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Comparing Volumetric Dimensional Stability and Accuracy of Newly Formulated Polyvinyl Siloxanether, Polyvinyl Siloxane and Polyether Impression Materials Using Micro-Computed Tomography

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ABSTRACT

Objective: The purpose of this study was to compare volumetric dimensional accuracy and stability of polyvinylsiloxane, polyether and new formulated polyvinylsiloxanether impression materials by using micro-computed tomography.

Methods: A total of 42 impressions were made of stainless steel metal dyes. Polyvinylsiloxane, Polyether and Polyvinylsiloxanether impressions were taken for volumetric dimensional accuracy and stability to measure by Micro-computed tomography (µCT). Impression materials were measured for dimensional stability after the impression was taken, 24 hours later and 144 hours later. For dimensional accuracy 21 impressions and 21 stone models of these impressions were measured. One-way analysis of variance was be used to test for statistically significant difference within groups and Tukey's test was be used to test for across groups with a significance value of $p < 0.05$.

Results: After polymerization, although polyether impression negative was shown to have the highest volumetric expansion, the highest shrinkage was observed in the same group after pouring to dental stone. Stone model of the polyether was observed as the most accurate value of volume in comparison to the master model. The lowest volumetric dimensional change was observed in polyvinylsiloxanether at day 1 (-0.004±0.001%) and the highest change was observed in polyether at day 7 (-0.052±0.004%).

Conclusion: From the standpoint of volumetric accuracy and stability, all three elastomeric impressions are acceptable and µCT is a useful tool for assesments of volumetric dimensional changes.

Keywords: Volumetric dimensional accuracy and stability, Micro CT, polyvinylsiloxanether

1.INTRODUCTION

Elastomeric dental impression materials have been used for several years in the field of dentistry to reproduce oral environment details and to fabricate an accurate fixed and removable prosthesis (1, 2).

An accurate impression is the first and a crucial step in the process of fabricating indirect dental restoration (3). The dimensional stability and accuracy of polyvinyl siloxane and polyether are well documented in the existing literature (1, 4-7). Studies show that these elastomeric impression materials have high precision due to their improved properties (8-10).

Currently, a novel impression material, named as a vinyl siloxanether by the manufacturer, has been introduced to the market. The manufacturer argues that this material has excellent mechanical and flow characteristics, along with good wetting properties in the unset and set condition (11). One of the novelties introduced by this paper is to establish the accuracy of the new formulated vinyl siloxanether impression material, which, to our knowledge, has not yet been explored by the existing literature (12).

Polyether and impression materials are dimensionally accurate for 7 to 14 days (10-15). There are several studies about dimensional changes of impression materials; however, it is difficult to compare and analyze these studies due to differences in experimental methods (16-23). Assessments of dimensional accuracy and stability are essentially made by tophometric and photogrammetric measurements (24-26). Microscopes, laser scanners, coordinate measuring systems and X-ray micro-computed tomography (µCT) are the common devices for dimensional accuracy and stability measurements (17, 27-32).

Among these devices, µCT is superior due to its non-invasive 3 dimensional volumetric measuring feature. Micro computed tomography (µCT) scans three-dimensionally (3D) image dental models and volumetrically compare impressions. 3D structures of materials can be created with high quality resolution. The working principle of the µCT device is based on X-rays passing through the material and collected by a detector and repeated slice by slice along the length of the material. This two-dimensional (2D) data are processed and 3D reconstruction of the images is created (33-36).

Significant developments in both hardware and software decreased slice thickness from conventional CT changes to micrometers and nanometers (37). µCT has been widely used in almost all kind of biomedical research. There are

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many studies for structure and macro morphology of bone, tooth and materials. On the other hand, a systematic research of µCTs ability to accurately show the volume of polymers, restoratives or tooth structures has not yet been demonstrated (38,39). This study addresses this gap in the literature.

Measurements can be examined from impression surface or stone models (33-35). Measuring impressions may be advantageous, as it allows for a more thorough and scientifically correct examination, by restricting the materials involved and demonstrating the interactions. On the other hand, stone model measurements are more aligned with actual clinical and laboratory practice, despite the fact that they complicate the experimental procedure (33-37). The disadvantage of µCT scanning is the expense of the equipment and the time taken to acquire the image (34).

In this study, a µCT-based method to measure volumetric dimensional accuracy and stability of elastomeric impressions materials is presented. To the best of found knowledge, no reports have been published on the method of direct measurements of elastomeric impression materials and therefore the comparison between the impression volume and its stone model. Linear dimensional changes of impression materials are well documented. But there are few studies about volumetric dimensional changes of impression materials and none of them is a direct method.

The purpose of this study therefore is to assess the volumetric dimensional accuracy and stability of the newly formulated PVSE impression material by using µCT in comparison to PE and PVS impression materials. The primary null hypothesis was that there would be no differences in the dimensional accuracy and stability among 3 impression systems.

2.METHODS

2.1. Study Design

An aluminum (7075, Referans Metal) master model representing a single die was prepared according to µCT scanning requirements (Fig. 1). Standard master model with stainless steel is fabricated having one tapered abutment with a base milled on computer numerically controlled (CNS) milling machine. According to µCT scanning requirements abutment had a volume of 18.42 mm^3 and a circular plate with a 3 mm of height and 15 mm of diameter. A special tray from PMMA (polymethyl metacrylate) was made for the study. In order to achieve precision, impression thickness is important and it is necessary to avoid a thin impression layer. The individual tray has a 4 mm equivalent space around the master model (40).

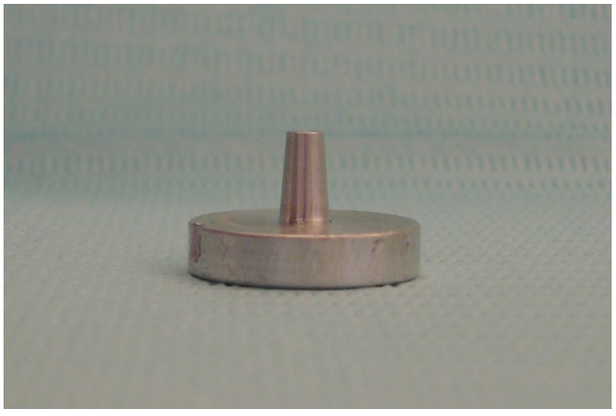

Figure 1. *Aluminum master model*

Impressions were made by perforated PMMA custom tray with a dental surveyor for insertion path. In this study a total of three elastomeric impression materials used: polyether (PE) (Impregum Penta Soft Quick, 3M ESPE; USA), poly vinylsiloxane (PVS) (Virtual Monophase, Ivoclar Vivadent AG, Lichtenstein), vinyl siloxanether, (PVSE) (EXA'lence 370, GC, USA). The impressions were stored under the manufacturer's recommended conditions in a sealed bag.

A total of 60 impressions were made with 10 impressions in each group. The tray adhesive supplied by the manufacturer was evenly applied over the inner surface of the tray. Tray adhesive was applied to the impression surface of the PMMA tray and allowed to dry for 5 minutes before loading the tray. Polyether and polyvinyl siloxanether material was mixed using automix mixing unit (Pentamix 3; 3M ESPE, USA) and the material was loaded into tray for monophase impression technique. Polyvinyl siloxane material was mixed and dispensed through an auto mixing system (Dispenser Gun, Coltène / Whaledent AG, Switzerland) loaded into tray for monophase impression technique. To achieve a homogenous mix, first 2 cm of each of the impression materials were not used. The impression material was then allowed to set as the manufacturer's recommended setting time. After the impression material had set tray was gently removed. Impressions were checked for voids and inaccuracies and were discarded when not found satisfactory.

The impression making steps of various study groups were as follows:

Study Group I: To assess the dimensional accuracy, 30 of the impressions were stored at room temperature for half an hour before pouring with gypsum product (Glaston 3000, Dentsply, USA). To standardize the effect of the setting expansion of the improved stone, the powder was accurately weighed and the water was dispensed using a graduated cylinder in a ratio of 100 gm/20ml in a mixing bowl. The impression was poured and was allowed to set for 60 minutes before being separated. Thirty stone models were measured.

Study Group II: Thirty of the impressions stored for dimensional stability measurements without pouring gypsum. According to the µCT configuration, ten samples from each of the three impression materials were measured for dimensional

stability, and measurements were taken in the following order: immediately after the impression was made, 24 hours later and 144 hours later. All the impressions were stored in vacuum bags.

µCT device (Skyscan 1174, Skyscan, Belgium) was used to measure volumetric dimensions of the master model, impressions and dental stones. During acquisition, more than 300 hundred 2-D images were saved through 360° of rotation in digital format. To create a 3-D rendering, the transformed data were stored as projections into new 2D images with a slice thickness of 21.0 µm. The 3-D image was achieved by juxtaposition of 2-D images of adjacent slices.

Figure 2. *Scanning image of impression*

A data collection for reconstruction has shadow image acquisitions from 200 to 400 views with object rotation of more than 360 degrees. For the reconstruction of complete 3-D objects, a serial reconstruction of axial cross-sections can be used. After the serial reconstruction, axial cross-sections of the object can be displayed on the screen. From the reconstruction results, it is possible to reconstruct 3-D objects with the use of an external program (Mimics, Materialise, Belgium). Three hundred seventy one slices were taken for each measurement (Fig. 2).

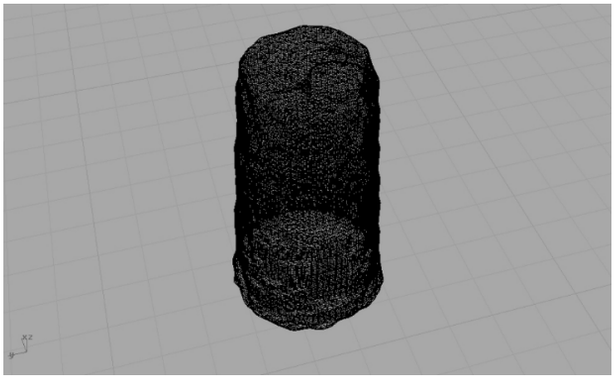

Figure 3. *STL data that obtained from TIFF images*

The raw TIFF (Tagged Image File Format) data that were obtained from measured models were converted to STL (Stereo Lithography) format to reproduce 3D digital models by using Mimics software (Fig 3). Total volumes of the digital models were calculated using 3D Studio Max (Autodesk Inc., USA) (Fig4). The percentage changes in volumes were calculated using the measurement data that was obtained.

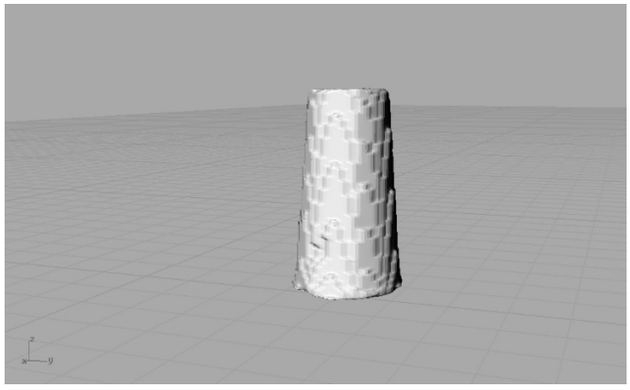

Figure 4. *3D rendered images for calculating volumetric changes*

2.2. Statistical Analysis

One-way analysis of variance (ANOVA) was used to test for statistically significant difference within groups and Univariate ANOVA and Tukey test were used to test across groups with a significance value of $p < 0.05$.

3.RESULTS

3.1.Measurement dimensional accuracy

The measurements obtained from directly scanning the surface of the master model, impression surface and stone model of three impression materials are shown on Table 1. According to µCT scans data, the master model had a total volume of 18.42 mm^3. All impressions were expanded in volume compared to the direct volumetric measurements of the master model. The maximum change was recorded in PE group (19.47 ±0.015 mm^3) and the minimum change was recorded in PVSE group (18.63 ±0.012 mm^3). Stone models obtained from impressions showed adverse reaction. All stone models were shrunk in volume compared to the direct volumetric measurements of the impressions. The maximum change was recorded in PE group (18.37 ±0.016 mm^3) and the minimum change was recorded PVSE group (18.06 ±0.014 mm^3).

Table 1. *Average dimensional volume of the test materials (mm^3)*

Material	Volume (mm^3)
Master model[a]	18.42
PVS impression[b]	19.17 (0.011)
PVS stone model[c]	18.16 (0.013)
PE impression[d]	19.47 (0.015)
PE stone model[e]	18.37 (0.016)
PVSE impression[f]	18.63 (0.012)
PVSE stone model[g]	18.06 (0.014)

Identical lower-case superscript letters denote difference significantly within one experimental formulation (i.e., columns) (ANOVA, Tukey test, $p < 0.05$).

***3.2. Measurement dimensional stability*:** Percentages of time dependent volumetric change of three impression materials shown in Table 2. All impressions were expanded at 1 and 7 days in volume compared to baseline measurements (0 day). The highest volumetric dimensional change of the impression materials was seen in PE (-0.023 ±0.002) group at day 1 followed by PVS (-0.009 ±0.002) and PVSE (-0.004 ±0.001) respectively. The lowest volumetric dimensional change was observed in PVSE group at day 7 (-0.010 ±0.0003) and the highest change was observed in PE group at day 7 (-0.052 ±0.0004).

Table 2. *Percentage dimensional change of the impression materials by time*

Material	Day	N	Average
PVS[a]	0-1	7	-0.009 (0.002)
PE[b]	0-1	7	-0.023 (0.002)
PVSE[c]	0-1	7	-0.004 (0.001)
PVS[d]	0-7	7	-0.025 (0.003)
PE[e]	0-7	7	-0.052 (0.004)
PVSE[f]	0-7	7	-0.010 (0.003)
	Sum	21	

Identical lower-case superscript letters denote difference significantly within one experimental formulation (i.e., columns) (ANOVA, Tukey test, $p < 0.05$).

Average percentage change in each type of material has been analyzed statistically using one way ANOVA (Table 3). This method tests the null hypothesis that the changes in PE, PVSE and PVS materials are equal to each other. The validity of the analysis of variances relies on the assumption that the number of samples is distributed with a normal distribution and group variances are equal.

Table 3. *Results of ANOVA for dimensional stability of 3 impression materials*

		Sum of Square	*Df*	Mean Square	F	P
Day 1-	Between grou.	0.0007	2	0.0004	514.236	0.001
	Within groups	0.0000	27	0.0000		
	Sum	0.0007	29			
Day 7	Between grou.	0.0025	2	0.0012	1024.482	0.001
	Within groups	0.0000	27	0.0000		
	Sum	0.0025	29			

After having obtained the results of this analysis, multiple comparisons have been made using the Tukey HSD test (Table 4). The difference between the groups was statistically significant at day 1 and 7 ($p<0.05$) (Table 4).

The difference between impression and stone model; master model and impression; master model and stone model was statistically significant ($p<0.05$) (Table 5).

Table 4. *Results of Tukey HSD test for dimensional stability of 3 impression materials (Multiple comparisons)*

Dependent Variable	Mat. (I)	Mat. (J)	Mean diff. (I-J)	p	%95 Confidence int. Lower bound	Upper bound
Day 1 measurements	PVS	PE	-0.0141	0.0000	-0.0152	-0.0130
		PVSE	-0.0086	0.0000	-0.0098	-0.0075
	PE	PVS	0.0141	0.0000	0.0130	0.0152
		PVSE	0.0055	0.0000	0.0044	0.0066
	PVSE	PVS	0.0086	0.0000	0.0075	0.0098
		PE	-0.0055	0.0000	-0.0066	-0.0044
Day 7 measurements	PVS	PE	-0.0258	0.0000	-0.0273	-0.0243
		PVSE	-0.0072	0.0000	-0.0087	-0.0057
	PE	PVS	0.0258	0.0000	0.0243	0.0273
		PVSE	0.0186	0.0000	0.0171	0.0201
	PVSE	PVS	0.0072	0.0000	0.0057	0.0087
		PE	-0.0186	0.0000	-0.0201	-0.0171

Mean differences are significant for alpha=0.05

Table 5. *Results of ANOVA for stone models*

		Sum of squares	Df	Mean sq.	F	P
Impression-Stone model	Between groups	0.0027	2	0.0013	2632.645	0.001
	Within groups	0.0000	27	0.0000		
	Total	0.0027	29			
Master model-impression	Between groups	0.0074	2	0.0037	7874.729	0.001
	Within groups	0.0000	27	0.0000		
	Total	0.0075	29			
Master model-stone model	Between groups	0.0011	2	0.0005	891.492	0.001
	Within groups	0.0000	27	0.0000		
	Total	0.0011	29			

All the three groups of impression materials showed statistically significant differences between impression and stone model; master model and impression; master model and stone model ($p<0.05$) (Table 6).

Table 6. *Tukey HSD test results of stone models (Multiple comparison)*

Dependent Variable	Mat. (I)	Mat. (J)	Mean diff. (I-J)	P	%95 Confidence int. Lower bound	Upper bound
Impression-Stone model	PVS	PE	-0,0035	0,0000	-0,0044	-0,0025
		PVSE	0,0220	0,0000	0,0210	0,0230
	PE	PVS	0,0035	0,0000	0,0025	0,0044
		PVSE	0,0255	0,0000	0,0245	0,0264
	PVSE	PVS	-0,0220	0,0000	-0,0230	-0,0210
		PE	-0,0255	0,0000	-0,0264	-0,0245
Master model-Impression	PVS	PE	-0,0160	0,0000	-0,0169	-0,0150
		PVSE	0,0295	0,0000	0,0285	0,0304
	PE	PVS	0,0160	0,0000	0,0150	0,0169
		PVSE	0,0454	0,0000	0,0445	0,0464
	PVSE	PVS	-0,0295	0,0000	-0,0304	-0,0285
		PE	-0,0454	0,0000	-0,0464	-0,0445
Master model-Stone model	PVS	PE	0,0115	0,0000	0,0104	0,0125
		PVSE	-0,0057	0,0000	-0,0067	-0,0046
	PE	PVS	-0,0115	0,0000	-0,0125	-0,0104
		PVSE	-0,0171	0,0000	-0,0182	-0,0161
	PVSE	PVS	0,0057	0,0000	0,0046	0,0067
		PE	0,0171	0,0000	0,0161	0,0182

Mean differences are significant for alpha=0.05

4. DISCUSSION

This study evaluates volumetric dimensional accuracy and stability of 3 elastomeric impression materials from the impressions and their final models. Numerous studies have evaluated the dimensional accuracy and the stability of different impression materials (6, 14, 15). The primary null hypothesis of this study was that there would be no differences in the dimensional accuracy and stability among 3 impression systems. Thus, the null hypothesis indicating no difference between the different impression techniques was accepted.

Although the studies are correlated, most of them measured linear dimensional changes (3, 6, 7, 14). Only a few studies measured volumetric dimensional changes. Some investigators preferred to calculate three dimensional results from linear measurements and some preferred to use photometric or topographic methods (23, 24, 26, 27, 30).

In our study µCT device (Skyscan 1174, Skyscan) was used for direct three-dimensional modeling of elastomeric impressions and stone models. Advantages of µCT device are surface and volume measuring, reliability, independent from positioning and operator errors.

Kamegawa et al (33) evaluated using µCT in measuring accuracy of elastomeric impressions. Within the limitations of this study, micro focus X-ray CT indicated that the accuracy is sufficient to measure for direct 3D modeling of elastomeric impressions (34). To be able to make a precise statement, direct measurements of the impressions and their models were made. Therefore the difference between the master model, impression and stone model were evaluated. According to the study results, all the impression materials were expanded in a different volume and this volume differences were compensated by stone models.

From the standpoint of accuracy the three impression materials that we investigated demonstrated a very high dimensional accuracy under the experimental conditions presented, with very small differences between them. Although PE impression was shown to have the highest volumetric expansion after polymerization, the highest shrinkage was observed at the same group after pouring to dental stone. Stone model of the PE group was observed as the most accurate value of volume to the master model.

Our study focused on the dimensional accuracy of the elastomeric impression materials without considering moist, technique, disinfection solution and stone types. Since the dimensional accuracy and stability of impression materials is a primary basis of treatment, all other factors that could affect dimensional accuracy and stability were standardized. There are several studies which explain such factors (6, 16, 25, 28).

Only a few studies are aimed at solely examining the dimensional accuracy of elastomer impression materials. Piwowarczyk et al (20) evaluated short-range dimensional accuracy of 8 elastomeric impression materials (6 polyvinylsiloxane and 2 polyether impressions). Under the conditions of this study, the impression materials tested demonstrated a very high dimensional accuracy similar to our study. Even though dimensional stability was measured linearly, the arithmetic means of the dimensional changes were observed consistent with volumetric dimensional changes in our study.

According to our study results, PE group (19.47 ±0.015 mm^3) expanded more than PVS (19.17 ±0.011 mm^3) and PVSE (18.63 ±0.012 mm^3) after 1 hour of impression procedure. Despite high expansion volume, PE group had the maximum shrinkage after dental stone pouring. PE stone model (18.37 ±0.016 mm^3) showed significantly similar volume to the master model (18.42 mm^3). However all three stone model volume was clinically acceptable.

This study was designed to compare the dimensional accuracy of resultant stone models and dimensional stability of impressions using polyvinyl siloxane, polyether and the vinyl siloxanether elastomeric impression material. The null hypothesis was that no difference would exist in the dimensional accuracy and stability among three different elastomeric impression materials. The hypothesis was rejected since there were significant differences. In most situations, the changes detected were minor amounts and clinical significance.

In this study a statistical analysis of the differences in volumetric dimensions was done between the stainless steel model, impressions and the stone models in order to verify the effects of each impression material. This confirms the hypothesis that selection of impression material is crucial in determining the dimensional accuracy of the impression. This was in accordance to the studies by authors like Chee and Donovan (8) and Craig (13).

For measurement of dimensional accuracy, the study revealed that there was a change in the volumetric dimension of stone cast and impression for all the three groups of elastomeric impression materials. All impressions were expanded in volume compared to the direct volumetric measurements of the master model. The maximum change was recorded in polyether group and the minimum change was recorded in polyvinyl siloxanether group. All stone models shrank in volume compared to the direct volumetric measurements of the impressions. The maximum change was recorded in polyether group and the minimum change was recorded polyvinyl siloxanether group. The similar results were shown by the studies conducted by various authors such as Piwowarczky et al (20) and Craig (13). Polyvinyl siloxanether impression group shows most accurate result among all three groups and the polyether casts were more accurate compared to the casts obtained from polyvinyl siloxanether and polyvinyl siloxane. Similar results were seen in a study carried out by Enkling et al (12).

Many researchers have assessed the dimensional stability of impression materials for periods ranging from 24 hours, a week or 30 days (13, 20, 21). Polyether impression materials

were observed as the highest volumetric dimensional change at day 1 and 7. The lowest volumetric dimensional change was observed in polyvinylsiloxane impression materials at day 1 and day 7. In this study, an impression made from polyether should be poured only once and within 24 hours after impression making, because of the distortion of the material over time. Silicone impression material has better dimensional stability than polyether. PVS impressions have shown better dimensional stability then PE. Furthermore PVSE impressions have shown better dimensional stability than PVS and PE. However all three impression materials were measured with high accurate dimensional stability which were in clinically excellent range. In our study similar results were shown as in Thongthammachat et al (22). According to our results PVS, PVSE and PE impressions used in our study is dimensionally acceptable in day 1. PVSE and PVS are highly stabile during the first 1 week period and can be pouring after 1 week. PE impression material has a clinically unacceptable volume loss (%5, 2) at the 1 week and has to be poured at day 1.

5. CONCLUSION

The results of this study may be useful for selecting appropriate impression material. Further studies should be focused on the biological, rheological and wetting properties of this novel impression material to compare with poly vinyl siloxane and polyether and for its clinical acceptability. Also, since the dimensional changes of impression materials are primary basis for all successive treatment steps, all the factors that could exercise a further influence on dimensional accuracy were standardized or excluded in the current study.

µCT device can be successfully used for volumetric dimensional changes of impression materials. However clinical aspect is not so well developed yet, having impression surface and three dimensional measurements is the greatest advantage of the device.

The results of this study showed that newly formulated polyvinyl siloxanether impression material is dimensionally accurate and stabile as well as polyvinyl siloxane and polyether impressions. This impression material should be useful as an alternative to polyether and polyvinyl siloxane in terms of easy handling, accuracy and long term stability.

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Clinical and Experimental Health Sciences

What is the Impact of Implant-supported Mandibular Overdentures on Oral Health-Related Quality of Life? A Retrospective Study

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ABSTRACT

Objective: Oral health-related quality of life (QoL) is significantly influenced by the type of the prostheses that is used for prosthetic rehabilitation of patients with complete edentulism. This study aims to retrospectively evaluate the outcomes of mandibular implant-supported overdentures (MODs) through patients' perceptions by analyzing the results from OHIP-14 index.
Methods: Relationships between OHIP-14 scores, and clinical and patient-based findings are investigated.
Results: Forty-seven patients were included in the study. OHIP-14 scores ranged from 0 to 35, with a mean score of 5.81 (±6.89), indicating an overall "very high" quality of life. Patients with "very high" QoL had significantly lower pain scores than those with both "high" and "low" QoL (p=0.000, p=0.036 respectively). Further analysis revealed a positive correlation between total OHIP points and pain level (r= 0.738, p=0.000).
Conclusion: Within the limitations of this study, it can be concluded that patients with complete edentulism of the mandible can effectively be rehabilitated with two implant-supported mandibular overdentures and be provided with a "very high" oral health-related QoL.
Keywords: quality of life, edentulous, mandible, overdenture, dental implant

1. INTRODUCTION

A minimum of 20 natural teeth or occluding posterior pairs of teeth are essential in order to have a satisfactory oral health (1). With increasing age tooth loss becomes inevitable, leading to a decrease in oral health-related quality of life (2,3). However, even though the incidence of complete edentulism is on the decline and is reported to be 4.1% globally, total elimination of it remains unlikely in the near future (4). In our day, complete edentulism is managed by means of conventional dentures or implant-supported overdentures (5).

