, and trabecular strength ($p = 0.001$, 0.011, and 0.003, respectively), (5) vertebral, peripheral, and trabecular strength ($p = 0.001$, 0.001, and 0.023, respectively), (6) anteroposterior bending stiffness ($p = 0.001$) and (7) HSA-estimated femoral narrow neck cross-sectional area and outer diameter ($p = 0.003$, and 0.049, respectively)	NI	Hip and spine BMD and strength, both improved with group A regimen in comparison to group B

Continued

					Group A showed relatively to group B		
McClung 2009 [25]	To assess the prevention of bone loss with ibandronate among postmenopausal women	Group A: ibandronate 150 mg once-monthly Group B: placebo Both regimens: (1) 12 months duration and (2) included vitamin D 400 IU daily	Randomized double-blind	$n_A = 77$ $n_B = 83$	At 3 months - median sCTx reduction, respectively: >55% vs. ~4% (statistical significance NI)	At 12 months: (1) larger increases in lumbar spine BMD ($p < 0.0001$) and (2) lumbar spine BMD change of 0% vs. 38.6%, respectively (statistical significance NI)	Both group's regimens were well tolerated	Group A regimen prevented further bone loss in postmenopausal women with preexisting low bone mass
Miller 2005 [26]	To assess a once-monthly ibandronate regimen in postmenopausal osteoporosis	Group A: 2.5 mg daily Group B: 50 mg in two consecutive days (monthly) Group C: 100 mg monthly Group D: 150 mg monthly All regimens: (1) 12 months duration and (2) included vitamin D 400 IU daily	Randomized double-blind	$n_A = 402$ $n_B = 404$ $n_C = 402$ $n_D = 401$	Lumbar BMD: (1) increased in all groups (no statistically significant difference), (2) groups B and C regimens were noninferior to group A regimen and (3) group D regimen was superior to group A regimen ($p = 0.002$) Hip BMD gains were superior in groups C and D regimens in comparison with group A regimen ($p < 0.001$) Serum levels of C-telopeptide: decreased in all groups The proportion of women who achieved predefined threshold levels for BMD % change from baseline (groups C and D): 6% and 3% for lumbar spine and total hip, respectively (statistical significance NI)		All group's regimens were similarly well tolerated	Groups B, C and, D regimens were at least as effective as group A regimen

Continued

Miller 2008 [27]	To assess the non-inferiority of once-monthly ibandronate comparatively to weekly alendronate regarding the lumbar spine and total hip BMD in postmenopausal osteoporosis	Group A: ibandronate 150 mg once-monthly Group B: alendronate 70 mg weekly Both regimens: (1) 12 months duration and (2) included vitamin D 400 IU daily	Randomized double-blind	n_A = 887 n_B = 873	BMD increased similarly in both groups (statistical significance for magnitude increase NI), meeting non-inferiority criteria of group A regimen relative to group B regimen	Both regimens were well tolerated	Group A regimen was comparable to group B regimen at increasing lumbar spine and total hip BMD
Miller 2012 [28]	To assess the efficacy of monthly ibandronate in sustaining BMD after 5 years (an extension of Reginster 2006)	Group A: 100 mg monthly Group B: 150 mg monthly Both regimens: (1) 3 years duration (plus the previous 2 years from Reginster 2006), (2) included vitamin D 400 IU daily, and (3) maintained women who showed ≥75% adherence to protocol in Reginster 2006 (Reginster 2006 groups A and B patients were reallocated or randomized to Miller 2012 groups A and B, the former ones being extinguished)	Randomized double-blind	n_A = 358 n_B = 361	Relatively to Reginster 2006 results (statistical differences were not calculated): (1) groups A and B showed 8.2% and 8.4% increase in lumbar spine BMD, respectively, (2) 698 out of 719 patients showed maintenance of proximal femur BMD gains and (3) markers of bone metabolism were stable	There were no tolerability concerns	Groups A and B regimens were both effective and well tolerated for up to 5 years in postmenopausal osteoporosis
Nakamura 2007 [29]	To assess if once-monthly ibandronate is well tolerated and efficacious in Japanese osteoporotic women	Group A: placebo Group B: 20 mg Group C: 50 mg Group D: 100 mg Group E: 150 mg (groups B to E: ibandronate) All regimens: (1) 4 months duration and (2) included vitamin D 200 IU daily	Randomized double-blind	n_A = 28 n_B = 27 n_C = 27 n_D = 26 n_E = 26	Median reductions in urinary CTx from baseline - groups A, B, C, D, and E, respectively: (1) 28.9%, (2) 35.7%, (3) 43.0%, (4) 70.9% and (5) 81.7% Increases in lumbar spine BMD for groups A, B, C, D, and E, respectively: (1) 0.7%, (2) 1.4%, (3) 3.1%, (4) 4.0% and (5) 3.2% (statistical significance NI for none of the above endpoints)	No serious drug-related adverse events were reported	Monthly ibandronate reduces bone turnover and increases lumbar spine BMD in Japanese women with osteoporosis