Prosthetic rehabilitation enhances physical, psychological and social well-being of patients. However mandibular conventional dentures stand to be a major handicap for many patients due to lacking denture retention (6). This may cause disappointing outcomes even when excellent dentures are fabricated (7). Functional limitations during eating and speaking, psychological and social disabilities, mobility, and discomfort are the mainly encountered problems with mandibular conventional complete dentures (5,8). On the other hand, mandibular implant-supported overdentures (MODs) provide superior retention and stabilization, ease of use and good esthetics (6,9). Masticatory efficiency is also positively affected after edentulism is treated with an implant-supported overdenture, compared to conventional complete dentures, which cause a decrease in masticatory efficiency to almost 30% to that of natural dentition (6,10,11).

Previously, a 14-item questionnaire titled "Oral Health Impact Profile (OHIP-14) Index" has been developed to mainly cover the negative impacts of oral health-related QoL, contrary to several other oral health-dependent QoL-questionnaires, which capture both positive and negative impacts (9-12). OHIP-14 consists of two questions for each functional limitation, physical pain, psychological discomfort, physical, psychological and social dimensions of disability and handicaps, and higher scores are indicative of a lower quality of life (13).

Oral health-related quality of life (QoL) is significantly influenced by the type of the prostheses (8,9,14). Therefore, this study aims to retrospectively present our findings regarding the outcomes of MODs through patients' perceptions by analyzing the results from OHIP-14 index. Additionally, relationships between OHIP-14 scores, and clinical and patient-based findings are also investigated.

2. METHODS

A retrospective study was conducted at the Department of Oral and Maxillofacial Surgery, Akdeniz University, Antalya, Turkey. Seventy-four patients with mandibular complete

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edentulism who were treated with two implant-retained mandibular overdentures between January 2012 and March 2015 were invited to follow-up. Socio-demographic information (age, education, oral hygiene frequencies) was collected. Oral Health Impact Profile Index (OHIP-14) questionnaire was completed by each patient before clinical examination under the assistance of the researcher. Answers were numbered from 0 to 4, corresponding to never, hardly ever, occasionally, fairly often and very often, respectively. Total scores were obtained by adding item scores without weighting (15). Higher scores revealed worse and lower scores indicated better oral health-related quality of life. These scores were further categorized into groups as shown in Table 1. Patients were asked to rate their pain, while using their MODs, through a Visual Analogue Scale (VAS) which ranged from 0 to 10. A score of 0 referred to no pain and a score of 10 corresponded to the worst pain imaginable.

Table 1. *Interpretation of OHIP-14 Scores*

Score	Quality of life
0-14	Very High
15-28	High
28-42	Low
42-56	Very Low
OHIP: Oral Health Impact Profile	

All dentures were removed for clinical examination. Soft tissues of the oral cavity were inspected for any signs of inflammation, swelling, bleeding or pus drainage. Peri-implant tissues were also visually examined first; then, pocket probing depth and bleeding on probing from six sites of each implant, as well as implant mobility were evaluated. To achieve optimum probe force reproducibility and accuracy, all examinations of peri-implant tissues were performed under light force (0.2-0.25N – about 25 grams of pressure) using the same type of stainless steel periodontal probe (Williams Probe, Hu-Friedy Manufacturing Co., LLC, Chicago, IL, United States) graded at 1-2-3-5-7-8-9 and 10mm. New orthopantomographic images were obtained only for patients whose radiographs were not taken within one year. Clinical and radiographic examination results were incorporated to detect peri-implant pathologies, diagnosed according to the criteria stated on the Consensus Report of the Seventh European Workshop on Periodontology(16).

All patients were informed about details of the study. The study was approved by the Ethical Committee of Akdeniz University, Antalya, Turkey (No: 2018-447). All procedures on human subjects were conducted in accordance with the Declaration of Helsinki, and with the adequate understanding and written consent of the patients.

2.1. Statistical analysis

All data were analyzed using the Statistical Package for Social Sciences version 22.0 (IBM SPSS Statistics 22, SPSS Inc., Chicago, IL, USA). Appropriate analyses were employed according to relevant data characteristics. Spearman correlation test was used to determine a correlation between OHIP-14 scores and VAS results. P values of < .05 were used to assess the significance for all statistical analyses. All values for each parameter were tested for normality using the Shapiro-Wilk test, which rejected the hypothesis of normality for all parameters (p=0.000)

3. RESULTS

Forty-seven patients out of 74, whose details on socio-demographics are summarized in Table 2 presented to their follow-up appointments. Twenty-eight female and 19 male patients within their fifth, sixth, seventh and eight decades of life were included.

Table 2. *Socio-demographic characteristics*

Characteristics	N
Age	
50-59	11
60-69	18
70-79	15
80-89	3
Gender	
Female	28
Male	19
Educational Level	
None	6
Elementary	20
Middle School	4
High School	7
University	10
Oral Hygiene Habits – Frequency	
Never	6
Once a day	18
Twice a day	18
Three times a day	5

Six patients were uneducated, 10 patients were college graduates and the remaining had at least elementary level education. Forty-one patients reported to clean their dentures and brush their implants at least once a day; whereas, 6 patients had no oral hygiene habits. A majority of patients (n= 27) had conventional dentures on the opposite arch, 17 had partial prostheses, 2 were using implant-supported maxillary overdentures and the remaining patient had fixed dentures.

OHIP-14 scores ranged from 0 to 35, with a mean score of 5.81 (±6.89), indicating an overall “very high” quality of life. Forty-one patients each scored less than 14 points corresponding to a “very high” QoL. Five patients received a score equivalent to a QoL of “high” and the remaining patient achieved a score indicating a “low” QoL.

Mean peri-implant probing depths on the right and left implants were 2.04mm (SD: 1.13) and 2.14mm (SD: 1.45) respectively. The difference between the probing depths of left and right peri-implant tissues were statistically not significant (p=0.866, Wilcoxon test). Similarly, no differences were found between probing depths of patients with “very high”, “high” or “low” QoL (Table 3; p>0.05, Kruskal-Wallis test).

Table 3. *Test Statistics*

Null Hypothesis	Test	Sig.	Decision
The distribution of "Right Periimplant Probing Depth" is the same across the categories of "Quality of Life"*.	Kruskal-Wallis	0.568	Retain the null hypothesis
The distribution of "Left Periimplant Probing Depth" is the same across the categories of "Quality of Life"*.	Kruskal-Wallis	0.371	Retain the null hypothesis

**Categories of "Quality of Life"; "very high", "high" or "low"*
Sig.; Significance

After their examinations, 16 patients were diagnosed with stomatitis while others had no prosthesis-related pathologies. Peri-implant examinations revealed 8 patients with peri-implant mucositis and 4 patients with peri-implantitis (16). Figure 1A and 1B analyze OHIP score interpretations for patients with prosthesis and implant related pathologies, respectively. Overall, no statistically significant associations were found between OHIP-14 scores, and age, gender, education level, oral hygiene routines, type of maxillary prosthesis or pathologies related to implants or dentures (Table 4; p>0.05, Kruskal-Wallis test).

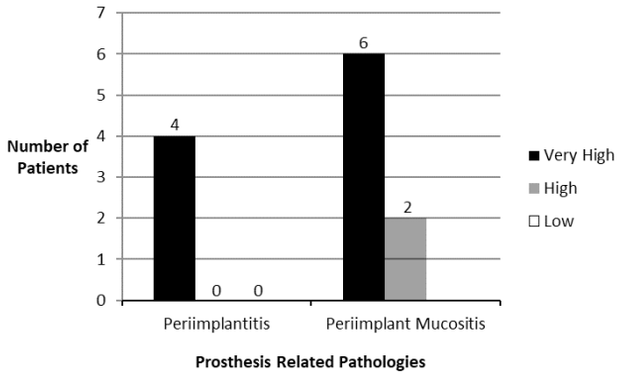

Figure 1A: *Bar chart showing OHIP score interpretations for patients with prosthesis related pathologies.*

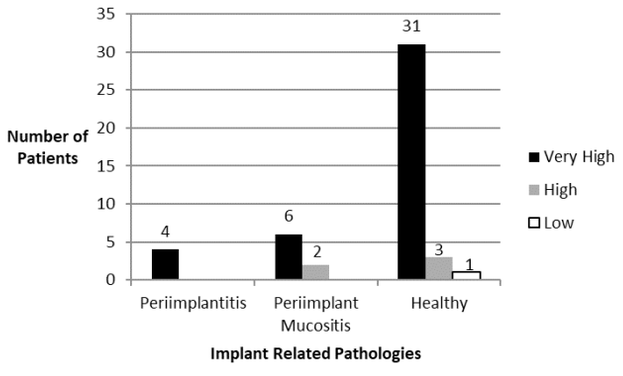

Figure 1B: *Bar chart showing OHIP score interpretations for patients with implant related pathologies.*

Table 4. *Test Statistics*

Null Hypothesis	Test	Sig.	Decision
The distribution of "Age" is the same across the categories of "Quality of Life"*.	Kruskal-Wallis	0.536	Retain the null hypothesis
The distribution of "Gender" is the same across the categories of "Quality of Life"*.	Kruskal-Wallis	0.478	Retain the null hypothesis
The distribution of "Education Level" is the same across the categories of "Quality of Life"*.	Kruskal-Wallis	0.205	Retain the null hypothesis
The distribution of "Oral Hygiene Routines" is the same across the categories of "Quality of Life"*.	Kruskal-Wallis	0.155	Retain the null hypothesis
The distribution of "Type of Maxillary Prosthesis" is the same across the categories of "Quality of Life"*.	Kruskal-Wallis	0.241	Retain the null hypothesis
The distribution of "Implant-Related Pathologies" is the same across the categories of "Quality of Life"*.	Kruskal-Wallis	0.723	Retain the null hypothesis
The distribution of "Denture-Related Pathologies" is the same across the categories of "Quality of Life"*.	Kruskal-Wallis	0.355	Retain the null hypothesis

**Categories of "Quality of Life"; "very high", "high" or "low"*
Sig.; Significance

Pain was the only parameter that showed a significant difference among different levels of QoL (p=0.000, Kruskal-Wallis test). Post-hoc analyses revealed that patients with "very high" QoL had significantly lower pain scores than those with both "high" and "low" QoL (p=0.000, p=0.036 respectively). Details of these findings are shown in Table 5. Further analysis revealed a strong positive correlation between total OHIP points and pain level (Table 6; r= 0.738, p=0.000; Spearman correlation test).

Table 5a. *Test Statistics*

Null Hypothesis	Test	Sig.	Decision
The distribution of "Pain" is the same across the categories of "Quality of Life"*.	Kruskal-Wallis	0.000	Reject the null hypothesis

**Categories of "Quality of Life"; "very high", "high" or "low"*
Sig.; Significance

Table 5b. *Post-hoc Analyses*

"Quality of Life" Comparisons	Sig.
Very High – High	0.000
Very High – Low	0.036
High – Low	0.693

Table 6. *Spearman's Test of Correlation*

		OHIP Score	Pain
OHIP Score	Correlation Coefficient	1	.738**
	Sig. (2-tailed)		.000
	N	47	47
Pain	Correlation Coefficient	.738**	1
	Sig. (2-tailed)	.000	
	N	47	47

*** Correlation is significant at the 0.01 level (2-tailed)*
OHIP: Oral Health Impact Profile

4. DISCUSSION

According to the World Health Organization, oral health is defined as "being free of chronic oro-facial pain, oral and pharyngeal cancer, oral tissue lesions, birth defects such as cleft lip and palate and other diseases and disorders that affect the oral, dental and craniofacial tissues" (17). Oral health is vital for general health and well-being as well as good quality of life, and should not just be associated with good teeth (17,18). Poor oral health compromises chewing and eating abilities, consequently affecting nutritional intake negatively (6,10,17). It is not surprising to expect edentulism to have adverse effects on the quality of life, since not only chewing and swallowing but also speaking and smiling are among essential functions of the orofacial complex (2,8,17).

Conventional or implant-supported overdentures may be fabricated to rehabilitate an edentulous patient (5). Conventional mandibular dentures are dissatisfactory usually because of denture instability and discomfort (19). Unstable dentures are the reason for pain and pathological conditions such as traumatic ulcers and irritation-induced hyperplasia (20). The main reason behind the instability of mandibular conventional dentures is due to the alveolar bone resorption following tooth extraction. Patients experience a more dramatic reduction in bone volume in the mandible than in the maxillary bone. Thus, not only denture adaptation and acceptance becomes problematic by patients, but also the construction becomes challenging for the dentists (19). Moreover, patients with conventional dentures experience more residual ridge resorption than MOD users, which may even worsen the adaptation process as the patients continue to use the conventional dentures (21). Also in the long term, denture instability is known to reduce masticatory function, impair phonetic abilities and negatively affect social and psychological life of the patient (8,11). Altered perception in taste and burning mouth syndrome have also been reported (19).

On the other hand, implants, particularly in the anterior mandible, are shown to slow the resorption process and reduce mandibular bone loss (22,23). Implant-supported mandibular overdentures not only provide better stability, but also increase comfort and ease denture acceptance (24,25). However, main disadvantages of MODs are their high cost and relatively lengthy treatment duration (19).

In 2002, the McGill consensus on overdentures concluded that conventional complete dentures were no longer the most appropriate treatment for the restoration of edentulous mandible due to the conclusive evidence in favor of two-implant supported MODs and against conventional prostheses (26). The same statement was articulated by the British Society for the Study of Prosthetic Dentistry in 2009 who defined MODs as the "first choice of standard of case for edentulous patients" and published their declaration under the title "the York Consensus Statement" (5).

A meta-analysis in 2012, also proved that patients with MODs had greater oral-health related QoL and were more satisfied with their dentures, which was compatible with the results of the current study and in agreement with the McGill and York consensuses (5,26,27).

Pain was the only parameter in this study to be significantly associated with OHIP-14 scores. Knipfer et al. suggested that freedom of pain had a noticeable role in an improved oral-health related quality of life (28). The most recent systematic review comparing conventional dentures and implant-retained overdentures similarly stated that MODs were associated with less physical pain, and reported the superiority of MODs with regards to patient satisfaction and quality of life (29).

In 1990, a prevalence of 75% was reported among the elderly population of Turkey for edentulism (2). In 2004, this rate was decreased to 48% but it is still considered high compared to other countries (30,31). Despite growing technology and innovations, complete edentulism does not seem to be eradicated in the near future (4). Today, MODs seem to have taken over conventional complete dentures, since more and more studies reporting favorable outcomes of implant-retained overdentures are being published (29,32,33). According to the results of the present study, and the literature, patients with implant-supported MODs are satisfied with the outcome of MOD-treatment.

Main limitations of this study are its retrospective nature, the unavailability of pre-implant OHIP-14 scores or the lack of a control group, which prohibited a true comparison between patients with MODs and conventional mandibular dentures.

5. CONCLUSION

Within the limitations of this study, it may be concluded that patients were satisfied with their MODs and presented a "very high" QoL, which was in accordance with the literature. Moreover, higher pain scores were associated with lower QoL.

Conflict of Interest: Dr. Altay has provided consultancy for Checkpoint Surgical LLC. İn 2014. Other authors declare that they have no relevant conflicts of interest.

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Clinical and Experimental Health Sciences

Plasma Nesfatin-1 Levels and its Relationship with Anxiety Levels in Obesity Diagnosed Population: A Controlled Study

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ABSTRACT

Objective: Nesfatin-1 is a satiety neuropeptide involved in the regulation of metabolic pathways and food intake. Some studies have shown nesfatin-1 to be also associated with stress responses and stress-related behaviors. In the present study, we evaluated nesfatin-1 levels in obese individuals and investigated whether nesfatin-1 levels could be associated with anxiety levels in obese populations.

Methods: Fifty-eight obese (29 anxious and 29 non-anxious) patients and 25 healthy control subjects between 18 and 65 years old were enrolled in the study. Plasma nesfatin-1 levels were measured with a commercial enzyme-linked immunosorbent assay, and anxiety levels were measured using the Hospital Anxiety and Depression Scale.

Results: Plasma nesfatin-1 levels were significantly lower in both obese and anxious subjects and obese and non-anxious subjects than in the control group. No significant differences were found between the obese+anxious group and the obese+nonanxious group.

Conclusion: Our results suggest that plasma nesfatin-1 levels are decreased and not associated with anxiety levels in obese populations
Keywords: Nesfatin-1, Obesity, Anxiety

1. INTRODUCTION

Nesfatin-1 is a multifunctional peptide with pleiotropic functions secreting from different systems. The most established functions associated with nesfatin-1 have been reported as anorexigenic effect, feed regulation, and appetite (1). Studies on animals showed that nesfatin-1 is derived from nucleobindin-2 and is expressed in several regions of the central nervous system (CNS), including the limbic system, brainstem, and hypothalamus (2). Several studies showed that nesfatin-1-secreting neurons are distributed in the regions of the CNS associated with neurovegetative functions, such as food intake regulation (3). Some data revealed that nesfatin-1 is expressed in the regions other than the CNS in the human body, including adipose tissue, and has potential regulatory functions in association with some other metabolic hormones, such as ghrelin (4). There is also evidence supporting that nesfatin-1 is implicated in adipogenesis and obesity (5). Obesity and metabolic syndrome, as well as diabetes and cardiovascular diseases, have been associated with the dysfunction of nesfatin-1 and its associated pathways (6). Nesfatin-1 levels have been reported to be increased in obese individuals, whereas they have been found to be decreased in cases with anorexia nervosa (7). In line with this data,a positive correlation between nesfatin-1 levels and body mass index (BMI) has been observed in some studies, whereas some conflicting data regarding a negative correlation between nesfatin-1 levels and BMI also exist (8). There is evidence of low concentrations of nesfatin-1 in populations with high BMI. A previous study showed a negative correlation between BMI and nesfatin-1 in non-obese populations (8). Nesfatin-1 has been reported to be expressed in several hypothalamic nuclei and regions associated with appetite and emotional status (9). Furthermore, central regulatory neuropeptides, such as neuropeptide Y, vasopressin, and oxytocin, that contribute to energy balance are expressed from neurons in the arcuate, paraventricular, and supraoptic hypothalamic nuclei similar to nesfatin-1. Although a specific nesfatin-1 receptor is still unknown, current data showed a proposed mechanism of action that involves nesfatin-1 interacting with a G protein-coupled receptor that results in an inhibitory hyperpolarization of neuropeptide Y/agouti-related peptide neurons that have an orexigenic effect in the arcuate nucleus (10). In addition, nesfatin-1 has been reported to stimulate oxytocin-mediated melanocortin that has an anorexigenic effect in the paraventricular nucleus (10, 11). Neurovegetative functions, including appetite and sleep, as well as some other hypothalamic

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functions, are related to and influenced by an individual's emotional state. As nesfatin-1 is a satiety neuropeptide involved in the regulation of metabolic pathways and food intake, some studies showed that nesfatin-1 is also associated with stress responses and stress-related behaviors (7, 12). A previous study conducted on rats showed that intracerebroventricular nesfatin-1 injections yield anxiety – and fear-related behaviors (9). Data on the association between nesfatin-1 and stress responses in human subjects are limited. However, in recent years, nesfatin-1 has been studied in subjects with psychiatric disorders, such as depression and anxiety in particular. Some studies found a relationship between nesfatin-1 levels and anxiety disorders, such as panic disorder, generalized anxiety disorder, and obsessive–compulsive disorder (13, 14, 15). In a previous study, nesfatin-1 levels were found to berelatively higher in patients diagnosed with panic disorder than in the control group (13). However, data regarding nesfatin-1 levels in patients diagnosed with generalized anxiety disorder are conflicting (15, 16), and studies examining nesfatin-1 levels in subjects with affective disorders are limited. One study showed nesfatin-1 levels to be significantly higher in subjects with major depression than in the control group, whereas another study reported decreased nesfatin-1 levels during manic episodes (17, 18). All of this data supports nesfatin-1 as a central neuropeptide participating in metabolic regulation, emotional state, and stress responses. To our knowledge, although nesfatin-1 levels have been studied in relation to obesity and some psychiatric disorders, such as depression and anxiety, data on the association between nesfatin-1 levels and anxiety in obese populations are limited. In the present study, we evaluated nesfatin-1 levels in obese individuals and investigated whether nesfatin-1 levels are associated with anxiety levels in obese populations.

2. METHODS

The study was performed in accordance with the Declaration of Helsinki. The local ethics committee of Balıkesir University Faculty of Medicine approved the study (2014/04). Written informed consent was obtained from all the participants in the study. Fifty-eight obese patients and 25 healthy controls (non-obese and non-anxious) between 18 and 65 years old were enrolled in the present study. Patients were divided into two groups based on whether they had comorbid anxiety (29 obese and anxious and 29 obese and non-anxious). Patients were selected from those who applied to the psychiatry outpatient clinic and were diagnosed with anxiety disorder or from those who were directed to the psychiatry outpatient clinic due to their psychiatric complaints from the dietary outpatient clinic. All patients were diagnosed with obesity with BMIs measuring >30 kg/m2. Diagnosis of obesity was made after BMI was measured by a dietitian. A psychiatric evaluation and diagnosis were made by a psychiatrist. Patients met the criteria for anxiety disorders, as confirmed by the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, 4th Edition Axis I Disorders (SCID-I) (19). The control group was selected from individuals who had no psychiatric diagnoses, as confirmed by the SCID-I, as well as no obesity confirmed by BMI measurements <25 kg/m2.The Hospital Anxiety and Depression Scale (HADS) was used to determine the severity of their anxiety (20). The HADS was developed to detect anxiety and depression levels in outpatient clinic settings. The Turkish version of the HADS was erformed by Aydemir et al.with a cut-off value of 10 for anxiety to be used in the Turkish version (21). Patients with psychiatric or neurological diagnoses other than anxiety disorders, such as mental retardation, alcohol/substance use disorder, history of electroconvulsive therapy, history of psychiatric drug use in the last 3 months, a severe physical illness, such as diabetes or another endocrinopathy, cardiovascular diseases, malignity, infectious diseases, and pregnancy, were excluded from the study. Patients were selected, instructed about the study, and handed written informed consent on their first visit. Venous blood samples wereobtained between 07:00 and 08:00 AM in the morning of the second admission after an overnight fasting period. All blood samples were collected in standard ethylenediaminetetraacetic acid tubes (Becton, Dickinson, USA). After blood was withdrawn, plasma samples were centrifuged at 1300 ×g for 10 min. Plasma samples were placed into tubes, and 1% concentrated protease inhibitor cocktail (Sigma Aldrich, USA) was administrated in all tubes. Samples were stored at −20 °C until further processing. Nesfatin-1 levels were measured using a commercial enzyme-linked immunosorbent assay kit (ELISA, RayBiotech, USA). All samples were processed in one batch without dilution. Intra-assay and inter-assay variabilities were <10% and <15%, respectively, according to the manufacturer.

2.1. Statistical Analysis

Data were analyzed using the SPSS software version 15.0 (IBM Inc., Chicago, IL, USA). The ANOVA test was used to analyze the differences between mean values of the groups when normally distributed variables are homogenous. The Tukey test was used for post hoc comparisons. The chi-square test was used to compare categorical variables. The linear regression model was used to predict relationships between nesfatin-1 levels and independent variables. A P value <0.05 was considered as statistically significant.

3. RESULTS

Table 1 shows the sociodemographic characteristics, plasma nesfatin-1 values, plasma glucose levels, and BMI measurements. There were no significant differences between the three groups in terms of age (p=0.057), gender (p=0.997), tobacco use (p=0.387), and marital status (p=0.825). There were significant differences in

terms of BMI between the three groups (p<0.001) (Table 1).

Table 1. *Baseline characteristics of the study groups*

	Obese + anxious (n=29)	Obese + non-anxious (n=29)	Non-obese + non-anxious (n=25)	p
Age (year)a	45.9±10.1	46.7±11.0	40.2±10.6	0,057
BMI (kg/m2)[a]	37.2±5.4	38.3±5.5	22.4±2.1	<0.001[b]
Glucose (mg/dL)[a]	101.7±11.5	104.0±9.1	92.7±9.4	<0.001[b]
Nesfatin (ng/mL)[a]	28.4±7.1	28.7±6.9	34.6±10.9	0.014[b]
Gender (female)	79.3%	79.3%	80.0%	0,997
Smoking (yes)	20.7%	10.3%	24.0%	0,387
Marriage (yes)	89.7%	86.2%	84.0%	0,825

[a]Mean±standard deviation, [b]Statistically significant, BMI: Body Mass Index.

In comparison, there were significant differences between the control group and both patient groups (obese+non-anxious and obese+anxious) (p<0.001)(Table 2). Similarly, there were significant differences in terms of serum glucose levels between the three groups (p<0.001) (Table 1).In comparison, there was a significant difference between the control group and both patient groups (p=0.004 for obese+anxious group and p=<0.001 for obese+non-anxious group) (Table 2).

Table 2. *Pairwise comparisons of the BMI, glucose, and nesfatin-1 levels between the study groups*

	Obese + anxious	Obese + non-anxious	Non-obese + non-anxious
BMI			
Obese+anxious	1	0,667	<0.001[b]
Obese+non-anxious	0,667	1	<0.001[b]
Non-obese+non-anxious	<0.001[b]	<0.001[b]	1
Glucose			
Obese+anxious	1	0,676	0.004b
Obese+non-anxious	0,676	1	<0.001[b]
Non-obese+non-anxious	0.004[b]	<0.001[b]	1
Nesfatin-1			
Obese+anxious	1	0,988	0.023[b]
Obese+non-anxious	0,988	1	0.034[b]
Non-obese+non-anxious	0.023[b]	0.034[b]	1

Table 3 shows the relationship between age, HADS scores, BMI measurements, and plasma nesfatin-1 levels. Plasma nesfatin-1 levels were found to be significantly different when compared in the three groups (p=0.014) (Table 1). In post-hoc comparisons, plasma nesfatin-1 levels were significantly lower in obese and anxious subjects than in controls (p=0.023), as well as in obese and non-anxious subjects than in controls (p=0.034). There were no significant differences between the obese+anxious group and the obese+non-anxious group (p=0.988).

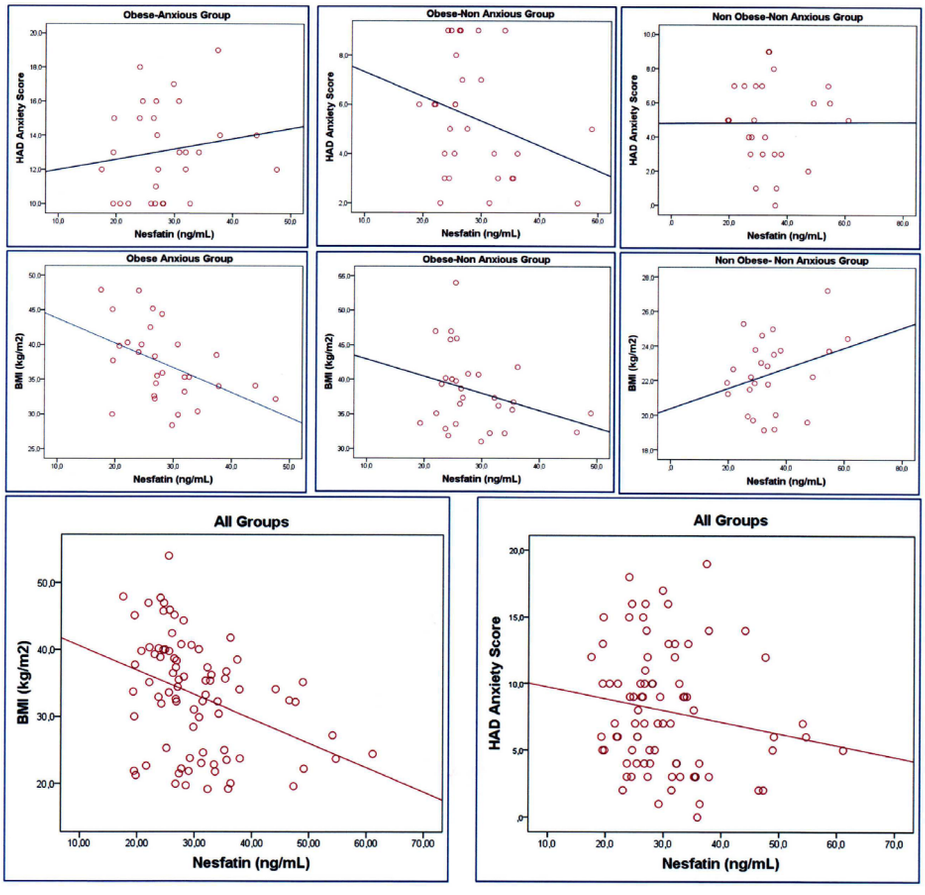

Fig 1. *The spesific anxiety scores visualized by histogram graphic. Distrubition of spesific anxiety scores in the groups were reflected.*

Table 3. *Correlations between age, HAD anxiety scores, BMI, and plasma nesfatin-1 levels*

		Age	Nesfatin-1 Levels	BMI	HAD Anxiety Scores
Age	r	1	0,074	0,164	0,148
	P value		0,508	0,139	0,180
Nesfatin-1 Levels	r		1	-0,372	-0,168
	P value			0,001	0,129
BMI	r			1	0,359
	P value				0,001
HAD Anxiety Scores	r				1
	P value				

The multivariable linear regression model was used to identify the associations between age, HADS scores, BMI measurements, and plasma nesfatin-1 levels. The regression models were visualized by correlation graphics (Fig. 1). BMI has been identified as an independent variable in the prediction of plasma nesfatin-1 levels (B=−0.384, p=0.001), whereas age and HADS scores were not found to be associated with predicting nesfatin-1 levels (B=−0.139, p=0.100 for age and B=0.113, p=0.592 for HADS scores). Fig. 2 shows the specific anxiety scores as visualized by box plots.

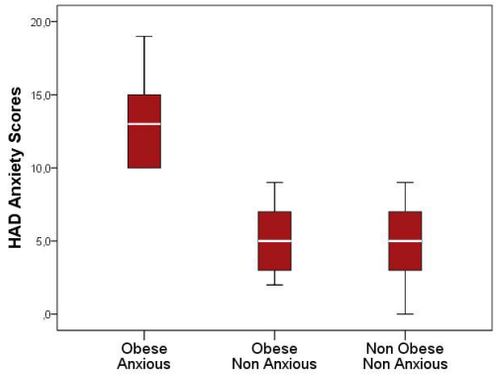

Fig 2. *The regressions models visualized by correlation graphics*

4. DISCUSSION

In our study, we have found a negative relationship between plasma nesfatin-1 levels and BMI. In line with current data, our results support that nesfatin-1 levels may be involved in the development of metabolic abnormalities and obesity. Although studies regarding nesfatin-1 levels in obesity are confounding, our results are consistent with data reporting a negative correlation between nesfatin levels and BMI (8, 22, 23). Animal studies showed that central administration of nesfatin-1 has been associated with decreased food intake, as well as increased anxiety – and fear-enhancing effects (9). Anxiety-related functions of nesfatin-1 levels have been described not only by directional effects but also by interrelational pathways in the CNS. Similar to nesfatin-1, the corticotropin-releasing hormone (CRH) is one of the peptides with anorexigenic and anxiogenic effects that is abundantly found in the hypothalamic region. Recent studies found that nesfatin-1 and CRH act in a collaborative and serial manner, as CRH expression is influenced by the hypothalamic nesfatin-1 neurons (9). Activation of the melanocortin system, which has been shown to regulate food intake and anxiety-related behaviors, has also been assumed to be involved in the anxiogenic effects of nesfatin-1 (24). Nesfatin-1 has also been associated with the inhibition of neuropeptide Y, which has anxiolytic effects (25). These experimental studies support the association between anxiety and nesfatin-1. Moreover, in a human study, plasma nesfatin-1 levels have been positively correlated to levels of anxiety in obese populations (26). However, there is some evidence to support that low nesfatin-1 levels are associated with anxiety disorders (15), whereas some studies report no relationship (16). Additionally, a study conducted on obese subjects found a sex-specific, positive correlation between plasma nesfatin-1 levels and anxiety in favor of the female population (27). In a recent study, a sex-specific inverse correlation was observed between NUCB2/nesfatin and anxiety levels, whereas there was no significant change in NUCB2/nesfatin following improvement of anxiety (28). However, our results showed no association between anxiety and plasma nesfatin levels in obese populations. Although our samples were predominantly women, no relationship was observed between anxiety and plasma nesfatin-1 levels. The association between nesfatin-1 levels and anxiety is a complicated issue that needs to take several factors into consideration. For instance, the peripheral measurement of a central acting peptide may not be sufficient to determinate its central role. As animal and clinical studies indicated that central nesfatin-1 is involved in the regulation of emotional and stress responses, results of the studies that measured peripheral nesfatin-1 levels in psychiatric conditions are confounding (9, 15, 16, 29). In one study, the authors suggested that nutritional status can be associated with different expressions of nesfatin-1 levels in psychiatric populations (15). Although nesfatin-1 has been shown to have the capacity to cross the blood–brain barrier, the effect of peripheral nesfatin-1 on the CNS or interaction between central and peripheral nesfatin-1 has not been well established. However, as studies focused on peripheral measurements of other regulatory neuropeptides, such as neuropeptide Y and oxytocin, which are involved in central processes and have been related to mood disorders and stress responses (30, 31), future studies are required to clarify the association between peripheral nesfatin-1 levels and anxiety disorders, as well as stress-related responses. There are some limitations to our study. First, the sample size was small. Second, individual factors, such as feeding habits and sedentary lifestyles, have not been taken into consideration during the study. Only performing peripheral measurements of nesfatin-1 levels is also a limitation of the study.

5. CONCLUSION

In conclusion, our results suggest that peripheral nesfatin-1 levels are not associated with anxiety levels in obese populations. Further studies with a larger sample size are warranted to determine whether there is an association between anxiety and peripheral nesfatin-1 levels.

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Clinical and Experimental Health Sciences

Frequency and Related Factors of Depressive Symptoms Among Elders Who Live in a Residential Home in Istanbul

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ABSTRACT

Objective: The elderly population, defined as ≥65 years old, is increasing with time in society. Depressive symptoms in old age lead to worsening of physical and cognitive abilities. This study investigated the prevalence of depressive symptoms in elderly people living in a residential home in Istanbul and factors affecting this indication.

Methods: The study was conducted in a descriptive and cross-sectional manner. The questionnaire, which included sociodemographic questions and inquiries on factors affecting depression, Geriatric Depression Scale Short Form-15 (GDS-15), and Mini-Mental test, was administered to 77 elderly people.

Results: Twenty-nine of the participants were females and 48 were males, with a mean age of 75.9 ± 8.2 years. The mean GDS-15 score of the elderly was 4.04 ± 3.42. Concerns regarding leaving the residential home, low telephone call frequency, persistent physical illness, and inability to complete self-care activities were significantly associated with depressive symptoms.

Conclusion: Depressive symptoms are common in the elderly living in residential homes. This occurrence is closely related to social support and health status. Further studies are warranted to determine if factors associated with such symptoms are risk factors for depression.
Keywords: Social Support; Depression; Self Care; Health Status

1. INTRODUCTION

The average life span has been extended due to improvements in the health field and in living conditions (1). The proportion of the elderly population (defined as ≥65 years) in the general population is 21%–26% in countries such as Japan and Germany, and 8.3% in Turkey in 2016 (2). Depression causes “loss of ability” and “mortality” in the elderly and worsens the prognosis of accompanying health problems. It also causes increased loss of function compared with diseases such as diabetes and hypertension. However, depression in old age is less well known to physicians, and the diagnosis is difficult. Depression is generally believed to be related to the aging process or other medical conditions (3). Furthermore, it is more prevalent in the elderly who live in residential homes than in those living elsewhere; therefore, the former constitutes a layer of society that is more fragile and requires additional social support (4, 5). Although many studies have described varying ratios, the prevalence of depression in individuals aged ≥65 years is up to 40% in those living in residential homes and approximately 8%–15% in the general population (6).

Many factors affect the prevalence of depression in the elderly. These factors may be person-specific reasons, inadequate social support, or factors related to an institution and its residents. Ryden et al. found an inverse relationship between existence of depressive symptoms and levels of satisfaction from a residential home (7). Zunzunegui reported that low education level, being a female, being widowed, and having low social support for their children are associated with depression in 1284 people from a study population in Spain (8). A study conducted by Sütoluk et al. in Adana residential homes revealed that non-housewives and individuals without hobbies were more at risk for depression than other residents (9). In the study by Kavakçı, depression was commonly found in women and in individuals with cognitive impairments. Additionally, male sex, duration of education, and smoking are negatively correlated with depression (10). Hagerty and Williams reported that loneliness, a lack of sense of belonging, and social support are factors affecting the development of depression (11).

The fact that many of these causes are commutable factors and the incidence of depressive symptoms is high in the elderly make depression a public health problem.

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This study aimed to determine the prevalence of depression and investigate the factors affecting depression at a residential home in İstanbul.

2. METHODS

Descriptive studies were conducted from October to December 2016 on individuals living in a residential home in Istanbul. Permission was obtained from the director of the residential home. A total of 165 residential home residents were invited to participate in the study; 130 individuals had no mental or physical problems such as Alzheimer's, dementia, or paralysis that prevented them from answering questions. Thirty-five elderlies with impaired function required care due to their cognitive or physical illness and stayed in a rehabilitation center connected to the residential home. Twenty-eight people refused to participate in the study, and 25 were not included in the study because they did not pass the Mini-Mental test. As a result, we had a final population of 77 elderlies, who provided their informed consent. The participation rate was 59%. This cross-sectional study was considered descriptive owing to its low participation rate. However, the nature of the work is a condition that is expected with a limitation. The residents were assessed through question forms using the Mini-Mental test, Geriatric Depression Scale Short Form-15 (GDS-15), and questionnaire about factors affecting depression including sociodemographic questions. The Mini-Mental test is divided into four main sections: orientation, recording memory, attention and calculation, and recall and language. The short form of GDS-15 was administered, which had 15 questions that included yes/no answers (Table 1). Five questions (question number; 1, 5, 7, 11, and 13) were positive and others were negative. A total score of ≥6 is significant for the diagnosis of depression (12). A total of 33 sociodemographic questions were in the questionnaire. Such questions were about the sociodemographic characteristics of the elderly, the way in which they perceive themselves, their health and environment, their relatives, and relations with the residents of rest homes. All questions were prepared by examining the relevant literature (5, 9, 10, 13).

Table 1. *Geriatric Depression Scale (Short Form)*

1. Are you basically satisfied with your life?
2. Have you dropped many of your activities and interests?
3. Do you feel that your life is empty?
4. Do you often get bored?
5. Are you in good spirits most of the time?
6. Are you afraid that something bad is going to happen to you?
7. Do you feel happy most of the time?
8. Do you often feel helpless?
9. Do you prefer to stay at home, rather than going out and doing things?
10. Do you feel that you have more problems with memory than most?
11. Do you think it is wonderful to be alive now?
12. Do you feel worthless the way you are now?
13. Do you feel full of energy?
14. Do you feel that your situation is hopeless?
15. Do you think that most people are better off than you are?

Data were collected between October 10–30, 2016, and the questionnaire was administered in person. The approval of the ethics committee was obtained in October 2016 from the ethics committee of the medical faculty of the university to which the researchers are affiliated.

2.1. Statistical Analysis

For the statistical evaluation of the data, percentages, mean numbers, standard deviations, and figures were used. Furthermore, the Mann–Whitney U test, Chi-square test, Fisher exact test, and Kruskal–Wallis variance analyses were also employed. For statistical significance, $p < 0.05$ was considered.

3. RESULTS

Sociodemographic characteristics: The 77 elderlies who constituted the sample of our study comprised 29 (37.7%) females and 48 (62.3%) males. The mean age was 75.9 ± 8.2 (minimum; 60 years, maximum; 95 years). The majority of the participants was widowed (58.4%), had children (71.4%).

Twenty-two of the elderlies (28.6%) were depressive and 55 were normal (71.4%). Depressive symptoms were assessed according to variables reported in the table and reported as factors that may be associated with depression in the literature. In univariate analysis, low telephone call frequency, concerns of leaving the residential home, persistent physical illness, and inability to complete self-care activities were significantly associated with existence of depressive symptoms ($p < 0.05$; Table 2).

The mean GDS-15 score of the elderly was 4.04 ± 3.42 (minimum; 0, maximum; 14). When the average of the scores was examined according to the variables, GDS-15 scores were found to be higher in those with low telephone call frequency ($p < 0.01$), who were concerned about leaving the residential home ($p < 0.05$), who felt very sick ($p < 0.01$), and who were continuously ill ($p < 0.05$; Table 3). When other factors were examined, no statistically significant difference was found between the mean scores ($p > 0.05$).

4. DISCUSSION

Many risk factors have been identified for depression in the elderly. Various studies showed that being a woman, having low socioeconomic status, loss of partner, living alone, inadequate physical activity, inadequate social support, experiencing sleep disorders, having cognitive or chronic diseases, lack of ability to perform self-care activities, reluctance to participate in social activities, and receiving no visits are factors that contribute to depression (5, 9, 13, 14). Therefore, it is important to target individuals who lack social support and have risk factors in interventions.

Table 2. *Comparison of Depressive Symptom Inventory with One-Way Analysis by Factors Affected by Depression*

		Depression				p
		Depressive		Normal		
		n	%	n	%	
Age (Mean ± Standart Deviation)		75.23 ± 7.3		76.20 ± 8.6		0.693 [c]
Gender	Female	9	31.0	20	69.0	0.710 [a]
	Male	13	27.1	35	72.9	
Having Children	Yes	17	30.9	38	69.1	0.473 [a]
	No	5	22.7	17	77.3	
Social İnsurance	No	3	50.0	3	50.0	0.345 [b]
	Yes	19	26.8	52	73.2	
Education	No training	3	30.0	7	70.0	0.976 [a]
	Primary school	9	27.3	24	72.7	
	Middle school and higher	10	39.4	24	70.6	
Income Level of Perception	Low	9	39.1	14	60.9	0.407 [a]
	Middle	11	23.9	35	76.1	
	High	2	25.0	6	75.0	
Reasons For Coming To Residental Home	Own wish	19	29.2	46	70.8	0.763 [b]
	İnvoluntary	3	25.0	9	75.0	
Compliance problem with Children	No	12	31.6	26	68.4	0.406 [a]
	Yes	5	21.7	18	78.3	
Telephone Call Frequency	Several times a week	12	32.6	26	68.4	**0.023** [a]
	Several times a month	8	42.1	11	57.9	
	Once a year or never	2	10.0	18	90.0	
Visitor Status	Several times a week	6	20.8	16	59.3	0.215 [a]
	Several times a month	5	23.8	16	76.2	
	Once a year or never	11	40.7	16	59.3	
Homecoming Frequency	Several times a week	6	15.8	32	84.2	0.051 [a]
	Several times a month	6	40.0	9	60.0	
	Once a year or never	10	41.7	14	58.3	
Length of Live In Residental Home	Less than one year	1	9.1	10	90.9	0.163 [b]
	Longer than one year	21	31.8	45	68.2	
Satisfaction From Management	Partially satisfied	12	33.3	24	66.7	0.386 [a]
	Fully satisfied	10	24.4	31	75.6	
Satisfaction From Personnel	Partially satisfied	9	39.1	14	60.9	0.144 [a]
	Fully satisfied	13	24.1	41	75.9	
Satisfaction With The Physical Condition of The Institution	Partially satisfied	5	29.4	12	70.6	0,931 [a]
	Fully satisfied	17	28.3	43	71.7	
Satisfaction From Residents	Not at all satisfied	3	33.3	6	66.7	0.597 [a]
	Partially satisfied	14	31.8	30	68.2	
	Fully satisfied	5	20.8	19	79.2	
Institutional Social Activity	Not enough	7	30.4	16	69.6	0.813 [a]
	Enough	15	27.8	39	72.2	
The Desire To Participate İn The Activities	Reluctant	7	36.8	12	63.2	0.505 [a]
	Sometimes willing	9	30.0	21	70.0	
	Always willing	6	21.4	22	78.6	
Residental Home Residents' To Perspective	Strange or anyone	10	35.7	18	64.3	0.476 [a]
	Friend	9	27.3	24	72.7	
	Family and ally	3	18.8	13	81.3	
The Concern About Leaving From The Residental Home	Sometimes	6	60.0	4	40.0	**0.018** [b]
	Never	16	23.9	51	76.1	
Feeling Healthy	Healthy	7	19.3	29	80.7	0.144 [a]
	Normal	3	25.0	9	75.0	
	Sick	12	41.4	17	58.6	
Continuous Physical İllness	No	5	16.1	26	83.9	**0.047** [a]
	Yes	17	37.0	29	63.0	
Duration Of Physical Illness	less than one year	0	0	2	100.0	0.528 [b]
	Longer than one year	17	37.8	28	62.2	
The Sharing of The Room	Single	1	10.0	9	90.0	0.265 [b]
	Two or more people	21	31.3	46	68.7	
Fear of Falling And Bone Fracture	Yes	9	42.9	12	57.1	0.089 [a]
	No	13	23.2	43	76.8	
Sleeping Problem	Yes	8	34.8	15	65.2	0.431 [a]
	No	14	25.9	40	74.1	
Chronic Pain	No	17	28.8	42	71.2	0.932 [a]
	Yes	5	27.8	13	72.2	
Urinary Problems (Jam etc.)	Yes	5	33.3	10	66.7	0.752 [b]
	No	17	27.4	45	72.6	
Defecation Problems (Constipation etc.)	Yes	9	42.9	12	57.1	0.089 [a]
	No	13	23.2	43	76.8	
Doing self-care	Not exactly	6	60.0	4	40.0	**0.028** [b]
	Exact	16	23.9	51	76.1	
Mobility	Yes	5	50.0	5	50.0	0.138 [b]
	No	17	25.4	50	74.6	

[a] *Chi-Square test.* [b] *Fisher's exact test.* [c] *Mann Whitney U test.*

Table 3. *Comparisons of Factors Related to Depression according to GMS Score's Mean*

		GMS Total Score			
		n	%	Mean(Std. deviation)	p
Telephone Call Frequency	Everyday	20	26.0	3 (0.3)	**0.002**[d]
	Several times a week	18	23.4	2.17 (0.6)	
	Several times a month	20	26.0	4.75 (0.7)	
	Once a year	17	22.1	6.59 (4.1)	
	Never	2	2.6	2.5 (0.7)	
The Concern About Leaving From The Residental Home	Yes	3	3.9	8.67 (2.5)	**0.045**[c]
	Sometimes	7	9.1	5.29 (4.5)	
	Never	67	87.0	3.7 (3.1)	
Feeling Healthy	Very healthy	7	9.1	1.86 (2.8)	**0.020**[d]
	Healthy	35	45.5	2.94 (2.4)	
	Normal	3	3.9	4 (2.6)	
	Sick	31	40.3	5.45 (3.5)	
	Very sick	1	1.3	.	
Continuous Physical Illness	No	31	40.3	2.87 (2.5)	**0.016**[c]
	Yes	46	59.0	4.83 (3.7)	

[c] *Mann Whitney U test.* [d] *Kruskal Wallis test.*

In a study conducted in Turkey, the prevalence of depressive disorder (major + minor) in the general population was 9% (15). Depression occurs in approximately 15% of patients >65 years old who apply for a doctor for various reasons and 25% in residential homes abroad (16). In a study conducted in Turkey, 34% of the elderly living in their own homes had depression, whereas 48% of those living in residential homes had depression (14). Despite the low rates of depression in prevalence studies, which are generally diagnosed in a structured manner in accordance with standard clinical diagnostic criteria, depression rates were high in studies using scales that diagnosed at the level of symptoms (5). In this study, the prevalence of depression was found to be 28.6% with GDS as a diagnostic scale. Harris et al. found a 23.8% similarity in our study of depression to our study of GDS in the UK (17). Şahin et al. compared the prevalence of depression among those living in residential homes and those living in their own homes in a study in Edirne. The prevalence among those living in residential homes was found to be 48.1% (14). In Şahin's study, no information was provided regarding the inclusion of elderly people with loss of function due to physical illnesses (14). We did not include patients who were directed to a rehabilitation center owing to cognitive or physical illness; therefore, we possibly found the prevalence of depression to be lower despite using the same scale. In a survey conducted by Demet et al. in a residential home, the prevalence of depression was found to be 35.9% (5). This difference may be due to the fact that 37.9% of the respondents in the rehabilitation center consisted of the elderly of low socioeconomic status. The prevalence of depression found in a study by Kavakçı et al. involving 3039 individuals of 55 years old was 13.6% (10). Considering that their study sample was not from a residential home and comprised a younger group, a lower prevalence of depression may have been found in our study. The prevalence of depression was 48% among the elderly in some residential homes. This percentage indicates that the significantly high scores from the GDS were from insufficient social support for the elderly, and depressive symptoms were overlooked. Interventions would be appropriate in this regard. When we considered the variables related to depression, we found a significant difference between the frequency of telephone calls and depression in our study. Bekaroğlu et al. found that the lack of care is a risk factor for depression in the elderly at residential homes, and this finding was also confirmed in our study (18).

We found an association between depression and anxiety of withdrawal from the residential home. Demet et al. also noted that depressive symptoms were more frequent in the elderly who were concerned about leaving the residential home, and this finding was consistent with that of the literature (5).

When health status and effects of mobility on depression were examined, results revealed that depressive symptoms were more frequent in those who stated that they had persistent physical illness and were unable to perform self-care activities. Şahin et al. demonstrated that physical health problems increase the prevalence of depression in the elderly (14). According to our findings, the presence of physical illness was related to depression.

Linden et al. detected depression in 50% of patients being examined by psychiatrists after evaluation and treatment by a physician (19). For this reason, physicians may be advised to assess and screen elderly patients who have physical problems for depression. Kurtoğlu reported that 77% of the elderly who were diagnosed with depression had a disability. Valvanne and Tilvis found that depression is associated with loss of health and function in the elderly. Disability, health problems, and inability to complete self-care activities can both be the cause and consequence of depression. Considering that we are unsure about temporality of the factors we investigated and depression, the relationships we found may not be causal.

Factors such as sex (14), educational status (8, 20), marital status (8), social insurance, and income (5), which are defined as risks for the formation of depression in the literature, were not effective indicators in our study.

5. CONCLUSION

As a result, depressive symptoms in elderly living in residential homes reached significant levels, which were related to inadequate self-care, concern about leaving from the residential home, low telephone call frequency, and persistent physical illness. The risk of becoming depressed

among the elderly residing in residential homes may be high; therefore, health care providers should evaluate such patients.

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Clinical and Experimental Health Sciences

Idiopathic Osteosclerosis of the Jaws in Turkish Subpopulation: Cone-Beam Computed Tomography Findings

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ABSTRACT

Objective: Idiopathic osteosclerosis (IO) was defined as an asymptomatic, incidental radiographic finding of intrabony sclerosis with unknown origin. The purpose of this retrospective study is to evaluate IO distribution, location, relationships and radiographic features by cone beam computed tomography (CBCT) in Turkish subpopulation.