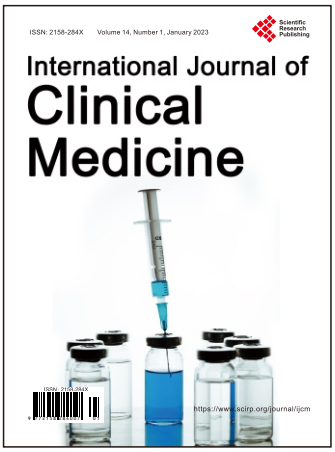
Continued

Reginster 2006 [30]	To assess the efficacy and tolerability of once-monthly ibandronate in postmenopausal osteoporosis (a continuation of Miller 2005 study)	Group A: 2.5 mg daily Group B: 50 mg in two consecutive days (monthly) Group C: 100 mg monthly Group D: 150 mg monthly All regimens: (1) 24 months duration and (2) included vitamin D 400 IU daily	Randomized double-blind	$n_A = 402$ $n_B = 404$ $n_C = 402$ $n_D = 401$	Lumbar, total hip, and femoral neck BMD increased in all groups (statistically significant difference between groups A and D regimens - $p < 0.001$ and <0.05 - for lumbar and total hip/femoral neck BMD, respectively) sCTx levels: (1) decrease observed after 3 months and sustained up to 24 months in all groups, (2) percentage of patients with a >50% decrease in sCTx from baseline was greater in group D relative to the other groups ($p = 0.002$) and (3) a greater proportion of patients presented sCTx decrease with group D regimen in comparison to group A regimen ($p = 0.006$)	All group's regimens were well tolerated	Groups B, C, and D regimens were at least as effective and well tolerated as group A regimen. Once-monthly administration may improve adherence, thereby optimizing outcomes
Stakkestad 2008 [31]	To assess the efficacy of monthly ibandronate in sustaining BMD improvement after 3 years (an extension of Reginster 2006)	Group A: 100 mg monthly Group B: 150 mg monthly Both regimens: (1) 1-year duration (plus the previous 2 years from Reginster 2006), (2) included vitamin D 400 IU daily, and (3) maintained the women who completed Reginster 2006 (Reginster 2006 groups A and B patients were reallocated or randomized to Stakkestad 2008 groups A and B, the former ones being extinguished)	Randomized double-blind	$n_A = 359$ $n_B = 360$	Relatively to Reginster 2006 for groups A and B, respectively (statistical significance NI): (1) mean lumbar spine BMD increased a further 1.1% and 1.5%, and (2) total hip BMD changed −0.08% and 0.3% Considering a total of 3 years of treatment (Reginster 2006 followed by Stakkestad 2008) for groups A and B, there were: (1) 6.4% and 7.6% increases in lumbar spine BMD, respectively ($p < 0.0001$), (2) 3.4% and 4.1% increases in total hip BMD, respectively ($p < 0.0001$) and (3) sCTx decreased for both groups ($p < 0.001$)	Groups A and B regimens were well tolerated	Group B regimen is an effective and well-tolerated long-term treatment for postmenopausal osteoporosis, with consistent improvement in BMD and bone turnover during 3 years of continuous treatment

Continued

Yoon 2017 [14]	To assess the effects of a combination of ibandronate and cholecalciferol in bone metabolism, muscle strength and BMD in postmenopausal Korean women with osteoporosis	Once-monthly ibandronate 150 mg plus cholecalciferol 24,000 IU for 6 months	Self-paired	62	The following endpoints showed statistically significant changes (serum): (1) 25-hydroxyvitamin D ($p < 0.01$), (2) CTx ($p = 0.03$), and (3) PTH ($p = 0.03$) The following endpoints showed no statistically significant changes: (1) handgrip strength and (2) lumbar and femoral neck BMD	NI	The tested regimen was effective in improving 25-hydroxyvitam in D serum levels and bone metabolism, however, there was no improvement of muscle strength and BMD

CTx: C-telopeptide of type 1 collagen; DXA: bone densitometry; FEA: finite element analysis; GI: gastrointestinal; HSA: hip structural analysis; NA: not applicable; NI: not informed; OPSAT-Q: Osteoporosis Patient Satisfaction Questionnaire; QCT: quantitative computed tomography; RCT: randomized clinical trial; sCTx: serum C-telopeptide of type 1 collagen.



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