Methods: The study group consisted of CBCT images of 279 individuals, 140 females and 139 males aged 20-69. In received images IO distribution, location in the jaws, dental and cortical relationships, shape and internal structure were evaluated. In axial and cross-sections superoinferior (SID), mesiodistal (MDD) and buccolingual (BLD) distances of IO were measured. The data was compared with age groups and gender.

Results: Ninety-two IO in 75 individuals were detected with 26.9% distribution rate. There was a higher prevalence in mandible (82.6%) than maxilla (17.4%). The most frequently involved area was posterior mandible (43.4%). No statistically significant difference in the distribution of IO was found between genders ($p>0.05$). There was a higher prevalence among young group than middle-aged and above middle-aged groups ($p=0.026$). According to relation of IO with dental roots separate IO (76.1%) was the most frequent relationship. Seven IO (7.6%) were detected as not related with any cortical structure. Mean SID, MDD and BLD were recorded 5.58; 4.80 and 4.18 mm respectively.

Conclusion: IO was detected at a high rate in Turkish subpopulation. CBCT was found as an efficient method to evaluate radiographic features, relationships and location of IO within the jaws before surgical and orthodontic operations.

Keywords: Cone beam computed tomography, Osteosclerosis, Jaw, Mandible, Maxilla.

1. INTRODUCTION

Idiopathic osteosclerosis (IO) is one of the terms that is used for describing intrabony sclerosis with unknown origin since 1990s (1-5). The other terms are known as 'dense bone island', 'bone scar', 'bone whorl', 'enostosis', 'eburnated bone', 'focal periapical osteopetrosis' and 'focal osteosclerosis' (2, 6-8). It is accepted that these lesions are almost always asymptomatic and incidental radiographic findings. None of the inflammatory, dysplastic, or neoplastic features might be seen on radiographic and histological examinations (1-9). This entity is not unique for jaw bones; it can be found mostly on pelvis, femur and the other long bones extracranially (10). Previous studies showed that IO is commonly located at premolar-molar regions of mandible (1-10).

Even though the etiologic factors of IO formation have not been clearly understood yet; bone reaction related with increased occlusal forces, stimulating effect of residual root fragments and sufficient blood supply, torus-like developmental anatomic variations have been discoursed as possible causes of IO formation (1, 5, 13-15, 19-22).

Radiographic image of IO is described as localized, well-defined, non-expansile and usually homogeneous radiopaque masses potentially round, elliptic, or irregular in shape. There is no radiolucent halo around this mass; conversely characteristic radiating bony streaks blended with surrounding normal trabecular bone bring brush-like border in its appearance (9, 10). With this radiologic appearance; IO can be differentiated from sclerotic lessions surrounded with radiolucent border like osteoma, osteoblastoma, periapical cemental dysplasia and from the lessions caused cortical expansion like torus and exostosis (7, 16-18). The distribution of IO was reported between 1.7% and 31% in many studies investigated among various populations by different radiographic equipment (1-6, 8-23).

Idiopathic osteosclerosis is usually required no treatment protocol because of its asymptomatic nature. However some complications caused by IO were reported like changes in tooth position or eruption path, root resorption, obstruction or slowdown of orthodontic tooth movement (4, 24, 25). Besides, the consequences of implant replacement in a region with IO have been unknown in default of investigation. Therefore the radiographic features of IO such as location

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in trabecular bone, size, internal structure, borders and relationship with anatomic structures should be investigated before orthodontic treatment to regulate the biomechanical forces and surgical procedures like implant planning or maxillofacial trauma. The radiographic features explained in detailed is also necessary to differentiate IO from other radiopaque lessions. Because many of the lessions such as osteoma, odontoma, osteoblastoma and soft tissue calsifications need treatment much as IO need no treatment itself (12, 16-18, 24, 25).

Many studies about IO of the jaws have been based on panoramic radiography (2-4, 8, 15-22), which provides two-dimensional (2D) aspect of image layer. Nevertheless, cone-beam computed tomography (CBCT) enables clinicians to evaluate three-dimensional (3D) images of dentomaxillofacial structures with low dose of radiation compare to computed tomography (CT) (26-28). CBCT imaging techniques supports to investigate concurrently three orthogonal planes together with cross-sections. Thus the exact locations and characteristics of IO can be identified in detail (12, 14, 23). Along with a limited number of studies were performed by CBCT to evaluate IO of the jaws; fewer studies investigated distribution and radiographic features of IO in Turkish subpopulation by CBCT (12, 14, 23). Therefore, the purpose of this retrospective study is to evaluate distribution, location, relationships and detailed radiographic features of IO by CBCT in a Turkish subpopulation.

2. METHODS

The data of patients who referred to Department of Oral and Maxillofacial Radiology, Faculty of Dentistry, Marmara University with various purposes (impacted tooth, temporomandibular disorder, implant or orthodontic planning) from 2013 to 2014 were retrospectively examined and 279 patients those 20 years old and more were selected as study group. The patients with systemic or metabolic bone disease, trauma anamnesis, maxillofacial deformation and history of surgical operation of dentofacial region were excluded from the study group. The study protocol numbered as 140.014.8979 was approved by the Local Committee of Research of Ethics of Marmara University.

Osteosclerotic lesions surrounded by radiolucent rim; clearly identifiable residual roots of deciduous or permanent teeth; radiopaque lesions associated with teeth which have deep caries, large restorations or root canal treatment; radiopaque lesions caused cortical expansion, root resorption, replacement of roots or neurovascular canals; radiopaque lesions known as tori, exostoses or soft tissue calcifications and radiopaque-radiolucent mixed lesions were also excluded from the study. Thus, the asymptomatic sclerotic areas without radiolucent border, and cortical expansion; in edentulous region, dentate region without tooth relation or related with tooth without deep caries, large restorations, root canal treatment and resorption; round, elliptical or irregular in shape and vary in size was defined as IO.

All projections were taken with the same radiographic equipment (Planmeca Promax SD Mid CBCT device, Helsinki, Finland, with 90 kVp and 12 mA). All tomographic images were carried out by the same technician. Romexis 2.92 software program (Planmeca Oy, Helsinki, Finland) was used for reconstruction and evaluation of all projections. The images were exported and saved as a single frame DICOM files. The assessment of images was fulfilled directly on monitor screen (N56VZ-S4283H model of Asus Computer, ASUSTeK Computer Inc. Beitou District, Taipei, Taiwan, with NVIDIA GeForce GT 650M 4GB screen cart and 15.6 inch Full HD LED 1920X1080 pixel monitor).

To ensure a professional and efficient evaluation, oral diagnosis and radiology clinician and specialist (A.D.) who had been working in the Department of Oral Diagnosis and Radiology evaluated the clinical images. During meetings for the pilot study, the clinician and radiology specialist trained to evaluate tomographic images by specialist (F.N.P.) who had been working in Oral Diagnosis and Radiology for fifteen years or more, and an agreement on the objective criteria for the qualitative evaluation of the images was forged among the evaluators.

The existence of IO was investigated on coronal, sagittal and axial sections. Then the mandibular location of IO was detected as incisive, canine, canine-premolar, premolar, premolar-molar, molar and angle-ramus regions; the maxillary location of IO was detected as incisive, canine, canine-premolar, premolar, premolar-molar and molar regions on the images with IO. The shape of IO was defined as round, elliptical and irregular; the internal structure of IO was defined as homogeneous (HO) and heterogeneous (HT) (Figure 1).

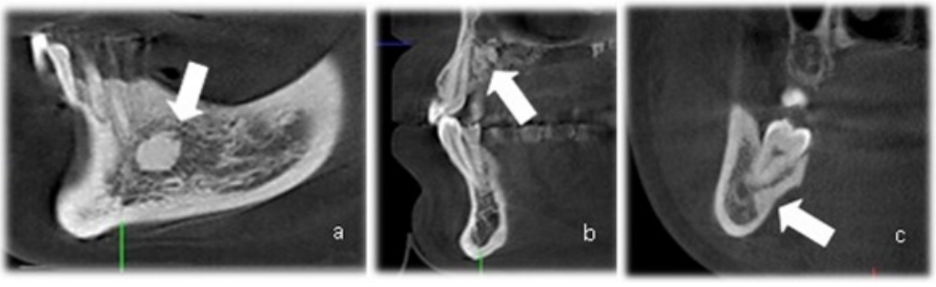

Figure 1: *Arrows show homogeneous round IO in mandibular canine-premolar region (a); heterogeneous irregular IO in maxillary canine region (b) and homogeneous elliptical IO in mandibular molar region (c).*

In addition; the images with IO were evaluated on cross-sections and, the dental relationship of IO was defined as apical, interradicular, apical-interradicular and separate; the relationship of IO with jawbones' cortical structures was defined as buccal, lingual, buccal-lingual and separate. The IO relationship with neurovascular canal (mandibular canal, mental foramen and incisive canal) cortices and maxillary sinus or nasal floor cortices were also investigated on cross-sections (Figure 2).

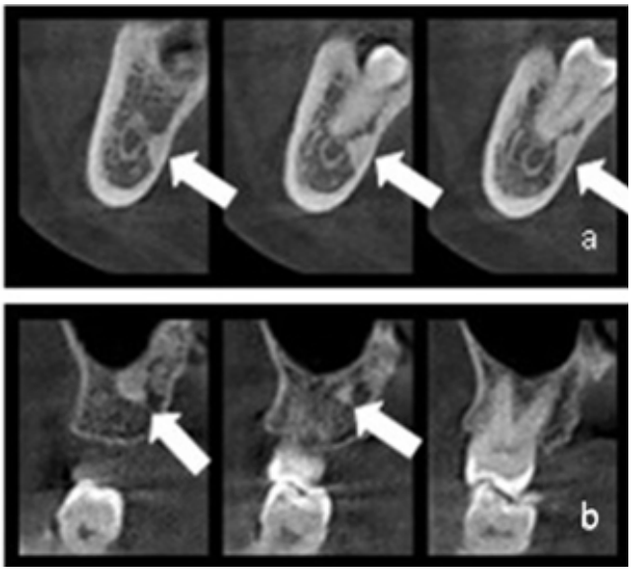

Figure 2: *Arrows show lingual and mandibular canal cortex related IO separated from dental root (a); maxillary sinus cortex related IO separated from jawbones' cortical structures (b).*

Moreover, the superoinferior (SID) and buccolingual (BLD) distances of IO were measured on cross-sections; mesiodistal (MDD) distance of IO was measured on axial sections (Figure 3). The obtained data were compared with gender and age groups.

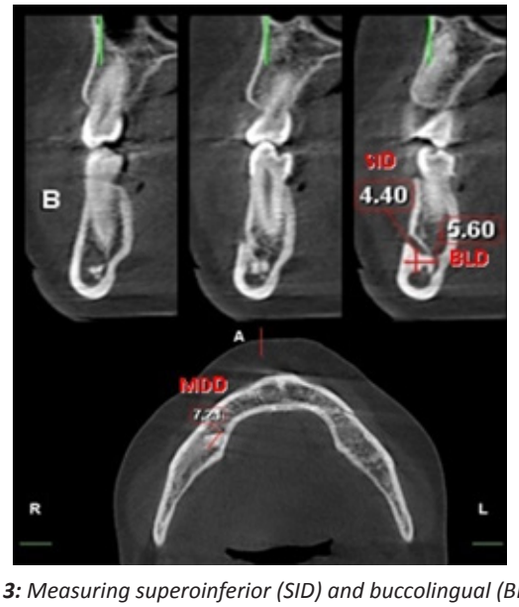

Figure 3: *Measuring superoinferior (SID) and buccolingual (BLD) distances of IO is shown on cross-section images; mesiodistal (MDD) distance of IO on axial section.*

2.1. Statistical Analysis

The data was analyzed with Statistical Package for Social Sciences (SPSS) for Windows 15.0 (SPSS, Inc., Chicago, Illinois). Descriptive statistical methods (mean, standard deviation and frequency) were used for evaluation of the data. One Way Anova test was used to compare quantitative data and age groups and Tukey HDS test was used to differentiate which groups caused the difference. Student t test was used to compare gender and the parameters. Chi square test, Fisher's exact test and Continuity correction were used to compare qualitative data. Values of $p<0.05$ were interpreted as significant.

3. RESULTS

The study group consist of 279 patients (139 males, 140 females) ranging in age from 20 to 69 years (average age 33.11±10.41years). One hundred twenty five of the patients were at 20-29 age range (44.8 %), 87 of the patients were at 30-39 age range (31.2%) and 67 of the patients were above 40 years of age (24.0%).

In 75 patients, a total of 92 IO were identified. Sixty patients had 1 IO (21.5%), 13 patients had 2 IOs (4.7%), 2 patients had 3 IOs (0.7%).

Idiopathic osteosclerosis was detected 40 of female patients (28.6%) and 35 of male patients (25.2%). Females with IO were slightly higher than males but there was no statistically significant difference between genders (p=0.564).

The highest rate of IO was found as 20-29 age range with 35 of the patients (25.0%). Twenty two of the patients were found between 30-39 age range (17.1%) and 16 of the patients were found above 40 years of age (11.5%). The occurrence of IO was significantly higher at young group than middle-aged and above 40 years of age groups (p=0.026). There was no statistically significant difference between age groups either mandible (p=0.259) or maxilla (p=0.521). Besides there was no correlation between age groups and the occurrence of IO in mandible or maxilla (p=0.233).

The vast majority of IO occurred in mandible; only 16 IO were detected in maxilla (17.4%) while 76 IO were detected in mandible (82.6%). There was a statistically significant difference between jaws (p<0.0001). In mandible; the occurrence of IO in molar region (30.4%) was significantly higher than the other regions (p<0.0001); there was no statistically significant difference between maxillary regions (p=0.623) (Table 1).

Irregular IO (42.4%) was found higher than round (25.0%) and elliptical IO (32.6%) but there was no statistically significant difference between shapes (p=0.082). Idiopathic osteosclerotic areas were mostly irregular (38.0%) in mandible and elliptical (9.9%) in maxilla. There was no statistically significant difference between shapes either mandible (p=0.062) or maxilla (p=0.144).

Homogeneous IO was found 85 of the lesions (92.4%). Round (25.0%) and elliptical (32.6%) IOs were all found HO. All

Table 1: *Regional distribution of IO in jawbones.*

	Incisive	Canine	Canine Premolar	Premolar	Premolar Molar	Molar	Angle Ramus	p	[1]Total	p
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)		n (%)	
[1]Mandible	2 (2.2%)	3 (3.3%)	6 (6.5%)	15 (16.3%)	12 (13.0%)	28 (30.4%)	10(10.9%)	**<0.0001***	76(82.6%)	**<0.0001***
[1]Maxilla	2 (2.2%)	1 (1.1%)	3 (3.3%)	3 (3.3%)	2 (2.2%)	5 (5.4%)	-	**0.623**	16(17.4%)	
[2]Total	4 (4.3%)	4 (4.3%)	9 (9.8%)	18 (19.6%)	14 (15.2%)	33 (35.9%)	10(10.9%)	**0.250**	**92**	

[1]*Chi Square Test* [2]*Fisher' s Exact Test p<0.05 p<0.05*

HT IOs were found irregular in shape (7.6%). There was no correlation between shapes and the occurrence of IO as HO (p=0.455). But it was shown that the occurrence of IO as HT was depend on the shape of IO (p=0.006).

Heterogeneous IO was found 6 in mandible (6.5%) and 1 in maxilla (1.1%). Homogeneous IO was found significantly higher than HT in mandible (p<0.0001), maxilla (p<0.0001) and total (p<0.0001). There was no correlation between the occurrence of IO as HO or HT and the occurrence of IO in mandible or maxilla (p=0.822).

Thirteen of the IOs were found apical (14.1%), 6 of the IOs were found interradicular (6.5%), 3 of the IOs were found apical-interradicular (3.3%) relation with the dental roots and 70 of the IOs were found separate (76.1%) from the dental roots. Separate IO (76.1%) was found significantly higher among dental root related IO (p<0.0001).

Separate IO from jawbones' cortical structures (34.8%) was found significantly higher than buccal cortex related IO (20.7%), lingual cortex related IO (31.5%) and both buccal and lingual cortex related IO (13.0%) (p=0.001). Lingual cortex related IO (31.5%) was found significantly higher among the jawbones' cortical structure related IO (p=0.026). Compared to total IO related with any jawbones' cortical structures (65.2%); separate IO from jawbones' cortical structures (34.8%) was found significantly lower (p=0.004).

Fifty six of 92 IO (60.9%) were found related with the cortical structures of neurovascular canals (53.3%) and maxillary sinus or nasal cavity floor (7.6%). Mandibular canal related IO (31.5%) was found significantly higher than incisive canal related IO (5.4%) and mental foramen related IO (16.3%) (p<0.0001). The IO related with any neurovascular canal cortex (53.3%) was found significantly higher than maxillary sinus or nasal cavity floor related IO (7.6%) (p<0.0001).

Twenty five of 32 separate IO from jawbones' cortical structures were found related with neurovascular canals and maxillary sinus or nasal cavity floor (25.2%). Among these separate IO from jawbones' cortical structures; neurovascular canals related IO (62.5%) was found significantly higher than maxillary sinus or nasal cavity floor related IO (15.6%) (p<0.0001); and mandibular canal related IO (40.6%) was found significantly higher than incisive canal related IO (6.3%) and mental foramen related IO (15.6%) (p=0.008).

The exact number of separate IO from any cortical structure was found 7 (7.6%) in total of 92 IO. Compared to IO related with cortical structures in anyway (92.4%); separate IO from any cortical structure (7.6%) was found significantly lower (p<0.0001).

The average dimensions of IO were measured 4.80±2.64 mm for MDD, 4.18±1.57 mm for BLD and 5.58±2.81 mm for SID. There was no statistically significant difference between gender and the average dimensions of MDD (p=0.610), BLD (p=0.101) and SID (p=0.753).

Except BLD (p=0.043); there was no statistically significant difference between age groups and the mean dimensions of IO (p=0.528 for MDD and p=0.173 for SID). The mean BLD for 20-29 age group was found significantly lower than 30-39 age group (p=0.029) and above 40 age group (p=0.045). There was no statistically significant difference in the mean BLD between age groups of 30-39 and above 40 (p=0.436) (Table 2).

Table 2: *Age distribution of the dimensions of IO.*

	20-29				30-39				Above 40			p
	Min (mm)	Avg±SD (mm)	Max (mm)		Min (mm)	Avg±SD (mm)	Max (mm)		Min (mm)	Avg±SD (mm)	Max (mm)	
[1]MDD#	1.44	4.45±2.56	13.12		2.00	5.14±2.46	11.12		1.65	4.98±3.10	12.46	**0.528**
[1]SID#	2.40	4.95±2.12	12.43		2.00	6.06±3.49	18.80		2.80	6.06±2.69	13.58	**0.173**
[1]BLD#	1.44	3.71±1.21	6.80		1.70	4.52±1.84	8.40		2.40	4.57±1.56	8.25	**0.043***
	p between 20-29 and 30-39				**p between 30-39 and above 40**				**p between 20-29 and above 40**			
[2]BLD		**0.029***				**0.436**				**0.045***		

[1]*Oneway ANOVA test* [2]*Tukey HDS test p<0,05*

#MDD:MesioDistal Distanec, SIM: SuperoInferior Distance, BLD: BuccoLingual Distance

4. DISCUSSION

Trabecular structure of bone becomes narrower and cortical content of bone increases and becomes denser in line with the extent of functional requirements during remodeling process. The term of sclerosis usually describes this intrabony density difference if the process has a pathologic mechanism (29, 30). Clinically asymptomatic sclerotic areas detected as incidental radiographic finding without any expansion or surrounding radiolucent rim are known as idiopathic osteosclerosis unless there is inflammatory, dysplastic or neoplastic features (1-9).

Many studies investigated among various populations by different radiographic equipment reported the distribution of IO between % 1.7 and % 31 mostly without gender discrimination and with mandibular posterior predominance (1-6, 8-23). The difference in ethnic groups living different geographic regions; having distinctive genetic variations, habits and addictions was implied for one of the reasons of this distribution discrepancy in addition to unstandardized IO description between investigators and difference in radiographic technique of choice (3, 6, 15, 16).

In two different study with full-mouth radiography in American population; IO distribution was reported 5.4% of 1921 patients by Geist and Katz (1) and 5.7% of 1585 patients by William and Brooks (4). Similarly in a study with CBCT, Chen et al. (12) reported IO as 5.1% of 400 American patients.

The distribution of IO was reported 31% of 100 patients and 1.8% of 7389 patients in Chinese population (6, 16). Although panoramic radiography was performed on both study, the numbers of populations were seen remarkably different. Also in Korean population; IO was detected 2.7% of 6220 patients by full-mouth radiography and 6.7% of 2001 patients by panoramic radiography (11, 15). In European population; IO was detected 7.6% of 210 patients by full-mouth radiography and 2.8% of 1200 patients by panoramic radiography (13, 22).

In Turkish population; IO distribution was reported between 2.4% and 6.1% on the studies performed with panoramic radiography [18-21] and 4% of 500 patients on a study performed with CBCT (14).

Researchers agreed with accepting the radiopacities related with roots of teeth with deep caries, large restorations, canal treatment or crown as condensing osteitis (CO) and excluding from the studies. And as well many researchers; including of all Turkish population studies; preferred to exclude sclerotic areas detected in edentulous regions based on the probability of remaining surgical scars or residual CO. Idiopathic osteosclerosis was reported between 2.4% and 9.5% by the studies excluded radiopacities in edentulous regions (5, 14, 15, 18-21). However, it is usually expected that CO is reshaped with time to normal trabecular bone area by remodeling when the cause of inflammation process is removed by dental extraction, root canal therapy, periodontal treatment or other essential treatment approaches. Although approximately 30% of CO is known persistent after treatment; it is almost impossible to ascertain the exact cause of these abandoned sclerotic areas a few months or years after treatment approach except without a meticulously documented history. The term of IO is usually used to define focal sclerotic areas without knowing the cause-effect relationship for certain. On the other hand, the abandoned sclerotic areas in the edentulous alveolar bone have no correlation to any sign of infectious because of being apart from teeth (4, 6, 22, 29, 31). In this context, IO was reported between 5.1% and 11% by some other researchers preferred to include sclerotic areas in edentulous regions (3, 12, 13). In a study performed in Turkish population by CBCT; Kalyoncu et al. (14) shared the idea yet still by excluding the sclerotic areas detected in edentulous regions they reported IO 4% of 500 patients. Moreover the sclerotic areas under 3 mm in size were excluded from some of the studies without any justification and IO was reported between 2.8% and 7.6% (5, 13-15, 22).

In this study, the sclerotic areas detected in edentulous regions were included if there is no sign of cortical expansion and resorption or replacement of neighboring anatomical structures. Also the sclerotic areas under 3 mm in size were included since there was no explainable reason. Thus IO distribution was found as 26.9% of 279 patients. This rate was closed to the panoramic radiography study reported IO as 31% of 100 Chinese patients by Austin and Moule [6] and higher than all of the other studies (1-5, 9, 11, 12-23).

Idiopathic osteosclerosis was mostly detected slightly higher in females without statistically significant difference (1-6, 9, 11-15, 17-22) and in mandibular posterior regions dominantly (1-6, 9, 11-22). Similarly in this study IO was located significantly higher in mandibular molar region (30.4%) and there was no statistically significant difference between females (28.6%) and males (25.2%).

Some researchers reported the earliest age of IO detection as around 9 years old (9, 15, 16) and most of the studies reported IO mostly in 20-29 and 30-39 age groups without any significant difference (4, 5, 11, 13, 19, 20, 22). It has been thought that the detection of IO mostly around mid-thirties was coincided with the peak of bone formation in these periods (15, 16, 19, 32). The results in this study supported this idea with the aspect of the highest disturbance of IO in 20-29 age group; but the occurrence of IO was significantly higher at young group (25%) than middle-aged (17.1%) and above 40 years of age (11.5%) groups similar with Li et al. (16).

The dimensions of IO were measured from 0,5 mm to 7 cm by using different radiographic equipment (2-4, 6, 9, 12-14, 19, 21, 22) and in follow-up studies it was showed that IO tend to be growing in young and stabile in adults (4, 9, 13). Petrikowski and Peters (9) measured the mean diameter of IO 2.1 mm in 9-14 age group, 2.7 mm in 15-24 age group, 2.8 mm in 25-29 age group and 3.3 mm in mid-thirties. Kalyoncu et al. (14) supported Petrikowski and Peters (9) on the subject of increasing dimension of IO with age.

The mean SID, MDD and BLD of IO were measured 5.58 mm, 4.80 mm and 4.18 mm respectively in this study. Except BLD; there was no statistically significant difference between age groups and the mean dimensions of IO. The mean BLD for 20-29 age group (3.7 mm) was found significantly lower than 30-39 age group (4.5 mm) and above 40 age group (4.6 mm). These results supported the developmental etiological approach of IO formation due to its tendency of growing in young and being stabile in adults (4, 9, 13, 22).

Kalyoncu et al. (14) detected 20 IO in CBCT and reported that round IO (80%) in shape was significantly higher than irregular IO (80%). Contrarily no significant difference between shapes was reported in other studies investigated IO as round, elliptical and irregular in shape (3, 4, 12, 18, 19). However, HO IO was reported significantly higher than HT on the whole (5, 9, 12, 14). Similarly in this study, there was no statistically significant difference between round (25%), elliptical (32.6%) and irregular (42.4%) IO in shape and HO internal structure of IO (92.4%) was significantly higher. Besides all round (25.0%) and elliptical (32.6%) IOs were found HO and all HT IOs were irregular (7.6%) in shape. There was no correlation between shapes and the occurrence of IO as HO. But it was shown that the occurrence of IO as HT was depend on the shape of IO.

Through limited number of studies investigated IO by CBCT; Misirlioglu et al. (19) reported 16.7% of IO had bicortical relation, 80% IO related with mandibular canal cortex and only 1 IO located separately in trabecular bone without any cortical relation. Kalyoncu et al. (14) detected 13 IO located superior to mandibular canal and 3 IO at inferior location but it was not stated whether these 16 IO related with cortex of mandibular canal or not. Chen et al. (12) investigated IO in Taiwanese and American cohorts and detected 21% bicortical related IO, 21% buccal cortex related IO and 29% lingual cortex related IO for Taiwanese cohort; 20% bicortical related IO, 40% buccal cortex related IO and 33% lingual cortex related IO for American cohort. Supportively; Geist and Katz (1) reported a possible relation between IO formation and cortical bone formation taken shape into trabecular bone to bound anatomical structures like neurovascular bundles.

Separate IO from jawbones' cortical structures was found 34.8%, buccal cortex related IO was 20.7%, lingual cortex related IO was 31.5% and bicortical IO was 13.0% in this study. Compared to total IO related with any jawbones' cortical structures (65.2%); separate IO from jawbones' cortical structures (34.8%) was found significantly lower, similar with Misirlioglu et al. (19).

Differently from other studies; the relation of IO with cortical structures of neurovascular canals and maxillary sinus or nasal cavity floor was also investigated in this study. Neurovascular canal cortex related IO was found 53.3% and maxillary sinus or nasal cavity floor cortex related IO was 7.6%. Among neurovascular canal cortex related IOs; mandibular canal related IO (31.5%) was found significantly higher than incisive canal related IO (5.4%) and mental foramen related IO (16.3%).

Idiopathic osteosclerosis detected separate from jawbones' cortical structures was reevaluated according to their relation with cortical structures of neurovascular canals and maxillary sinus or nasal cavity floor. Thus 25 of 32 separate IO from jawbones' cortical structures (25.2%) were found related with neurovascular canals and maxillary sinus or nasal cavity floor. Compared to IO related with cortical structures in anyway (92.4%); separate IO from any cortical structure (7.6%) was found significantly lower. This results supported the etiological theory suggested by Geist and Katz (1).

5. CONCLUSION

The distribution of IO was found 26.9% mostly higher than the other studies because of the discrepancies about the study criteria and preferred radiographic technique. Idiopathic oscteosclerosis might be detected in any age without gender difference and dominantly in mandibular posterior regions. CBCT was found as an efficient method for detailed evaluation of IO. The radiographic features of IO should be explained in detailed by CBCT to make differential diagnosis if in doubt on plain films and to avoid complications before orthodontic treatment or surgical procedures like implant planning or maxillofacial trauma. Although many etiologic factors were suggested for IO formation this mechanism has still remained unknown. Further studies with larger samples and wider age range is needed to understand better the nature and biological behavior of IO especially in the presence of occlusal forces or implant applications.

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Clinical and Experimental Health Sciences

The Effect of Virtual Rehabilitation Added to an Accelerated Rehabilitation Program After Anterior Cruciate Ligament Reconstruction: A Randomized Controlled Trial

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ABSTRACT

Objective: This study aimed to determine the effectiveness of virtual rehabilitation on balance and functionality in patients with anterior cruciate ligament (ACL) reconstruction.

Methods: A total of 22 males who had undergone ACL reconstruction were divided into Nintendo and control groups. Both of the groups received six week accelerated rehabilitation in our department, and the Nintendo Wii© (Nintendo, Washington, USA) balance games were added to Nintendo group after three weeks for forty minutes a day, three times a week. Patients were evaluated for pain (visual analog scale), functionality (Lower Extremity Functional Scale), center of gravity (COG) and balance (Nintendo Wii©) at the baseline and end of the 3th and 6th week of rehabilitation program.

Results: Similar improvements were determined in the pain, functionality, COG and balance scores of the two groups at the end of the treatment program and there were no significant differences between the groups in the amount of change in all parameters (p= 0.256, 0.393, 0.707, 1.000).

Conclusion: According to the results of this study the Nintendo Wii© balance games applied in the clinic under physiotherapist supervision did not change the outcome of the rehabilitation in early period after ACL reconstruction.

Keywords: Anterior Cruciate Ligament, Nintendo Wii©, Postural Balance.

1. INTRODUCTION

Anterior cruciate ligament (ACL) is the most injured and surgically reconstructed ligament in the body (1). While tibiofemoral joint biomechanics are impaired after injury (2), damage also occurs in the mechanoreceptors in the ACL insertion zone (3). The change in proprioception affects many factors such as level of physical activity (4), balance (5), restoration of muscle strength of the quadriceps (Q) and re-injury.

The primary goals of ACL reconstruction surgery are to restore knee stabilization and high-level functional activity and correct abnormal movement patterns (6). Although the mechanical stability is obtained with surgery, functional recovery can not be fully achieved when there is continuing damage of the mechanoreceptors (7). The post-operative rehabilitation program after ACL reconstruction is an important factor that reveals the efficacy of the surgical treatment as in many other areas (8). There is no consensus on the ideal treatment algorithm for patients undergoing ACL reconstruction as there are various clinical practices for the management of this injury (9). Better outcomes may result from reconstruction or improvements to the neuromuscular control of the knee in terms of an early return to daily functional activities and reduced rates of recurrence of the injury (10).

The Nintendo Wii© Balance Board (WBB) (Nintendo, Kyoto, Japan), is a component of the popular video game Wii Fit, which was designed as a video game controller, is primarily used together with a video game console and the relevant software. As this system can provide instant feedback and motivation through increased levels of difficulty (11), it has already been integrated into neurological rehabilitation programs for subjects with impaired balance (12).

With developments in technology in recent years, the exercises in the rehabilitation programs have become more enjoyable and interesting with virtual game systems (13). Few studies investigated the efficiency of the virtual games widely used in the rehabilitation after ACL reconstruction surgery. The aim of this study was to investigate the effectiveness of Nintendo Wii© balance games added to the accelerated rehabilitation program after ACL reconstruction in order to provide new information to the literature in this area.

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2. METHODS

This prospective study enrolled patients with MRI proven ACL injury who underwent arthroscopic ACL reconstruction between 26 October 2015 and 26 June 2016 in the Kartal Dr. Lütfi Kırdar Training and Research Hospital. Approval for the study was granted by the Ethics Committee of Marmara University, Health Sciences Institute (26.10.2015 – 4).

The inclusion criteria were as follows: arthroscopic ACL reconstruction in the previous six months, age >18 years, and no other treatment which might affect rehabilitation outcomes. Patients with contraindications for exercise practice, prior lower extremity operations, knee instability, meniscus and posterior cruciate ligament (PCL) rupture, additional disease or medication that may affect postural control, spinal and lower extremity injuries that can affect physical activity, or congenital deformity, were excluded.

Patients who had signed the informed consent form were divided into two groups using the "Research Randomiser" program (14). Each patient selected a number in a closed envelope, which was sorted for the randomisation process, and the patients were separated into the following two groups; the Nintendo group and the control group. The acclerated rehabilitation program including a modified Shelbourne protocol (15) was applied to both groups by a physiotherapist in our department. The rehabilitation program was divided into four phases. Phase 1 included edema and pain control, and increasing range of motion; Phase 2, weight-bearing and strengthening exercises (thera-band ® exercises); Phase 3 and 4 strengthening exercises progressed and functional and balance exercises (with rocker board). The sessions were individual and lasted for 45 minutes, 3 times a week for 6 weeks. Nintendo Wii© balance games were added to the rehabilitation program of the Nintendo group in the 4th week. These games lasted 40 minutes after the main rehabilitation program, and the patients were given a 10 minute rest period before starting the Nintendo Wii© balance games. Each of the soccerheading, skiing, tabletilt and penguinslide games placed in the Nintendo Wii© game console were played for 10 minutes. In the last week of the virtual rehabilitation program, the difficulty levels of the games were increased.

Assessments were performed three times, at the start of the treatment program, at the end of the 3rd week and 6th week. A patient assessment form was completed at the first assessment session. Data including age, height, weight, and time after surgery were collected.

Pain was assessed before activity using the visual analog scale (VAS) (16), comprising a 100 mm line with 0 representing 'no pain' and 10 representing 'the worst pain' (17).

The 'Lower Extremity Functional Score' (LEFS), a self-reported questionnaire scoring system, was used to assess knee function (18). This questionnaire consists of 20 items ranging from 0 – 4 points. Scores are reported on a 0 – to 80 – point scale, with higher scores correlating with better functionality.

The center of gravity (COG) and balance were assessed with the Nintendo Wii© balance board. The Nintendo Wii© balance board is a part of the Nintendo Wii© game console that measures the balance and COG with pressure sensors. It can be used for evaluation and training purposes (19). This research was carried out in accordance with the Helsinki Declaration.

2.1. Statistical analysis

Statistical analysis were performed using SPSS v.11.5 for Windows software. Conformity of the data to normal distribution was analysed with the Shapiro-Wilks test. Comparison of treatment groups was performed using an intention-to-treat analysis of difference between baseline-final scores with 95% confidence intervals. The Wilcoxon Signed-Rank test was used to compare outcomes before and after treatment. The Mann-Whitney U test was used to compare improvements and differences between groups. A value of $p<0.05$ was considered statistically significant for all analyses for a two tailed test.

3. RESULTS

A total of 51 patients who have undergone arthroscopic ACL reconstruction were screened for eligibility. Thirty patients (59 %) participated in the study (Figure 1). After the randomisation process, the patient distributions were as follows: the Nintendo group (n= 15), the control group (n= 15). A total of 22 patients were able to complete the study and assessments.

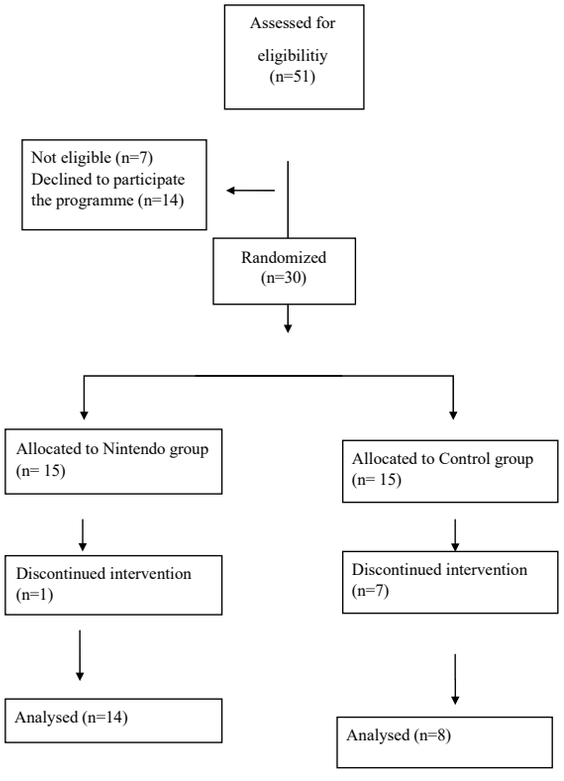

Figure 1. *Flow diagram of the participants.*

There were no significant differences between participants in the two groups for any demographic characteristics and baseline assessment scores and (Table 1 and 2). There were no significant differences between the groups in respect of time since surgical reconstruction (p= 0.945). The baseline, 3rd and 6th week pain levels did not differ between the groups (p= 0.365, 0.676 and 0.639). At the end of the treatment program, the pain values were significantly reduced in the Nintendo group (p= 0.005), but there was no statistically significant change in the control group (p= 0.058). In a comparison of the groups in terms of the pain score changes, there were no significant differences between the two groups (Table 3).

Table 1. *Comparison of Baseline Demographics and Surgery Time in Groups*

	Nintendo Group (n = 14) Mean ± SD[a]	Control Group (n = 8) Mean ± SD[a]	p[b]
Age (year)	31 ± 8.41	24 ± 5.94	0.123
Height (cm)	174.5 ± 5.80	178 ± 7.30	0.245
Weight (kg)	78 ± 10.41	76.50 ± 15.34	0.393
BMI[c] (kg/m²)	26.21 ± 2.72	22.80 ± 4.81	0.101
Time passed after surgery (days)	38.5 ± 40.5 24 (13-170)	26.6 ± 14.09 21 (18-60)	0.945

[a] *Standart Deviation*
[b] *Significance value in comparison between groups by Mann Whitney U Test*
[c] *BMI: Body mass index*

Table 2. *Measurement Results at Baseline, Week 3 and 6*

Measurements		Nintendo Group (n = 14) Mean ± SD[a]	Control Group (n = 8) Mean ± SD[a]	p[b]
Pain	**Baseline**	3.9 ± 1.1	3.1 ±1.8	0.365
	3rd week	2 ± 1.79	2.5 ± 1.48	0.676
	6th week	1 ± 1.07	1.5 ± 1.16	0.639
LEFS	**Baseline**	31.5 ± 16.25	40.5 ± 13.10	0.452
	3rd week	51 ± 11.68	59.5 ± 9.25	0.585
	6th week	69 ± 9.47	70.5 ± 4.40	0.758
COG-effected side (%)	**Baseline**	41.25 ± 6.94	40 ± 11.53	0.864
	3rd week	46.40 ± 4.53	49.50 ± 5.24	0.055
	6th week	49 ± 4.70	50.20 ± 5.11	0.561
Balance score (sec)	**Baseline**	11 ± 8.06	15 ± 6.84	0.372
	3rd week	17 ± 7.74	16.5 ± 7.40	0.754
	6th week	24 ± 6.59	21 ± 7.19	0.593

[a] *Standart Deviation*
[b] *Significance value in comparison between groups by Mann Whitney U Test*

The baseline, 3rd and 6th week LEFS levels did not differ between the groups (p= 0.452, 0.585 and 0.758). In consecutive assessment sessions, the LEFS scores of both groups improved statistically (p= 0.002 and 0.012), although neither group showed any superiority to the other in terms of LEFS changes (p= 0.811, 0.516 ve 0.393; Table 3).

In the baseline assessment, the limbs were asymmetrically loaded in both groups and COG was displaced to the unaffected extremity (p= 0.002 and 0.024). The COG asymmetry improved statistically significantly in the Nintendo group (p= 0.006), after 6 weeks of rehabilitation, but the change in the control group was not statistically significant (p= 0.106). The changes in the COG positioning were compared between the two groups, and there were no statistically significant differences in any of the assessment results (p= 0.277, 0.717, 0.707) (Table 3). However, at the end of the treatment, the location of the COG was statistically symmetrical in both groups (p= 0.345 and 0.944).

The baseline, 3rd and 6th week balance levels did not differ between the groups (p= 0.372, 0.754 and 0.593). When the intra-group changes were analysed at the end of the 6 – week treatment program, the balance score changes in both groups were not significant (p= 0.075 ve 0.161). According to the measurements, statistically significant differences were not observed in the comparison of the balance score changes between the groups in different assessment sessions (Table 3).

Table 3. *Mean Change in VAS, Functionality, Center of Gravity and Balance Scores from Baseline to Week 3 and 6, from Week 3 to 6*

Mean Change		Nintendo Group (n = 14) Mean ± SD[a]	Control Group (n = 8) Mean ± SD[a]	p[b]
Pain	**C1[c]**	2 ± 1.96	1± 2.13	0.298
	C2[d]	3 ± 1.20	1.5 ± 1.85	0.397
	C3[e]	1 ± 2.38	0.5 ± 2.35	0.256
LEFS	**C1[c]**	17.50 ± 13.79	18 ± 15.09	0.811
	C2[d]	12 ± 11.86	7 ± 8.02	0.516
	C3[e]	35.50 ± 18.77	27.50 ± 16.65	0.393
COG (%)	**C1[c]**	2 ± 5.29	5 ± 12.71	0.277
	C2[d]	3 ± 6.03	2.5 ± 6.92	0.717
	C3[e]	8.3 ± 7.18	7.70 ± 15.56	0.707
Balance score (sec)	**C1[c]**	4 ± 8.27	0 ± 6.53	0.305
	C2[d]	1± 5.19	7.5 ± 12.93	0.246
	C3[e]	4 ± 8.30	4 ± 11.23	1.000

[a] *Standart Deviation*
[b] *The statistical significance of the comparison of the differences between the evaluations*
[c] *C1: Mean change from baseline to week 3,*
[d] *C2: Mean change from week 3 to week 6,*
[e] *C3: Mean change from baseline to week 6. sec: second, %: percent*

4. DISCUSSION

The results of this study indicate that adding the Nintendo Wii© virtual games to the accelerated rehabilitation program does not provide additional benefit in terms of pain, functionality, COG and balance parameters in the early period of ACL reconstruction.

ACL-reconstruction aims to restore joint stability and prevent osteoarthritis and the risk of secondary meniscal tears (20) and an individualized postoperative rehabilitation program is necessary for a stable functional knee. Rehabilitation programs after ACL reconstruction are implemented at different intensities and for different durations (7, 21-23).

In this study, the individual exercise therapy sessions were performed for 45 minutes, 3 times/week (18 sessions) and the Nintendo Wii© balance games were added to the Nintendo group, for 40 minutes, 3 times/week after the 3rd week of the rehabilitation protocol. A 2–5 – year follow-up of 604 patients after arthroscopic ACL reconstruction, reported that moderate to severe subjective anterior knee pain related to activity, walking up and down stairs, and sitting with the knee flexed was found in 33.6% of patients (24).

In another study, significant knee pain and symptoms were found in 9%–39% of first – time ACL reconstruction patients at 6 years (20). Furthermore, it has been claimed that pain affects functioning (25).

Despite receiving treatment following reconstruction, a decrease in functionality has been reported in approximately 50% of cases (26). Many factors, such as quadriceps activity, decreased strength, decreased EMG activity of vastus medialis (VM) and vastus lateralis (VL) muscles, and increased musculotendinous stiffness, are considered to affect knee function after ACL reconstruction compared to the unaffected extremity (27).

Post-surgery rehabilitation programs and visual biofeedback exercises are methods that improve functionality (23, 27). A previous study has shown that Nintendo Wii games with visual and auditory biofeedback and traditional physiotherapy approaches have no superiority in terms of functional outcomes in post-op ACL rehabilitation (23). In this study, a significant improvement was observed in the pain values after the treatment program in the Nintendo group received Nintendo Wii© balance games added to the accelerated rehabilitation program. When the intra-group change of functionality scores were analysed, improvements were obtained in the scores of both groups after treatment. However, no superiority of either groups was determined in terms of changes in pain and functional scores. According to the results of the study, Nintendo Wii© balance games do not appear to provide additional advantages to the accelarated rehabilitation program in respect of improving pain and functionality in the early period after the reconstruction.

Changes in weight loading and reduced postural control are seen in individuals who have undergone ACL reconstruction (7). Although it has been suggested in the literature that these changes are seen in the short term (28) it has also been indicated that these could extend to 2 years after reconstruction (29). It has been reported that this condition may be caused by weak sensory input due to changes in mechanoreceptor and central nerve connections (30).

The average location of the weight of an object is the center of gravity (COG). When an individual stands on a Nintendo Wii© balance board, the COG of the subject is detected and displayed as feedback on the screen. This can then be used to encourage and improve the motor learning of the subject (31).

At the baseline of this study, COG asymmetry was present in both groups and symmetric COG distribution was obtained in the two groups after the 6 – week rehabilitation program. In one case study, COG symmetry was obtained in the 3rd week of Nintendo Wii© balance board exercises after posterior cruciate ligament reconstruction (22) but no comparison was possible because no other treatment approach was applied in this study.

When intra-group change was analyzed in this study before and after treatment, the mean COG distribution change was statistically significant in the Nintendo group. However, when the mean change amounts in COG distribution were compared, it was seen that the groups were similar and adding 3 weeks of Nintendo Wii© balance board exercises was not superior to the accelerated rehabilitation program applied alone. Due to the limited follow-up period of the current study patient population, it was not possible to determine the effect of Nintendo Wii© balance games on COG and other parameters in the long term.

Changes in neuromuscular control occur with damage to the mechanoreceptors after ACL injury (32). Continuation of damage to the mechanoreceptors (7), and poor proprioception lead to a deterioration in balance (4, 16), even if the mechanical stability of the knee is provided by reconstruction.

The results of this study showed that adding Wii games to the rehabilitation protocol did not provide superiority to the change of balance scores. Regaining dynamic joint stability between the 20th and the 32nd weeks after surgery may be seen as a reason for the failure of balance improvement in the early stage. It has also been noted in literature that early-stage balance training in ACL reconstructed individuals was not effective on balance (10).

A stable Nintendo Wii© balance board, providing an easy assessment for young and physically active patients, could have been another reason that similar balance score changes were obtained in both groups. Dynamic and more difficult balance assessments may provide more sensitive information (30).

A previous study reported that a reconstructed group had significantly lower balance scores than a healthy group in balance assessment, which included standing on one foot, but no difference in assessment when standing on both feet (33). Another important issue is that the eyes have to be open in the standing balance assessment with the Nintendo Wii© balance board. The balance system is complex and, vestibular, visual, and somatosensory/proprioceptive sensory systems, provide our sense of balance. That worse balance scores have been reported in balance assessments performed with the eyes closed may indicate the visual system compensation mechanism (34). It can be considered that no differences were determined between the groups in respect of balance improvements because of the contribution of visual feedback and that the assessment was made using a static balance board.

Studies in literature, examining the effects of virtual rehabilitation and Nintendo Wii© on balance and lower

extremity functioning in individuals with ACL reconstruction are rather limited. This study is one of the few studies in this area. The limited time of the study, not including long-term follow up, small sample size, and assessment balance scores with static and simple measurement can be accepted as limitations of this study. The results of this study need to be confirmed on larger samples with a randomized control group with long term follow-up.

5. CONCLUSION

The results of this study showed that the addition of Nintendo Wii© balance games played with the Nintendo Wii Balance Board in the last 3 weeks of the 6 – week rehabilitation program did not provide additional benefits to the accelerated ACL rehabilitation protocol in respect of the parameters assessed. However, the clinical observations showed that patients could become bored with the repetitive exercises of the rehabilitation program and had more enjoyment with the Nintendo Wii© balance games, which are becoming widespread with the development of technology. Patients reported that they played the games with active participation, found them enjoyable but not did not become exhausted. It can be said that the Nintendo Wii© games are easy to use and inexpensive. Nintendo Wii© balance board exercises can be more suitable for improving balance and symmetrical weight-bearing in the rehabilitation of sedentary and geriatric populations with neurological deficit.

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Clinical and Experimental Health Sciences

Women's Consumption of Probiotic Food; The Example of Yogurt and Kefir

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ABSTRACT

Objective: This study examined the relationship between pregnancy, women's knowledge level, and consumption of probiotic foods.
Methods: This descriptive and cross-sectional study was carried out with the participation of 560 pregnant (n:280) and non-pregnant (n:280) women who applied to the Gynecology and Obstetrics polyclinic at a university hospital between June and August 2017. Data were collected using a data collection form developed by the researchers based on relevant scholarly literature.
Results: The two groups (pregnant and non-pregnant women) were similar in average age and educational level. Of the participants, 59.1% knew the term probiotics. The rates of knowing the term probiotics (p: 0.001), recognizing kefir as a type of probiotic food, and consuming kefir as a probiotic food (p: 0.001) were higher in non-pregnant women than in pregnant women at a statistically significant level ($p<0.01$). Women consumed probiotic foods mostly for problems in the digestive system (87%) and strengthening the immune system (74.1%). Not knowing what probiotic meant was the most common reason (22%) for not consuming probiotic foods.
Discussion: Of the participants, 59.1% knew the term probiotics. Non-pregnant women's rate of knowing the term probiotics (67.9%) was statistically higher than that of the pregnant women (50.4%) (p: 0.001; $p<0.01$). In sum, some pregnant women did not know the term probiotics. In the scholarly literature, there are no studies on pregnant women's consumption and knowledge level of probiotic foods. Most of the studies' sample groups were students. Findings of all these studies show that the most significant reason for not consuming probiotic foods was not having the sufficient knowledge about probiotics. Considering the positive effects of probiotic foods on health, increasing the consumption of probiotics could contribute to a healthy pregnancy. In Turkey, we need to determine pregnant women's knowledge of probiotic foods to initiate and popularize the consumption of probiotics.
Conclusion: Findings of this study indicated that pregnant women did not have sufficient knowledge of the term probiotics. Pregnancy is the ideal period for women to develop behavior that protects and improve both their own and their babies' health. For this reason, raising awareness on and motivating pregnant women toward probiotic food consumption are significant.
Keywords: Pregnancy, probiotics, nutrition

1. INTRODUCTION

Nutrition is a key element supporting health and growth during the life cycle. Nutritional habits play a crucial role in maintaining a healthy life. A society's health status can be assessed by the presence of healthy individuals. Women's health must be tackled, protected, and improved, primarily because it is closely related to the health status of families and society. Nutrition is significant for individuals from all social levels, but women and children are the most affected groups. Women's healthy nutrition status provides an indicator of the well-being and development of primarily families and society because problems arising from women's health and nutrition are transferred to the next generations through their children (1,2). Although good health requires sufficient and balanced nutrition at all periods of life, pregnancy is one of the special times when the need for proper nutrition increases (1). Good nutrition and healthful life style of the mother during pregnancy is important both for her own and her baby's health. The aim of proper nutrition during pregnancy is to meet physiological needs, keep nutrition supplements in balance, and to provide the energy and nutritional elements necessary for the normal development of the fetus (2).

Probiotics are live microorganisms and/or their constituents that positively affect human health by balancing the intestinal flora. Probiotic products refer to foods that contain added microorganisms presumed to be beneficial for the body; most of the microorganisms used as probiotics are of the lactobacilli group (primarily, Lactobacillus and Bifidobacterium). Other microorganisms are also used as probiotics, S. boulardii among them (3).

Probiotics are added mostly to yogurt and other types of fermented products. Additionally, in the last few years, these bacteria have been added to beverages, turned into tablets, capsules, freeze dried products, and sold in markets (3, 4).

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One of the most widely known probiotic food is kefir, which has been produced and consumed for many years by local populations in Caucasia. It is a Turkish traditional fermented milk product obtained through the fermentations of ethyl alcohol and lactic acid using kefir grains. Microorganisms in kefir's structure enable easy digestion, and in this way, increase the absorption of nutritional elements (5).

Another commonly known prebiotic product is yoghurt. Yoghurt is a fermented dairy product that includes prebiotics and has been used by human for centuries. It contains high-quality protein, carbohydrates, and lipids with a high dry matter content and it is also rich in calcium, phosphor, and Vitamin B. Yoghurt provides rich sustenance. It is easy to digest and strengthens the immune system. Yoghurt can also be consumed easily by people with lactose intolerance, so it has an important place in people's lives (4-6).

Probiotic microorganisms have many positive effects on human health. They directly or indirectly affect the intestinal physiology, stimulate the immune system, and influence the host's oral and intestinal digestive system, upper respiratory tract, and mucosal surface of the urogenital system. Therefore, probiotics have a potential health-promoting effect that also decreases the risk for disease (6).

The published literature on the use of probiotic foods during pregnancy showed that probiotic use did not have any effect on the rates of cesarean sections, the week of birth, or birth weight. However, it was observed that some types of probiotics reduced the risk of developing atopic dermatosis in babies, premature birth, and the incidence of bacterial vaginosis. Accordingly, probiotics increased the transmission of some fatty acids to the fetus and cytokines, which signified the positive effects of kefir on the mother's immune system in the milk and blood. Probiotics also decreased the frequency of gestational diabetes in the mother and the level of maternal pre-prandial blood glucose; the scholarly literature did not report any harmful effects of probiotic foods (7-12).

In Turkey, the literature on the use of and the knowledge level of probiotic foods is limited (4, 13, 14), and there is no study on the use of probiotics during pregnancy. This study analyzed the relationship between pregnancy and women's knowledge level and consumption of probiotic foods.

2. METHODS

2.1. Research Type

This descriptive study was carried out to determine the relationship between pregnancy and non-pregnant women and the knowledge level and consumption of probiotic foods.

2.2. Field Site

The study was carried out at the polyclinics of the Department of Gynecology and Obstetrics of a university hospital, with the participation of pregnant women who applied to the polyclinic and stayed in the maternity ward, and non-pregnant women who stayed at the gynecology clinic.

2.3. Research Population and Sample

The research population comprised pregnant and non-pregnant women who applied to the Department of Gynecology and Obstetrics for monitoring and treatment. The number of pregnant women, who applied to the polyclinic monthly between the dates May and June 1, 2017, was 1026. Assuming that a similar number of pregnant women would apply to the same university on a monthly basis, the random sampling method was used; 280 women were included in each of the groups (pregnant and non-pregnant) (n: 560). The two groups were similar in terms of the age range and educational levels. Criteria for women's ınclusion in the study women, who agreed to participate in the study, did not have communication difficulty or mental insufficiency, were pregnant, or not pregnant were included in the study.

2.4. Data Collection Forms

Data were collected using a 34-question data collection form, which was developed by the researchers based on relevant scholarly literature (4, 13, 14). This data collection form was composed of questions to assess pregnant women's socio-demographic and obstetric characteristics, and their use of and knowledge level of probiotic foods.

2.5. Data Collection

Researchers collected the data by administering the 34-question data collection form to pregnant and non-pregnant women who applied and stayed at the polyclinic service, using the face-to-face interview technique. Each questionnaire was completed within an average of 8 to 10 minutes.

2.6. Data Analysis

IBM SPSS Statistics 22 (IBM SPSS, Turkey) was used for statistical analysis of the data. Descriptive statistical methods (mean, standard deviation, frequency) were employed for quantitative data, whereas the Chi-square test, Yate's Correction for Continuity, and Fisher's Exact Test were used to analyze qualitative data. Significance level was set at $p<0.05$.

2.7. Research Ethics

Çukurova University Faculty of Medicine's Ethics Committee, and Çukurova University Balcalı Hospital Department of Gynecology and Obstetrics' Academic Council approved this study. Participants were informed about the aim of this study and were asked to provide written consent using the Informed Consent Form.

3. RESULTS

3.1. Women's socio-demographic and pregnancy-related characteristics

In this study, 50% (n=280) of the women were pregnant and the other 50% (n=280) non-pregnant; their average age was 29.32 ± 6.27 years. Among all participants, 32.7% were high school graduates. Pregnant women's average pregnancy duration was 27.64 ± 9.99 weeks, and the average of number of pregnancies per pregnant woman was 2.55 ± 1.73 (Table 1).

Table 1. *Women's Socio-demographic and Obstetric Characteristics (n=560)*

Descriptive Characteristics	Pregnant Women	Non-pregnant Women	Total
	Mean± SD Min-Max	Mean± SD	
Age (years)	29.28±6.12 (18–44)	29.36±6.42 (18–45)	29.32±6.27 (18–45)
Week of Pregnancy	27.64±9.99 (4–41)		
Number of Pregnancy	2.55±1.73 (1–13)		
	n (%)	**n (%)**	**n (%)**
Educational Level			
Primary school	67 (23.9)	57 (20.4)	124 (22.1)
Secondary school	60 (21.4)	59 (21.1)	119 (21.3)
High school	87 (31.1)	96 (34.3)	183 (32.7)
University	66 (23.6)	68 (24.3)	134 (23.9)
Employment Status			
Employed	217 (77.5)	156 (55.7)	373 (66.7)
Unemployed	63 (22.5)	124 (44.3)	187 (33.4)
Partner's Educational Level			
Primary school	52 (18.6)	28 (10.0)	80 (14.3)
Secondary school	62 (22.1)	38 (13.6)	100 (17.9)
High school	89 (31.8)	107 (38.2)	196 (35.0)
University	77 (27.5)	107 (38.2)	184 (32.9)
Perceived Income Level			
High	85 (30.4)	89 (31.8)	174 (31.1)
Middle	184 (65.7)	176 (62.9)	360 (64.3)
Low	11 (3.9)	15 (5.4)	26 (4.6)
Place of Residence			
City	185 (66.1)	213 (76.1)	398 (71.1)
District	61 (21.8)	44 (15.7)	105 (18.8)
Village-Town	34 (12.1)	23 (8.2)	57 (10.2)

3.2. Women's knowledge and consumption of probiotic foods

Of the participants, 59.1% knew the term probiotics, and 53.6% recognized kefir as a probiotic food. It was found that 73% of the women consumed probiotic food, and 71.6% consumed yogurt as a type of probiotic. The most commonly cited reason for consuming probiotics was its benefits for the digestive system, at a rate of 87% (Table 2).

The rates of knowing the term probiotics (p:0.001), recognizing kefir as a type of probiotic source (p:0.001), and consuming kefir as a probiotic food (p:0.001) were higher in non-pregnant women at a statistically significant level than in pregnant women (p<0.01).

Of the pregnant women, 49.6% did not consume probiotic food because they "did not know what it was". Looking at the reasons for consuming probiotic food, the rate of health personnel's influence was 15%, whereas the rate of consuming probiotics for the baby's health was 34.3%. These findings for pregnant women were significantly higher than those for the non-pregnant women (p<0.01) (Table 2)

The reasons for non-pregnant women's consumption of probiotic food were strengthening the immune system (33.2%), easing the problems of constipation (17.3%), and alleviating existing problems with the digestive system (16.3%). There was a statistically significant difference between these findings for non-pregnant women and those for pregnant women (p<0.01; p<0.05, respectively) (Table 2).

3.3. Women's knowledge of probiotic food

Of the participants 71.6% agreed with the statement "probiotic foods strengthen the immune system"; 72.12% agreed with the statement "probiotic foods regulate the digestive tract"; 54.8% agreed with the statement "probiotic foods are helpful in preventing constipation"; 62.7 % agreed with the statement "probiotic foods are beneficial for the baby's health"; and 72.1% agreed with the statement "probiotic foods protect the body against allergies (eczema)" (Table 3).

Among the women, 48.8% had no idea about the statement "probiotic foods reduce the risk of cancer"; 58.2% had no idea about "probiotic foods are helpful in preventing diarrhea"; 51.1% about the statement "probiotic foods are appetizing", and 50.5% did not have any idea about the statement "probiotic foods enable the regulation of blood glucose level".

Table 2. *Women's Knowledge Regarding and Consumption Patterns of Probiotic Food*

	Pregnant Women (n=280) n (%)	Non-Pregnant Women (n=280) n (%)	Total (n=560) n (%)	Significance Level
Knowing the Term Probiotic				X^2
Know	141 (50.4)	190 (67.9)	331 (59.1)	*17.738*
Do not know	139 (49.6)	90 (32.1)	229 (40.9)	**p:0.001****
Recognizing the Type of Probiotic Food				
Yogurt				X^2
Know	218 (77.9)	232 (82.9)	450 (80.4)	*2.217*
Do not know	62 (22.1)	48 (17.1)	110 (19.6)	p:0.136
Kefir				X^2
Know	127 (45.4)	173 (61.8)	300 (53.6)	*15.192*
Do not know	153 (54.6)	107 (38.2)	260 (46.4)	**p:0.001****
Consumption of Probiotic Food				X^2
Yes, I consume probiotic foods.	207 (73.9)	202 (72.1)	409 (73.0)	*0.227*
No, I do not consume any probiotic foods.	73 (26.1)	78 (27.9)	151 (27.0)	p:0.634
Reasons for not Consuming Probiotic Food				
Not knowing what it is	65 (23.2)	58 (20.7)	123 (22.0)	
Thinking that it is unnatural	3 (1.1)	1 (0.4)	4 (0.7)	X^2
Not feeling the need to consume	2 (0.7)	1 (6.1)	19 (3.4)	*15.280*
Finding probiotic food tasteless	2 (0.7)	1 (0.7)	4 (0.7)	**p:0.009****
Thinking that probiotic foods have no positive effect on health	2 (0.7)	1 (0.0)	2 (0.4)	
Consumed Food Type				
Yogurt				X^2
Yes, I consume yogurt.	207 (73.9)	194 (69.3)	401 (71.6)	*1.484*
No, I do not consume yogurt.	73 (26.1)	86 (30.7)	159 (24.8)	p:0.223
Kefir				X^2
Yes, I consume kefir.	20 (7.1)	72 (25.7)	92 (16.4)	*35.169*
No, I do not consume kefir.	260 (92.9)	208 (74.3)	468 (83.6)	**p:0.001****
Frequency of Consumption	**(n=207)**	**(n=202)**	**(n=409)**	
Once a day	127 (61.4)	120 (59.4)	247 (60.4)	X^2
2–3 times a day	62 (30.0)	44 (21.8)	106 (25.9)	*11.729*
Once a week	16 (7.7)	32 (15.8)	48 (11.7)	**p:0.019***
Once every 15 days	2 (1.0)	6 (3.0)	8 (1.9)	
Source of Probiotic Food				
I make it myself at home.	161 (77.8)	135 (66.8)	296 (72.4)	X^2
I buy it from the market.	44 (21.3)	67 (33.2)	111 (27.1)	*8.990*
Other	2 (1.0)	0 (0.0)	2 (0.5)	**p:0.011***
Factors that Affect the Consumption of Probiotic Food (n=207)				
Television and the internet	46 (22.2)	56 (27.7)	102 (24.9)	
Health Problems	36 (17.4)	61 (30.2)	97 (23.7)	X^2
Recommendation of friends or immediate surroundings	47 (22.7)	48 (23.8)	95 (23.2)	*24. 310*
Health Personnel	31 (15.0)	9 (4.5)	40 (9.8)	**p:0.001****
Probiotic food is natural.	2 (1.0)	1 (0.5)	3 (0.7)	
Probiotic food is healthy.	45 (21.7)	27 (13.4)	72 (17.6)	
Reasons for Consuming Probiotic Food (n=207)				
For Problems Related to the Circulatory System				X^2
Yes	15 (7.2)	20 (9.9)	35 (8.6)	*0.613*
No	192 (92.8)	182 (90.1)	374 91.4	p:0.434
For a Constipation Problem				X^2
Yes	13 (6.3)	35 (17.3)	48 (11.7)	*11.001*
No	194 (93.7)	167 (82.7)	361 (88.3)	**p:0.001****
For Strengthening the Immune System				X^2
Yes	39 (18.8)	67 (33.2)	303 (74.1)	*10.931*
No	168 (81.2)	135(66.8)	106 (25.9)	**p:0.001****
For Problems related to the Digestive System				X^2
Yes	20 (9.7)	33 (16.3)	356 (87.0)	*42.038*
No	187 (90.3)	169 (83.7)	53 (13.0)	**p:0.044***
For my Baby's Health				X^2
Yes	71 (34.3)	15 (7.4)	86 (21.0)	*44. 463*
No	136 (65.7)	187 (92.6)	323 (79.0)	**p:0.001****
For Overall Health				X^2
Yes	142 (68.6)	126 (62.4)	268 (65.5)	*1.753*
No	65 (31.4)	76 (37.6)	141 (34.5)	p:0.186

χ^2: Chi-square Test, Yate's Correction for Continuity and Fisher's Exact Test *$p<0.05$ **$p<0.01$

Table 3. *Women's Knowledge of Probiotic Foods*

Knowledge of Probiotic Foods	Pregnant women (n=280) n (%)	Non-Pregnant Women (n=280) n (%)	Total (n=560) n (%)	Significance Level
Probiotic foods strengthen the immune system.				
Agree	200 (71.4)	201 (71.8)	401 (71.6)	X^2
Disagree	9 (3.2)	4 (1.4)	13 (2.3)	2.035
No Idea	71 (25.4)	75 (26.8)	146 (26.1)	p=0.361
Probiotic foods regulate the digestive tract.				
Agree	198 (35.4)	206 (73.6)	404 (72.1)	X^2
Disagree	8 (1.4)	3 (1.1)	11(2.0)	2.493
No Idea	74 (26.4)	71 (25.4)	145 (25.9)	p=0.287
Probiotic foods reduce the risk of cancer.				
Agree	138 (49.6)	130 (46.8)	268 (47.9)	X^2
Disagree	4 (1.4)	15 (5.4)	19 (3.4)	6.594
No Idea	138 (48.9)	136 (47.9)	273 (48.8)	**p=0.037***
Probiotic foods are helpful in preventing diarrhea.				
Agree	89 (31.8)	111 (39.6)	200 (35.7)	X^2
Disagree	19 (6.8)	16 (5.7)	35 (6.3)	3.788
No Idea	172 (61.4)	153 (54.6)	325 (58.0)	p=0.150
Probiotic foods are helpful in preventing constipation.				
Agree	157 (56.1)	150 (53.6)	307 (54.8)	X^2
Disagree	10 (3.6)	7 (2.5)	17 (3.0)	1.113
No Idea	113 (40.4)	123 (43.9)	236 (42.1)	p=0.573
Probiotic foods prevent the development of microorganisms that cause diseases.				
Agree	135 (48.2)	135 (48.2)	270 (48.2)	X^2
Disagree	15 (5.4)	6 (2.1)	21 (3.8)	4.158
No Idea	130 (46.4)	139 (49.6)	269 (48.0)	p=0.125
Probiotic foods are appetizing.				
Agree	109 (38.9)	80 (28.6)	189 (33.8)	X^2
Disagree	26 (9.3)	59 (21.1)	85 (15.2)	17.317
No Idea	145 (51.8)	141 (50.4)	286 (51.1)	**p=0.001****
Probiotic foods are beneficial for the baby's health				
Agree	185 (66.1)	166 (59.9)	351 (62.7)	X^2
Disagree	4 (1.4)	8 (2.9)	12 (2.1)	4.618
No Idea	91 (32.5)	106 (37.9)	197 (35.2)	p=0.202
Probiotic foods enable the regulation of blood glucose level.				
Agree	127 (45.4)	136 (48.6)	263 (47.0)	X^2
Disagree	4 (1.4)	10 (3.6)	14 (2.5)	3.674
No Idea	149 (53.2)	134 (47.9)	283 (50.5)	p=0.159
Probiotic foods protect the body against allergies (eczema).				
Agree	99 (35.4)	101 (36.1)	200 (72.1)	X^2
Disagree	14 (5.0)	9 (3.2)	23 (4.1)	1.134
No Idea	167 (59.6)	170 (60.7)	337 (60.2)	p=0.567

χ^2Chi-square Test **p<0.05* ***p<0.01*

4. DISCUSSION

The participating groups had similar characteristics: there were no statistically significant differences between participants (pregnant and non-pregnant women) in terms of their ages, duration of marriage, perceived economic status, and educational levels ($p>0.05$) (Table 1).

Of the participants, 59.1% knew the term probiotics (Table 2). Non-pregnant women's rate of knowing the term probiotics (67.9%) was statistically higher than that of the pregnant women (50.4%) ($p:0.001$; $p<0.01$). In sum, some pregnant women did not know the term probiotics. In the scholarly literature, there are no studies on pregnant women's consumption and knowledge level of probiotic foods. Most of the studies' sample groups were students (14-16). Findings of all these studies show that the most significant reason for not consuming probiotic foods was not having the sufficient knowledge about probiotics. Considering the positive effects of probiotic foods on health, increasing the consumption of probiotics could contribute to a healthy pregnancy. In Turkey, we need to determine pregnant women's knowledge of probiotic foods to initiate and popularize the consumption of probiotics.

Although non-pregnant women's rate of recognizing kefir as a type of probiotic food was 61.8%, this rate was only 45.4% for pregnant women (Table 2), illustrating that pregnant women did not have the sufficient knowledge of kefir to recognize it as a type of probiotic food. Women need to be better informed during pregnancy, a period that present an opportunity to strengthen the health of the fetus.

Among the pregnant women, 73.9% consumed yogurt, which is known to be the best probiotic food. The study by Zeren (2015) reported that 71.4% of the participants consumed yogurt, which is among the commonly preferred traditional foods in Turkish cuisine (17). In Turkey, yogurt is widely consumed due to the belief that it is both good for the health and helpful in preventing disease. We believe that women in Turkey do not consume yogurt for probiotic purposes: they consume yogurt as a healthy, natural, nutritious, and easily accessible food.

Table 3 displays the analysis of women's views on the effects of probiotic food on human health.

Of the participants, 32.5% did not have any opinion about the statement "***Probiotic foods are beneficial for the baby's health***". It is widely known that maternal nutrition during pregnancy is a significant contribution to fetal development. Previous studies have emphasized that probiotics prevented infections by strengthening the mother's health and the lowering rates of premature birth. Probiotics also improved the health of the mother and the baby by reducing the rate of maternal obesity (18-21).

Of the participants, 53.2% of the pregnant women and 47.9% of the non-pregnant women did not have any opinion about the statement "***Probiotic food enables the regulation of blood glucose level***". However, a study of a group of pregnant women highlighted that probiotic consumption during pregnancy lowered the frequency of gestational diabetes mellitus, maternal blood glucose level, and the frequency of preeclampsia (12, 22).

Of the participants, 59.6% of the pregnant women and 60.7% of the non-pregnant women did not have any opinion about the statement "***Probiotic foods protect the body against allergy (eczema)***". Previous studies have revealed that use of probiotic during and after pregnancy reduced the development of atopic dermatitis in babies (23-26).

The children of a group of pregnant women who ingested probiotic supplements starting from two months prior to birth and the following 2 months of breastfeeding were protected against eczema for 24 months after birth (27). If such findings are circulated in training or through the media, awareness could be raised on the importance of use of probiotics by pregnant women.

Among the participants in the present study, 40.4% of the pregnant women and 43.9% of the non-pregnant women did not have any opinion about the statement "***Probiotic foods are helpful in preventing constipation***". The scholarly literature reported that the rate of constipation during pregnancy ranged from about 11% to 38% (28). However, there are many studies proving that probiotics prevent constipation, a problem frequently encountered during pregnancy (29-31)

Looking at the "***Factors Affecting Women's Consumption of Probiotic Foods***", the influence of health personnel on consumption of probiotics was minor (9.8%) (Table 2). The study by Zeren (2015) emphasized that advertisements were the most influential factor that affect adults' consumption of probiotics (17). Other studies noted the great impact of television on probiotic consumption (15, 16, 32, 33). Our finding indicated that the health personnel did not provide pregnant women with effective and sufficiently detailed education on nutrition. Our experiences lead us to believe that routine clinical briefings have provided only limited information to the pregnant women.

This study provided information on small sample groups because it was carried out out at the polyclinics of the Department of Gynecology and Obstetrics of a university hospital in the Adana province. Hence, the study results could not be generalized over the whole society. Therefore, larger-scale studies are required at the national level for better results.

5. CONCLUSION

Probiotics play an increasingly important role, both in the health sector overall, and especially for pregnant women. Although there is an increasing number of studies highlighting the positive effects of probiotics on health, our findings determined that only 50.4% of pregnant women knew what probiotic foods were. The importance of probiotics should be emphasized, and women should be adequately

informed about this subject. We stipulate that consumption of probiotics would increase along with the awareness level.

Proper nutrition during pregnancy is crucial both for the mother and for the health of the growing fetus. Nutrition is cost effective: it improves the health and prevents diseases in the mother and the baby. Women sometimes may underestimate the importance of this period and be inattentive to their nutrition. Whereas health-seeking behaviors are expected during pregnancy, pregnant women in our study group did not know the necessary information about probiotics and their significant role in nutrition during pregnancy.

Raising the awareness of mothers and exemplary health personnel would enable an understanding of the significance of consuming probiotic foods for a healthy nutrition. In-service training programs on probiotic foods should be organized for all health personnel, especially midwives and nurses who meet pregnant women more frequently in primary health institutions. In this way, knowledge of probiotic foods should be disseminated. Moreover, as in all areas of life, today the media has a great influence on food selection and the field of nutrition. Women should be informed and awareness should be raised through the media about the importance of food for a healthy nutrition to improve maternal and fetal health.

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Clinical and Experimental Health Sciences

Effects of Intellectual Disability on Gross Motor Function and Health Related Quality of Life in Cerebral Palsy

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ABSTRACT

Objective: Cerebral palsy (CP) is a common developmental disorder which causes intellectual and motor disability, and affects quality of life. The aim of this study was to reveal the effect of intellectual disability (ID) on motor function and quality of life in CP.
Methods: Twenty-seven children with CP were divided into two groups as with or without ID. Motor function and health related quality of life was evaluated with Gross Motor Function Measurement–88 (GMFM-88) and Child Health Questionnaire-Parent Form 50 (CHQ-PF50) respectively.
Results: All dimensions of GMFM-88 and most of the dimensions of CHQ-PF50 were lower in children with ID compared to those without ID ($p<0.05$).
Conclusion: ID seems to have a disruptive effect on motor function and health related quality of life in CP. Adding approaches to improve the cognitive status to the CP rehabilitation program may be beneficial for motor function and quality of life.
Keywords: cerebral palsy, intellectual disability, motor function, quality of life

1. INTRODUCTION

Cerebral palsy (CP) is a common developmental disorder leading intellectual and motor disability in children (1). Intellectual disability (ID), which is being used instead of mental retardation in accordance with updated construct of disability recommended by WHO, covers social, cognitive, and adaptive deficits (2). Intellectual disability has a significant proportion (up to 60%) in CP cases and defined as impaired cognitive function and behaviour. 97.7% of severe disabled CP cases have been reported as having ID (3-5). The cerebral lesions causing CP affect the developmental process of various cognitive functions and usually lead ID. It has been reported that ID leads disability in daily activities, education and occupational processes in CP (6). In general, delay in the development of the central nervous system affects motor development in mentally disabled children (7).

Motor control, postural control, balance, and muscle tone abnormalities cause impairment of motor function in children with CP (8). These symptoms cause seconder musculoskeletal disorders like hip luxation, contractures, and scoliosis (9). Lower physical fitness, muscle strength and endurance; higher walking energy expenditure depending on gait abnormalities seen in children who have CP. Fatigue causes pain, functional disorders and limited quality of life in CP (10).

Mental, social, and physical satisfactions constitute health-related quality of life (HRQoL) (11-13). Children with CP have impaired functional and psychosocial HRQoL according to healthy ones (13, 14). It has been reported that severity of CP and motor function impairments affect physical HRQoL but not psychosocial (15, 16).

Motor function is known to be affected from cognitive status as well as sensorial systems (17). Cognition is also indicated as a factor affecting HRQoL in disabled children (18). However Wake et al. reported that cognitive impairment didn't affect the HRQoL of the children with CP (15). Therefore the literature is limited and the results are inconsistent about the motor function and HRQoL differences of children who have CP with and without ID. The objective of this study was to reveal the effect of ID on motor function and HRQoL in CP. Our hypothesis was that ID adversely affects motor function and HRQoL in CP.

2. METHODS

2.1. Participants

This cross sectional study was conducted by Bulent Ecevit University Faculty of Health Sciences Department of Physiotherapy and Rehabilitation. Twenty-seven children with CP (9 girls and 18 boys) from three different rehabilitation centres in Zonguldak, between 6-15 years of age, were

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included. Exclusion criteria were; history of operation within last 12 months, botulinum toxin A administration within last 6 months, and having no previous assessment about cognitive status.

The required permission was obtained from the Clinical Research Ethics Committee of Bulent Ecevit University (Protocol no: 2017-72-09/08). Participants (if applicable) and their parents were informed. 'Informed consent form' was signed by the participants (if applicable) and one of the parents of each participant.

2.2. Procedure

The demographic data of the participants were recorded according to the information received from the parents. Participants were divided into two groups as with or without ID on the basis of the Rehabilitation Research Center reports. All the assessments were performed at the research laboratory of the Bulent Ecevit University Faculty of Health Sciences.

2.3. Outcome measurements

Gross Motor Function Measurement – 88 (GMFM – 88)

This measurement has 5 dimensions (lying and rolling; sitting; crawling and kneeling; standing; walking, running and jumping) and 88 items. This measurement evaluates the rate of achievement of these activities. The higher score obtained from this measurement indicates better gross motor function (19). GMFM-88 assessment was performed by a physical therapist.

Child Health Questionnaire – Parent Form 50 (CHQ-PF50)

CHQ-PF50 measures HRQoL of children. This questionnaire contains 14 dimensions (including physical, psychosocial and parental aspects) filled by the parents. Score of the dimensions range from 0 to 100, and higher *score* indicates better HRQoL (20).

2.4. Statistical analysis

Data was evaluated using the SPSS 15.0 program for Windows (Statistical Package for the Social Sciences Inc.; Chicago, IL, USA). The significance level was set to $p<0.05$. The continuous variables were not normally distributed according to Shapiro–Wilk test. Mann Whitney U test was used to compare age, height, weight, BMI, GMFM-88 and CHQ-PF50 scores; Chi-square test was used to compare gender ratio between children with and without ID.

3. RESULTS

This study included 27 children with CP consisting of 13 with ID and 14 without ID. Demographic data are presented in Table 1.

Table 1: *Demographic features of the children with and without ID*

Demographic	Children without ID n = 14	Children with ID n = 13	p
Age (years) (mean ± SD)	10.71 ± 3.47	11.30 ± 3.49	0.583
Height (m) (mean ± SD)	1.42 ± 0.21	1.37 ± 0.21	0.756
Weight (kg) (mean ± SD)	41.57 ± 15.58	40.53 ± 14.20	0.943
BMI (kg/m^2) (mean ± SD)	20.23 ± 4.43	20.98 ± 3.45	0.830
Gender (M/F)	8 / 6	10 / 3	0.249

ID Intellectual disability, SD Standard deviation, BMI body mass index, F female, M male

All dimensions and total score of GMFM-88 were lower in children with ID compared to those without ($p<0.05$) (Table 2).

Table 2: *Comparison of GMFM scores between the children with and without ID*

		Children without ID n = 14 (mean ± SD)	Children with ID n = 13 (mean ± SD)	p
GMFM-88	**Lying and Rolling (%)**	97.61 ± 8.90	58.97 ± 41.72	**0.004***
	Sitting (%)	89.40 ± 27.47	33.07 ± 37.01	**0.001***
	Crawling and Kneeling (%)	85.37 ± 31.73	21. 97 ± 34.42	**<0.001****
	Standing (%)	81.13 ± 29.65	8.28 ± 16.28	**<0.001****
	Walking, Running and Jumping (%)	31.54 ± 12.07	2.56 ± 6.48	**<0.001****
	Total Score (%)	77.01 ± 20.88	24.97 ± 23.84	**<0.001****

ID Intellectual disability, GMFM-88 Gross Motor Function Measurement 88, SD Standard deviation
**p<0.05, **p<0.001*

Physical functioning; global health; role/social limitations – emotional/behavioural; role/social limitations – physical; general health perception; self-esteem; parental impact-emotional; parental impact-time; family activities and family cohesion dimensions of CHQ-PF50 were lower in children with ID compared to those without ($p<0.05$). No significant differences were found between children with and without ID in behaviour, bodily pain/discomfort, mental health, and change in health dimensions of CHQ-PF50 ($p>0.05$) (Table 3).

Table 3: *Comparison of CHQ-PF50 scores between the children with and without ID*

		Children without ID n = 14 (mean ± SD)	Children with ID n = 13 (mean ± SD)	p
CHQ-PF50	Global health	78.92 ± 19.72	52.30 ± 20.37	**0.003***
	Physical functioning	73.92 ± 25.22	15.69 ± 17.45	**<0.001****
	Role/social limitations – Emotional/ Behavioural	81.50 ± 24.33	27.92 ± 31.94	**<0.001****
	Role/social limitations – Physical	82.07 ± 27.40	21.53 ± 25.61	**<0.001****
	Bodily pain/ discomfort	92.85 ± 14.37	83.84 ± 25.34	0.375
	Behaviour	86.64 ± 9.96	76.53 ± 13.90	0.105
	Mental health	76.07 ± 12.73	65.84 ± 19.94	0.085
	Self-esteem	87.78 ± 16.90	51.84 ± 21.89	**<0.001****
	General health perception	75.92 ± 20.06	35.15 ± 13.75	**<0.001****
	Change in health	4.42 ± 0.64	4.25 ± 0.86	0.705
	Parental impact-Emotional	85.64 ± 18.31	43.46 ± 36.01	**0.002***
	Parental impact-Time	79.28 ± 26.76	49.92 ± 33.76	**0.025***
	Family activities	87.50 ± 19.21	66.07 ± 22.38	**0.012***
	Family cohesion	88.92 ± 14.16	74.61 ± 14.64	**0.019***

*ID Intellectual disability, CHQ-PF50 Child Health Questionnaire-Parent Form 50, SD Standard deviation. *p<0.05, **p<0.001*

4. DISCUSSION

This study aimed to reveal the effects of ID on gross motor function and HRQoL in CP. The results indicated that gross motor functions and most of the physical and psychosocial parameters of HRQoL were impaired in children with CP having ID compared to others.

Children with ID have lower physical and motor function capacity and inadequate occupational skills (6, 21). This depends on the developmental disability of the central nervous system as well as poor participation in physical activities of these children (22, 23). Delacy and Reid reported that cognitive impairment was more common in children with CP who have worse gross motor function levels (24). Hazneci et al. revealed that children who have CP with ID have lower GMFM scores compared to others without ID (25). The present study was consisted with the literature indicating ID is associated with impaired motor function in CP.

In the current study, general health, physical functioning, and physical role/social limitations scores of HRQoL, which are, concerning physical health was found to be lower in children with ID than in those without. Impaired motor function is known to affect physical HRQoL (15). ID may have a negative effect on physical well-being by disrupting motor function. Children with ID have learning disabilities so it's difficult for them to learn self-care skills or participate daily activities (26). This issue may contribute to reducing physical HRQoL.

Scores of some psychosocial health dimensions of the HRQoL consisting self-esteem, role/social limitations – emotional/ behavioural, and also parental impact, family activities and cohesion were poor in children with ID compared to those without ID according to the results of this study. Cerebral palsy is associated with limited social participation due to impairments of the motor and cognitive functions. Learning disabilities, communicational problems, emotional and behavioural issues due to cognitive impairment affect social participation in school and friendships adversely (6). So role and social limitations may be seen more in children who have CP with ID. Lower self-esteem score means reduced satisfaction of life concerning with capability, physical appearance, relationships and whole life in children with ID (27). Parents of the children with disabilities known to be have more emotional and psychosocial problems than those of healthy children (15). There are studies indicating parents of the children with CP or ID have psychosocial HRQoL problems due to restricted social relations, much time spent on caregiving, working life and financial difficulties (15, 28, 29). Conversely, Mugno et al. revealed that parents of the children with CP and ID had similar HRQoL scores to those of healthy ones (18). However, our study revealed that of the parents who have children with CP, those having children with ID have more psychosocial and family problems.

Pain and discomfort, behaviour, mental health and change in health scores of CHQ-PF50 were similar between children with and without ID in the present study. Pain is pervasive in CP and causes physical impairment, social and family problems (30). Our results indicates ID doesn't affect pain or discomfort in CP. Behavioural and mental problems seems more in children with CP compared to healthy peers and known to be associated with cognitive impairment (10). However the current study reveals similar results for behaviour and mental health dimensions of the HRQoL for children with and without ID. Change in health score was found to be similar for both groups. This result may depend on the general health improvement of all children participated in this study due to rehabilitation services.

This study revealed that physical and psychological parameters of the HRQoL except pain/discomfort, behaviour, mental health and change in health were impaired of the children who have CP with ID compared to those without. Previous studies reported that CP negatively affects HRQoL of the children (13, 15, 31). One of those studies pointed that ID doesn't have any significant effect on HRQoL outcomes in CP conflicting with the current study (15).

Researches show that the correlation of self-reports of children and their parents' proxy-reports is weak for the outcome measurements of health status (32). But conducting an evaluation of a self-reported HRQoL questionnaire in CP has some difficulties due to the cognitive impairments, so a parent reported questionnaire were performed to evaluate HRQoL in the current study. Also this study has a small

sample size. Studies with larger samples and more detailed measurements may be efficacious to achieve more objective results. These can be considered as limitations of the study.

5. CONCLUSION

ID was found to have a disruptive effect on motor function and HRQoL in CP. This finding supports the contribution of cognitive status to motor function and quality of life. Adding approaches to improve the cognitive status to the CP rehabilitation program may be effective for motor function and HRQoL. Future studies are needed to demonstrate the effects of cognitive and psychosocial rehabilitation approaches on motor function and HRQoL in CP.

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Clinical and Experimental Health Sciences

Urinary Symptoms in Multiple Sclerosis: Relation with Urodynamic Findings and Impact on Patient's Quality of Life

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ABSTRACT

Objective: We aimed to investigate the correlations of urinary symptoms with urodynamic findings in patients with multiple sclerosis (MS) and their effects on quality of life.

Methods: Nineteen MS patients with urinary symptoms were included. The data were obtained from files or with face-to-face interviews. Symptom types of patients were categorized as irritative, obstructive, and mixed. The Incontinence Quality of Life Scale, the King's Quality of Life Questionnaire (KQL) and the International Consultation on Incontinence Modular Questionnaire-Short Form were used to determine the effect of urinary symptoms on quality of life. The Extended Disability Status Scale (EDSS) was used to assess disability. All patients underwent urodynamic examination.

Results: The most frequent finding in urodynamic testing was detrusor overactivity (57.9%) while 26.3% had normal urodynamics. EDSS score did not correlate with urinary symptoms or urodynamic findings; it correlated only with the "Role limitation" subscale of the quality of life scales. While there was no relationship between symptom type and quality of life, the rate of detection of pathological findings on urodynamic examination and the bladder capacity in patients with mixed-type symptoms were significantly higher than the patients with irritative symptoms ($p<0.05$). The ''Emotions'' and ''Sleep/Energy'' subscale scores of the KQL were significantly higher in patients with abnormal urodynamic test compared with those without urodynamic pathology.

Conclusion: The urinary symptoms significantly affect the quality of life in MS patients. Since symptoms do not always correlate with the underlying pathology, it is more appropriate to give the treatment based on the bladder type in urodynamic testing.

Keywords: Multiple sclerosis, neurogenic bladder dysfunction, quality of life, urodynamic findings

1. INTRODUCTION

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system characterized by inflammation, demyelination, axonal loss, and gliosis (1). Urinary symptoms are common in MS patients. They adversely affect the quality of life in MS patients due to their effects on social, occupational, and sexual life (2).

The frequency of urinary symptoms is reported to be 52-97% in patients with MS (3-4). While urinary symptoms are the initial symptoms in 10-15% of patients, they are the only symptoms in about 2% of MS patients (5-7). Irritative urinary symptoms (i.e. frequent urination, urgency, incontinence, nocturia), obstructive symptoms (i.e. difficulty in starting urination, straining to void, incomplete emptying, weak urine flow), or mixed symptoms can be seen in MS patients. The patients most commonly complain of irritative symptoms (37-99%) or mixed symptoms (34-79%). Obstructive symptoms are seen less frequently (51-59%) (8-11).

Upper urinary tract complications are rare in MS patients (12). The incidence of upper urinary tract involvement was 0.34% in a study of 2076 MS patients (10), whereas in another review it was reported to be 12% on average (8).

The most common urodynamic finding in patients with MS is detrusor hyperactivity with an average of 65% (34-99%). The incidence of detrusor sphincter dyssynergia (DSD) is 35% (5-83%) while the frequency of detrusor hypoactivity is 25% (0-40%) on average (8, 13-17). In 1-34% of symptomatic patients, no pathologic finding is observed in the urodynamic investigation (8, 18, 19). In about 55% of the patients, the urodynamic pattern changes with time (14).

In a study of the effect of MS-related urinary symptoms on quality of life, Quarto et al. (20) investigated a group of women with urinary complaints (107 MS) and a control group including 100 women with overactive bladder symptoms but no neurological disease. Both groups were administered the King's quality of life scale (KQL), and it was found that urinary symptoms had a greater impact on quality of life in the MS group. Patients in the MS group were significantly more affected in the domains of general health perception, role limitation, physical limitation, social limitation, and urinary symptoms.

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In this study, we aimed to investigate the correlation of urinary symptoms with urodynamic findings and their effects on quality of life in patients with MS.

2. METHODS

2.1. Participants

We included 19 multiple sclerosis (MS) patients (18-65 years) who were followed at the Department of Neurology and were planned for urodynamic testing due to urinary symptoms (i.e. frequent urination, urgency, incontinence, difficulty in starting urination, straining to void, incomplete emptying, weak urine flow).

Exclusion criteria were as follows: 1) having an accompanying neurological disease, 2) worsening in the last 1 month, 3) having MS flare up, 4) having a urinary problem unrelated to MS, 5) having an active urinary tract infection, 6) receiving pharmacological treatment for urinary symptoms, 7) having difficulties in answering the questionnaires due to language or cognitive limitations, 8) refusing to participate in the study. Patients were informed about the study and consent was obtained before the study.

All participants provided written informed consent form and written permission from their physician allowing their participation and the hospital ethics committee had approved the study protocol.

2.2. Outcomes

The demographic (age, sex, occupation, education) and clinical data (age of MS onset, MS duration, MS type, bladder status at presentation, background, Expanded Disability Status Scale (EDSS) score, and EDSS bladder/bowel score) were obtained from the patient files or by face-to-face interviews.

In order to determine the effect of urinary symptoms on quality of life, the patients answered the Incontinence Quality of Life Scale (IQOL), the King's Quality of Life Scale (KQL), and the International Consultation on Incontinence Modular Questionnaire-Short Form (ICIQ-SF).

Expanded Disability Status Scale (EDSS) is one of the most commonly used evaluation forms for assessing clinical disability in MS. EDSS is an ordinal scale where a score of 0 represents a normal neurological status, 2 represents minimal disability, 4 represents moderate disability, 6 represents a need for walking aid, and 8 represents wheelchair dependence.

Incontinence Quality of Life Scale (IQOL) is an assessment tool specific for incontinence and self-administered by the patient. It is used particularly in the evaluation of stress incontinence, overactive bladder, and neurogenic detrusor overactivity. IQOL contains 22 items that address specific issues related to incontinence in particular. The items are collected in 3 domains: avoidance and limiting behaviors, psychosocial impact, and social embarrassment. Each item is scored on a scale of 5 points from 1 (severe) to 5 (none); high scores indicate better quality of life. The validity and reliability of the Turkish version has been demonstrated (21).

King's Quality of Life Scale (KQL) is a questionnaire with demonstrated validity and reliability and is of choice for patients with urinary symptoms due to the inclusion of both bladder-specific and general health questions. The questionnaire consists of three parts: Part 1 has 2 questions about the impact of general health and urinary symptoms on the quality of life, Part 2 has 19 questions that cover 7 dimensions of the quality of life (role limitations, physical limitations, social limitations, personal relationships, emotions, sleep/energy, and severity measures), and part 3 has 10 questions that measure the effect of or discomfort due to various urinary symptoms. The lowest score '0' indicates the best health condition, while the highest score '100' indicates the worst health condition. The validity and reliability study for the Turkish version of the KQL had been previously carried out with MS patients (22).

Short Form for the International Consultation on Incontinence Modular Questionnaire (ICIQ-SF) consists of 6 questions. It is a measure used to determine the frequency and severity of urinary incontinence, and its effect on the quality of life. Studies for the validity and reliability of the questionnaire in various languages were reported; a Turkish version was also demonstrated to express the quality of life (23). The scale is scored between 0 and 21 where higher scores represent greater effect on the quality of life.

2.3. Urodynamic Evaluation

A cystometric examination was performed in all patients with a Medical Measurement Systems urodynamics testing unit.

A double lumen cystometry catheter was used for intravesical pressure measurement and a rectal catheter (8 Fr) for abdominal pressure measurement. 0.9% NaCl was used for filling. The filling was done at physiological speed.

Before all urodynamic testing, the presence of infection was investigated with a urine culture. The urodynamic testing was performed after appropriate antibiotherapy in the patients with urinary tract infection. Patients were filled up to a maximum of 400 mL. The testing was terminated in patients who did not have incontinence up to this volume and in those who had pain during the testing. The administration and evaluation of urodynamics were based on the criteria set by the International Continence Society (24). The maximum cystometric capacity and the maximum detrusor pressure were recorded.

2.4. Statistical Analysis

SPSS 15.0 program was used for statistical analyses. Descriptive statistics (mean, standard deviation) were calculated. The Mann Whitney U test was used to analyze continuous variables (age, duration of illness, EDSS score, scores from the quality of life questionnaire, urodynamic findings). Chi-square test

was used to analyze categorical variables (sex, education, occupation, MS type, type of urinary symptom). Spearman's rho correlation coefficient was used for the correlation analysis. The significance level was set as $p<0.05$.

3. RESULTS

The average age at the onset of multiple sclerosis (MS) was 30 years (range=20-59 years). The average duration of MS was 94 months (range=14-184 months). The demographic characteristics of the patients were given in Table 1.

Table 1. *Demographic characteristics of patients (n=19)*

Parameters		
Age (mean ±SD)		38.74 ±9.66
Gender (n, %)		
	Male	3 (15.8)
	Female	16 (84.2)
Education (n, %)		
	Primary school	6 (31.6)
	Secondary school	4 (21.1)
	High School	5 (26.3)
	University	4 (21.1)
Occupation (n, %)		
	Government official	2 (10.5)
	Worker	1 (5.3)
	Retired	1 (5.3)
	Housewife	14 (73.7)
	Self-employment	1 (5.3)

SD: standard deviation

There were 12 patients (63.2%) with relapsing-remitting MS, three patients (15.8%) with primary progressive MS, three patients (15.8%) with secondary progressive MS, and one patient (5.3%) with progressive relapsing MS.

The mean EDSS score was 3.9 while the mean EDSS bladder score was 2.2. Six patients had irritative symptoms (31.6%), one patient (5.3%) had obstructive symptoms, and 12 patients (63.2%) had mixed symptoms. Urgency and frequency were present in all patients (100%), nocturia in 94.7% of the patients, urge incontinence in 89.5%, intermittent urination in 68.4%, stress incontinence in 63.2%, straining to void in 52.6%; difficulty in starting urination and dysuria were seen in 47.4% of the patients and enuresis nocturna in 31.6%.

IQOL Scale

Table 2 shows the distribution of scores in the domains of the IQOL questionnaire. The scores from the "avoidance and limitation behavior" subscale ranged from 12 to 78 with a mean of 37.2. The scores from the "psychosocial impact" subscale ranged from 11 to 94, with an average of 43.1 The scores from the "social embarrassment" subscale scores ranged from 5 to 85 with an average of 38.6. The average ICIQ-SF score was 8.8 ± 4.9 (range=0-16).

King's Quality of Life Questionnaire

The average score of General Health Perception in Part 1 of the King's Quality of Life Questionnaire (KQL) was 57.8. The average score of Incontinence Impact in Part 1 of the KQL was 75.4 (Table 2). When we look at the distribution of scores in Part 2 of King's quality of life scale, the highest score was in the "physical limitations" subscale (73,6); the lowest score was in the "personal relationships" subscale (30,3) (Table 2). The scores of Part 3 of the KQL were presented in Table 3. The most frequently encountered symptom in this section was frequency, followed by nocturia and urgency.

Table 2. *The distribution of scores in the IQOL, 1st and 2nd part of King's Quality of Life scale.*

Parameters	Min – Max	Mean ±SD
IQOL	0 – 100	70.42 ±31.85
Avoidance and Limiting Behaviors	0 – 100	73.65 ±29.57
Psychosocial Impacts	0 – 66.6	42.06 ±19.43
Social Embarrassment	0 – 100	30.37 ±28.40
KQL – Part 1	22.2 – 100	59.59 ±23.76
General Health Perception	33.3 – 100	61.37 ±28.36
Impact of Bladder Problem on the Quality of Life	25 – 100	55.23 ±22.25
KQL – Part 2	0 – 100	70.42 ±31.85
Role Limitations	0 – 100	70.42 ±31.85
Physical Limitations	0 – 100	73.65 ±29.57
Social Limitations	0 – 66.6	42.06 ±19.43
Personal Relationships	0 – 100	30.37 ±28.40
Emotions	22.2 – 100	59.59 ±23.76
Sleep/Energy	33.3 – 100	61.37 ±28.36
Severity Measures	25 – 100	55.23 ±22.25

IQOL: Incontinence Quality of Life Scale, KQL: King's Quality of Life Scale, SD: standard deviation

ICIQ-SF Questionnaire

The ICIQ-SF score ranged from 0 to 16 points, with an average of 8.84 ± 4.92.

Results of urodynamic testing

The urodynamic testing revealed that bladder capacity of the patients was 311 ± 122 ml (range=31-479 ml). Five patients (26.3%) had normal urodynamic findings, one patient (5,3%) had detrusor hyperactivity, 11 patients (57.9%) had detrusor hyperactivity + detrusor sphincter dyssynergia (DSD), and two patients (10.5%) had sensorial urgency.

Differences in evaluation parameters according to MS types

No significant difference was found between the MS types in terms of MS duration, quality of life scale scores, symptom type, and urodynamic test results ($p>0.05$)(Table 3).

Table 3. *The distribution of scores in the 3rd part of King's Quality of Life scale.*

Parameters	Presence and severity of the symptoms			
	Absent	A little	Moderately	A lot
Frequency (n, %)		2 (10.5%)	4 (21.1%)	1 3 (68.4%)
Nocturia (n, %)	1 (5.3%)	6 (31.6%)	5 (26.3%)	7 (36.8%)
Urgency (n, %)	-	1 (5.3%)	12 (63.2%)	6 (31.6%)
Urge incontinence (n, %)	2 (10.5%)	3 (15.8%)	9 (47.4%)	5 (26.3%)
Stress incontinence (n, %)	7 (36.8%)	7 (36.8%)	4 (21.1%)	1 (5.3%)
Nocturnal enuresis (n, %)	13 (68.4%)	3 (15.8%)	1 (5.3%)	2 (10.5%)
Intercourse incontinence (n, %)	17 (89.5%)	-	2 (10.5%)	-
Dysuria (n, %)	10 (52.6%)	2 (10.5%)	6 (31.6%)	1 (5.3%)
Straining to void (n, %)	9 (47.4%)	3 (15.8%)	4 (21.1%)	3 (15.8%)

Correlation between EDSS score and quality of life scores:

There was a statistically significant correlation only between the EDSS score and Role Limitation subscale of the KQL (p<0.05) (Table 4).

Table 4. *Correlations between EDSS score and quality of life scores.*

	r	p
IQOL		
Avoidance and Limiting Behaviors	-0.075	0.760
Psychosocial Impacts	-0.395	0.094
Social Embarrassment	-0.164	0.502
KQL – Part 1		
General Health Perception	0.325	0.175
Impact of Bladder Problem on the Quality of Life	0.360	0.158
KQL – Part 2		
Role Limitations	0.498	0.030*
Physical Limitations	0.337	0.158
Social Limitations	0.085	0.729
Personal Relationships	0.413	0.100
Emotions	0.394	0.095
Sleep/Energy	-0.001	0.997
Severity Measures	0.074	0.763
ICIQ-SF	0.329	0.169

*IQOL: Incontinence Quality of Life Scale, KQL: King's Quality of Life Scale, ICIQ-SF: International Consultation on Incontinence Modular Questionnaire-Short Form. *p<0.05*

Differences between the symptom types in terms of the evaluation parameters and the results of urodynamic testing

No significant difference was found between the symptom types in terms of quality of life scores (p>0.05). In the results of urodynamic testing, while no significant difference was found between irritative and mixed type symptoms in terms of maximum detrusor pressure, bladder capacity of patients with irritative symptoms was statistically higher than bladder capacity of those with mixed symptoms (p<0.05) (Table 5). Ayrıca; the normal urodynamic test findings were higher among the patients with irritative symptoms while abnormal urodynamic findings were higher among the patients with mixed symptoms (Table 5).

Table 5*. Differences in the evaluation parameters and the results of urodynamic testing according to the symptom types.*

	Symptom Type		
	Irritative	Mixed	p
EDSS (mean ±SD)	3.67 ± 1.60	3.79 ± 2.02	0.962
IQOL (mean ±SD)			
Avoidance and Limiting Behaviors	40.33 ± 19.83	34.58 ± 17.86	0.572
Psychosocial Impacts	40.33 ± 20.55	45.42 ± 25.94	0.708
Social Embarrassment	38.33 ± 12.91	38.75 ± 22.37	0.962
KQL – Part 1 (mean ±SD)			
General Health Perception	54.17 ± 29.22	60.42 ± 16.71	0.958
Impact of Bladder Problem on the Quality of Life	72.18 ± 25.11	77.75 ± 25.97	0.612
KQL – Part 2 (mean ±SD)			
Role Limitations	63.87 ± 40.02	71.23 ± 28.78	0.736
Physical Limitations	69.41 ± 35.60	74.97 ± 28.88	0.664
Social Limitations	38.86 ± 24.06	58.27 ± 53.99	0.705
Personal Relationships	16.64 ± 16.65	30.28 ± 24.50	0.242
Emotions	48.10 ± 13.44	62.90 ± 26.08	0.142
Sleep/Energy	52.75 ± 30.59	62.46 ± 26.71	0.399
Severity Measures	56.91 ± 11.09	56.22 ± 26.61	0.850
ICIQ-SF (mean ±SD)	9.83 ± 5.06	9.08 ± 4.52	0.572
Bladder Capacity (mean ±SD)	388.33 ± 84.88	268 ± 124.88	0.025*
Maximum Detrusor Pressure (mean ±SD)	21.50 ± 27.99	47.33 ± 48.71	0.159
Result of Urodynamic Testing (n, %)			
Normal	4 (80)	1 (20)	0.022*
Abnormal	2 (15.4)	11 (84.6)	

*IQOL: Incontinence Quality of Life Scale, KQL: King's Quality of Life Scale, ICIQ-SF: International Consultation on Incontinence Modular Questionnaire-Short Form, SD: standard deviation, *p<0.05.*

Differences in the evaluation parameters according to urodynamic examination results

Patients with normal and abnormal urodynamic results did not differ significantly in terms of their scores on the IQOL, Part 1of KQL, and ICIQ-SF. However, the scores of the patients with abnormal urodynamics were significantly higher in the emotions and sleep/energy domains of the KQL (p<0.05) (Table 6).

Table 6. *Differences in the evaluation parameters according to the results of urodynamic testing.*

	Results of urodynamic testing		
	Normal	Abnormal	p
IQOL (mean ±SD)			
Avoidance and Limiting Behaviors	37.20 ± 9.25	37.21 ± 20.45	0.609
Psychosocial Impacts	46.40 ± 22.63	42 ± 24.19	0.643
Social Embarrassment	39 ± 14.31	38.57 ± 20.60	0.851
KQL – Part 1 (mean ±SD)			
General Health Perception	60 ± 13.69	57.14 ± 22.84	0.834
Impact of Bladder Problem on the Quality of Life	66.62 ± 23.58	78.54 ± 24.85	0.315
KQL – Part 2 (mean ±SD)			
Role Limitations	76.64 ± 27.90	68.20 ± 30.83	0.738
Physical Limitations	79.96 ± 13.97	65.81 ± 22.82	0.962
Social Limitations	48.60 ± 12.67	71.40 ± 26.51	0.639
Personal Relationships	16.64 ± 16.65	58.30 ± 24.24	0.176
Emotions	42.18 ± 18.23	53.91 ± 24.58	0.044*
Sleep/Energy	33.30 ±0.0	36.09 ± 30.83	0.007**
Severity Measures	46.64 ± 13.93	71.40 ± 26.51	0.349
ICIQ-SF (mean ±SD)	11 ± 1.22	8.07 ± 5.54	0.429

*IQOL: Incontinence Quality of Life Scale, KQL: King's Quality of Life Scale, ICIQ-SF: International Consultation on Incontinence Modular Questionnaire-Short Form, SD: standard deviation, *p<0.05, ** p<0.01*

4. DISCUSSION

In our study, neither multiple sclerosis (MS) type nor MS duration had a correlation with urinary symptoms, quality of life, or urodynamic findings. Nakipoğlu *et al*. (6) evaluated the correlation between urinary symptoms and urodynamic findings in 52 patients. They also did not find a correlation between MS type and urinary symptoms and urodynamic findings. However, they reported a higher disease duration and age among the patients with urinary symptoms. Similar results were also reported by Award *et al*. (25). The lack of similar results in our study can be explained by the shorter disease duration and the lower functional disability scores among our patients. The expanded disability status scale (EDSS) score in that study was 5.1 ± 2.2, which was 3.89 ± 1.90 in our study.

Porru *et al*. (26) showed a correlation between the MS duration and urodynamic findings, particularly the frequency of detrusor sphincter dyssynergia (DSD) increased with the MS duration. The rate of DSD in this study was 13% in the 48th month and increased to 48% in the 109th month. This finding has been supported by other studies (8, 14, 27). In contrast, Ukkonen and colleagues (28) have not found any correlation between the MS duration and urodynamics. The mean duration of illness in our study was 94 ± 49 months. We think that due to the shorter disease duration in our patients, we did not find similar results.

In our study, there was no correlation between the EDSS scores and urinary symptoms and urodynamic findings. There was a statistically significant correlation only between the EDSS score and the 'role limitations' subscale of the King's Quality of Life Questionnaire (KQL). Previous publications on this issue are contradictory. While some studies have shown an association between the EDSS and urinary symptoms (9, 15, 29), the others failed to demonstrate a correlation (30). While some studies did not find a correlation between the EDSS and the urodynamic test results (8, 31), other studies have found a relationship between the presence of DSD and the EDSS scores (32,33). This relationship can be explained by the fact that MS is a progressive disease, and although the urodynamic parameters show variability (14), the DSD is stable (8). Therefore, as the disease progresses, an increase in the DSD frequency and the EDSS scores may be expected.

Differences in the EDSS scores between studies may have been caused by different inclusion criteria and functional differences of patients. We think that the reason for the lack of correlation in our study might be due to the better functional status and the lower EDSS score of the patients in our study.

The frequency of urinary symptoms is reported to be 52-97% in patients with MS (3-4). Most of the patients have irritative symptoms (37-99%). In our study, however, most patients had mixed symptoms (63.2%), followed by irritative symptoms (31.6%). In our study, only one patient had obstructive symptoms (5.3%). This prevented us from making comparisons between the patients with obstructive symptoms and those with other symptoms. These findings may be related to the low number of participants and the patient selection criteria in our study.

In our study, while an effect on the quality of life was detected in all patients regardless of urinary symptom type, there was no relationship between the urinary symptoms and the subscales of the quality of life questionnaires.

When the urodynamic testing results were evaluated, the bladder capacity was found to be significantly higher in the patients with irritative symptoms than those with mixed type symptoms. In addition, the percentage of the normal urodynamic testing result was higher in the patients with irritative symptoms. The abnormal urodynamic findings were obtained in 84.6% of the patients with mixed urinary symptoms. This result also explains why the bladder capacity of patients with irritative symptoms was significantly higher than that of the patients with mixed symptoms in our study. Previous publications on this issue are contradictory. Although a few studies have shown weak correlations between the urinary symptoms and the urodynamic findings (6, 28, 34, 35, 36), there was no correlation between the urinary symptoms and the urodynamic findings in most studies (8,11,13,14,18, 37, 38).

The most common urodynamic neurogenic bladder finding in MS patients was detrusor overactivity with an average of 65% (34-99%), while the frequency of detrusor overactivity + DSD was 35% (5-83%). The frequency of decreased detrusor activity is 25% (0-40%) on average (8,13-17). In 1-34% of the symptomatic patients, a normal urodynamics is found (8, 18,19). In a meta-analysis of 1900 patients, the most common urodynamic anomaly was detrusor hyperactivity (62%) (12).

In our study, no relation was found between the ICIQ-SF and I-QOL questionnaires and the urodynamic parameters. Only a statistically significant relationship was found between the 'emotions' and 'sleep/energy' subscale scores of the KQL and the abnormal urodynamic test results. This relationship may have occurred, especially in the presence of underlying neurogenic bladder pathology, due to the symptoms that continue even at nights and affect the sleep pattern of the patients, affecting the patients' scores in both the 'sleep/energy' and the 'emotions' subscales.

Quarto *et al*. (20) investigated the effect of urinary symptoms on quality of life among 107 female MS patients with the urinary symptoms and 100 women with the overactive bladder symptoms without a neurological disease. Both groups answered the KQL. As a result, it was found that the urinary symptoms in the MS group had more effect on the quality of life in the KQL, and patients in the MS group were found to be affected significantly more by general health perception, role limitations, physical limitations, social limitations, and urinary symptoms. Espuna Pons *et al*. (39) evaluated 674 female patients with urinary symptoms with the KQL and reported that the urinary symptoms affect all domains and impair their quality of life.

Eyigör *et al*. (21) evaluated the Incontinence Quality of Life Scale (IQOL) scores in MS patients. In this study, the 'avoidance' and the 'limiting behavior' score was 26.9 ± 8.8 the 'psychosocial impact' score was 33.3 ±10.4 and the 'social embarrassment' score was 18.7 ±6.0. While an effect was detected in all subscales of the quality of life in our study, the most effect was seen in the 'avoidance' and the 'limiting behavior' subscales in IQOL (37.2 ± 17.9). In the KQL, the most significant effect was in the 'To what extent does your bladder problem affect your household tasks?' question (75.0 ± 24.4). This can be regarded as an expected finding since the patients in the study were in a good functional status and their actual problems were the urinary symptoms.

Since we could not locate a study that used the ICIQ-SF on MS patients in the literature, we could not draw a comparison. However, in one study involving women with urinary incontinence in Turkey, it has been reported that the ICIQ-SF shows strong similarity with the I-QOL questionnaire and that the ICIQ-SF alone may be sufficient in measuring the quality of life (40). In addition, in another study involving 103 female patients with incontinence, Pons et al. compared the KQL and ICIQ-SF and reported similar specificity and sensitivity of both surveys in both types of incontinence (41). They suggested that the ICIQ-SF might be used in clinical practice with confidence since the KQL takes longer time to complete. In light of this information, the use of the ICIQ-SF in assessing the impact of incontinence on the quality of life in MS patients seems appropriate; however, this questionnaire requires further study to confirm its validity and reliability in MS patients.

Another debate in the management of MS patients with urinary symptoms is the use of urodynamic tests in the diagnosis and follow-up. Some authors do not recommend urodynamic investigation at primary care since the upper urinary tract involvement is less common than other neurogenic bladder diseases and due to cost-benefit analysis (42). On the other hand, others note that the elevations and persistence of detrusor pressure in particular are a major risk factor for the upper urinary tract involvement in MS patients; pointing out that the urodynamic pattern changes in MS patients, they also suggest the urodynamic examination as a routine in diagnosis and treatment (8). Similarly, although there was not enough evidence, Çetinel *et al*. (43) summarized the justifications in studies recommending urodynamic testing at primary care as: 1) the maximum detrusor pressure in the MS patients with upper urinary tract involvement is higher than those without, 2) there is no correlation between urinary symptoms and urodynamic findings, 3) the urinary dysfunction pattern may change over time, 4) 50% of MS patients without urinary symptom has abnormality in urodynamic tests, and 5) an appropriate treatment can be planned only after a urodynamic test.

As seen in the literature, the upper urinary tract involvement is quite rare in MS patients. While the incidence of the upper urinary tract involvement was 0.34% in a study in which 2076 MS patients were evaluated (10), it was reported to be 12% on average in another review (8). In our study, none of the patients had upper urinary tract involvement according to ultrasonography performed before the urodynamic tests. This may be because detrusor pressures in MS patients are lower than those in other neurogenic bladder diseases and there may be alterations in the bladder pathology and pressures during the remission periods. (14, 44) In the MS patients with urinary symptoms, a detailed query of medical history and neuro-urological examination, evaluation of voiding diary, complete urine and serum creatinine level analysis, urinary system ultrasonography, and the postvoid residual urine volume (PVR) measurements are appropriate. The urodynamic examination is required in order to confirm the underlying pathology if conservative treatment fails and/or the upper urinary tract is involved.

As a result, the physician will consider these factors and decide on the necessity of urodynamic tests according to patient's clinical findings and expectation.

One of the limitations of our study is the low number of patients. Another limitation is that the number of male patients was low in our study. This situation has prevented us from making the comparison of parameters in terms of gender. Since the number of participants was low and due to the selection criteria, only one patient had obstructive symptoms in our study, which hindered the evaluation of

obstructive type symptoms during the comparison of urinary symptoms with other parameters.

5. CONCLUSION

Symptoms related to urinary dysfunction are a major problem affecting the quality of life of an individual with MS. Because there is not always a constant relation between symptoms and the underlying pathology, it seems more appropriate to give treatment according to the bladder type detected after urodynamic testing.

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Clinical and Experimental Health Sciences

The Factors Associated with Mothers' Preventive Measures Against Home Accidents: A Descriptive Study from Istanbul, Turkey

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ABSTRACT

Objective: One of the most common causes of death among children in Turkey is accidents, and of this, 18-25% caused by home accidents. This study aims to identify the factors associated with safety measures against home accidents, that are taken by mothers who have children between 0-6 years of age.

Methods: This descriptive study was conducted among the mothers who admitted to three Family Health Centers in Istanbul, Turkey, in 2017. The data was collected with a questionnaire including "The Scale for Mother's identification of Safety Measures Against Home Accidents for Children of 0-6 Years Age Group". The data was analyzed with SPSS program using Chi square, Mann Whitney-U and Spearman correlation tests ($p<0,05$ considered significant). 224 mothers participated in this study.

Results: The most frequent home accidents were falling (48.9%), finger jam (36.6%) and crashing (30.6%). There was a weak positive correlation between the scale score and family's income ($p=0.039$; $r=0.157$); and a weak negative correlation between the scale score and child's age ($p=0.001$; $r=-0.331$). There was no association between education level of parents and safety measures. However, the scale scores were significantly higher among those who have specifically been educated about home accidents compared to those who haven't ($p=0.013$).

Conclusion: The current education program may not be sufficient to prevent home accidents. We believe that specific courses about home accidents and safety measures are needed; even if these courses can be integrated to secondary school or university curricula it can be more beneficial.

Keywords: Turkey, home accidents, preventive measures, health education

1. INTRODUCTION

The accidents are the fourth most common cause of mortality among children in Turkey (1, 2). Nearly a quarter of all accidents are home accidents (3). The consequences of unintentional injuries are more severe especially in children who are younger than five years. The rates of hospital admission and mortality are high compared to other age groups (4). The impacts of home accidents on children's lives are long standing, which may cause physical, psychological and social impairments and thus affect the social interactions, academic life and future occupation of the kids (4, 5).

Home accidents cause a considerable financial burden in economy and health systems, which might affect the poor countries in higher magnitudes. Home accidents have the second largest share of economic burden caused by accidents (6) and, the rates of home accident and their consequences are higher in families and countries with lower socio-economic status (7, 8). Because of the complex nature of home accidents, more research needed to be done to understand and prevent home accidents. Therefore, in this study we aimed to find the factors associated with safety measures of mothers with children aged 0-6 years against home accidents. We have chosen mothers as the study population because of the fact that mothers are generally the primary caregivers of children.

2. METHODS

This descriptive study was conducted among the mothers who admitted to three Family Health Centers (FHC), in Istanbul, Turkey, in 2017. Three different FHCs were chosen to cover neighborhoods from different socio-economic statuses. From a non-probabilistic sampling, 224 women volunteered to participate in the study. The aim and scope of the study was explained to the participants and a written informed consent was obtained from them. The study was approved by the Marmara University, School of Medicine, Ethics Committee with the protocol number 09.2017.381.

The data was collected through a questionnaire including "The Scale for Mother's identification of Safety Measures against Home Accidents for Children of 0-6 Years Age Group (MISMHA)". Turkish validity and reliability of the scale was done elsewhere (9) with a Cronbach Alpha value of 0.8205. This scale consists of 40 Likert type questions (34 positive, 6 negative statements). For the positive statements the scale was graded as follows: always, 5 points; often, 4 points; sometimes, 3 points; rarely, 2 points; never, 1 point. For the negative statements the grading

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system was reversed. Maximum scale score was 200. The higher score represents a higher level of preventive measures against home accidents. The questionnaires were either given to the participants and filled by them or asked face to face by their request.

2.1. Statistical analysis

The data was analyzed with the Statistical Packages for the Social Sciences (SPSS) version 20.0 (IBM Corp.; Armonk, NY, USA). Normality of the distributions were tested with Kolmogorov Smirnov test. Since the distribution of all the numerical variables were not normal, we used Mann-Whitney U, Kruskal-Wallis and Spearman correlation tests for associations. For multivariate analyses, we made binary logistic regression models, taking the type of the accident as the dependent variable (dichotomized as having the accident and not having the accident), and other factors as independent variables (mother's age; mother's age at marriage; number of children living in the house; family type, mother's education level; mother's work status; family income; child's gender and age; birth order; MISMHA score; and taking specific education about home accidents). P-values less than 0.05 were considered significant.

3. RESULTS

From the three FHCs, 224 mothers participated in this study. Median age of the mothers (32 years) was lower than of the fathers (35 years). Median age at marriage and at first delivery for the mothers were 24 and 25 years respectively. On the other hand, 7 mothers (3.3%) were married before the 18 years of age; and 2 (1%) of them also had their first deliveries before 18 years of age. The sociodemographic characteristics of the participants are shown in Table 1. We classified home accidents as falling (48.9%), crash (30.6%), burn (9.2%), choking (8.1%), cutting or piercing injury (4.8%), poisoning (3.4%), electric shock (0.5%) and finger jam (36.6%). The proportion of having any type of accident was 58.9%.

Table 1. *Socio-demographic characteristics of the study population.*

Characteristics	n*	Mean	SD**
Mother's age (year)	221	33	±6
Father's age (year)	218	36	±7
Mother's age at marriage (year)	213	24	±4
Mother's age at first delivery (year)	209	26	±5
Caregiver's age (year)	164	36	±11
Child's age (year)	109	3	±2
Family's income (Turkish Liras/month)	187	4120	±3296
	n*	**Median**	**IQR*****
Child's birth order	116	1	1-2
Number of children living in the house	219	2	1-2
Number of persons living in the house	220	4	3-5
Number of the rooms at the house	219	3	3-4

**n: number of the participants; **SD: Standard deviation; ***IQR: Inter-quartile range*

The majority (84.5%) of the families in the study were large families; that is, they were living with some of their relatives other than spouses or children. Of the women, 67.2% had education level equal to or lower than high school; 5% were illiterate. Also, 20.1% of them had been educated about home accidents. Of the children, 57% were male; and 60.8% were the first child of the mother. The majority of the children (76.6%) were given care primarily by their mothers and none of them by their fathers. Further information about the characteristics of the study population can be seen in table 2.

In order to investigate the internal consistency of the MISMHA scale in our study population we checked the Cronbach Alpha value and found as 0.853. Regarding the scale scores, we found no association between preventive measures against home accidents and family type, education level (both mother and father), work status (both father and mother), child's gender, child's birth order and the primary caregiver (Table 2). However, the scale scores were significantly higher among those who have been educated about home accidents (188.0; IQR: 177.0-193.0) compared to those who haven't been (181.5; IQR: 169.5-190.0) (p=0.013) (Table 2). Also, we found a weak positive correlation between the scale score and family's monthly income (r=0.157, p=0.039); and a weak negative correlation between the scale score and child's age (r=-0.331, p=0.001). There was no correlation between the scale score and mother's, father's and caregiver's age; mother's age at marriage and at the first delivery; number of children living in the house; number of people living in the house; and number of rooms in the house.

Table 2. *Socio-demographic characteristics of the study population by MISMHA scale scores.*

Variable	Categories	n*	Valid %	Score (median)	IQR**	P value
Family type	Nuclear	34	15.5	180.5	165.0-190.0	0.591[a]
	Large	185	84.5	184.0	172.0-192.0	
Mother's education level	Illiterate	11	5.0	185.0	172.0-194.0	0.098[b]
	Primary-secondary school	63	28.6	183.5	172.0-193.0	
	High school	74	33.6	180.0	168.0-188.0	
	University	64	29.1	188.0	175.0-192.0	
	Postgraduate	8	3.6	176.0	155.0-186.0	
Father's education level	Illiterate	3	1.4	196.0	185.0-196.0	0.277[b]
	Primary-secondary school	66	30.3	180.0	168.5-190.0	
	High school	64	29.4	185.0	174.0-192.0	
	University degree	71	32.6	183.0	170.0-191.0	
	Postgraduate	14	6.4	183.5	171.5-192.0	
Mother's work status	Employed	88	40.4	186.0	174.0-192.0	0.072[a]
	Unemployed	130	59.6	180.5	169.0-191.0	
Father's work status	Employed	198	90.8	184.0	171.0-192.0	0.411[a]
	Unemployed	20	9.2	178.0	172.0-186.0	
Educated about home accidents	Yes	44	20.1	188.0	177.0-193.0	**0.013**[a]
	No	175	79.9	181.5	169.5-190.0	
Child's gender	Female	49	43.0	184.5	172.0-192.0	0.061[a]
	Male	65	57.0	176.0	163.0-191.0	
Birth order	First	73	60.8	178.0	165.0-189.0	0.194[a]
	Others	47	39.2	183.5	172.5-192.0	
Caregiver	Mother	128	76.6	181.5	169.0-190.5	0.279[b]
	Grandmother	25	15.0	181.0	173.0-191.0	
	Babysitter	11	6.6	189.0	176.0-193.0	
	Aunt	3	1.8	194.0	174.0-195.0	

**n: number of the participants; **IQR: Inter-quartile range*
a: p values are derived from Mann-Whitney U tests; b: p values are derived from Kruskal-Wallis tests

We also compared the scale scores of the mothers whose children have had a certain type of accident and who haven't had. For each type of the accident the scores were higher among those haven't had the accident than those who have had the accident; however, the difference was statistically significant only for crash (p=0.033) (Table 3).

Table 3. *MISMHA Scale scores by the type of the accident*

Accident type	Status	n*	Valid %	Score (median)	IQR**	P value***
Fall	Yes	107	48.9	180.0	169.0-190.0	0.114
	No	112	51.1	185.0	173.0-192.0	
Crash	Yes	64	30.6	178.0	167.0-188.0	**0.033**
	No	145	69.4	185.0	172.0-192.0	
Burn	Yes	19	9.2	174.0	161.0-191.0	0.121
	No	188	90.8	184.0	172.0-192.0	
Chocking	Yes	17	8.1	175.0	165.0-187.0	0.108
	No	192	91.9	184.0	172.0-192.0	
Cutting or piercing injury	Yes	10	4.8	173.0	165.0-189.0	0.258
	No	197	95.2	183.0	172.0-192.0	
Poisoning	Yes	7	3.4	174.0	146.0-185.0	0.205
	No	200	96.6	183.0	172.0-192.0	
Electric shock	Yes	1	0.5	183.0	183.0-183.0	1.00
	No	207	99.5	183.0	171.0-192.0	
Finger jam	Yes	78	36.6	181.0	170.0-192.0	0.843
	No	135	63.4	184.0	172.0-191.0	
Any accident	Yes	129	58.9	180.5	173.0-192.0	0.313
	No	90	41.1	180.5	169.5-191.5	

**n: number of the participants; **IQR: Inter-quartile range ***p-values are derived from Mann-Whitney U test*

We also found a trend between the age of the child and the type of the accident (Figure 1). As seen in the figure, the percentage of falls increases critically from age 1 to 2, then follows a steady increase till its peak at age 5. The crash accidents follow a pathway similar to falls; the percentage increases dramatically from age 1 to 2; then follows a steady increase and reaches its peak at age 3; after that it decreases slowly. Finger jam trend shows a stepped increment, it shows a dramatic increase from age 1 to 2, then becomes steady for one year and increases again from age 3 to 4; after 4, it shows a small decrease. Burn accident follows a small decrease from age 1 to 4 and then increases dramatically to age 5. Cut/piercing injuries start at age 2 and follow a steady increase throughout the ages until 5. Choking follows a steady pathway until age 4 and the percentage decreases after that until age 5. Poisoning and electric shock are rare accidents which are seen at age 4 and after.

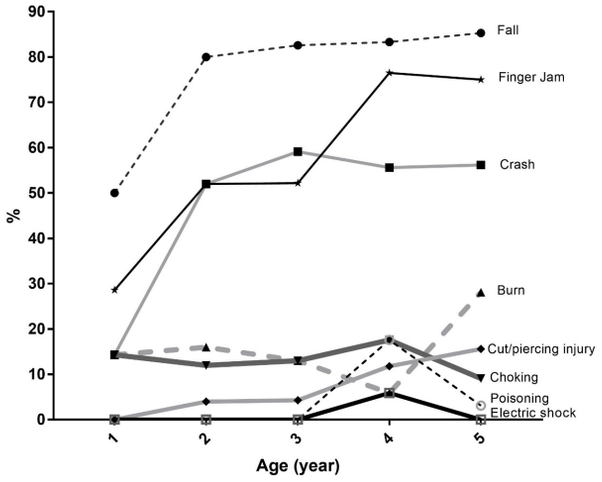

Figure 1. *Percentage of children having different types of home accidents by their age.*

In the last steps of the logistic regression models, we found that taking a specific education about home accidents is associated with lower rates of falling; being a girl is associated with lower rates of crash; and being young is associated with lower rates of finger jam (Table 4).

Table 4. *Independent predictors of different types of accidents, binary logistic regression, last models.*

Type of the accident	Variable	Categories	Exp (B) [OR]*	95% CI**	P value
Falling	Taking specific education	Yes (reference category)	1		**0.017**
		No	4.978	1.332-18.608	
Crash	Gender of the child	Girl (reference category)	1		**0.041**
		Boy	3.072	1.047-9.017	
Finger jam	Age of the child (years)	Continuous variable	0.567	0.374-0.859	**0.007**

**Exponentiation of the B coefficient or Odd Ratio [OR]; **Confidence interval*

4. DISCUSSION

The first five years of human life are considered as a critical period that children are very active and try to discover and learn what is happening around them (10). This period is an important period for preventing home accidents and accident-related injuries and mortality. Our study helps to understand the factors associated with preventive measures against home accidents.

Our study population has higher socio-economic status compared to Turkey's average, with higher income, educational status, age at marriage and age at first delivery. Such as the rate of illiteracy in our study population (5%) was lower than Turkey's average (9.0%) (11); mother's median age at marriage (24 years) was older than Turkey's national (21 years) and Istanbul's (21.4 years) median age at marriage. Similarly, mother's median age at first delivery in our study population (25 years) was older than Turkey's national (22.9 years) and Istanbul's (24.6 years) median age at marriage (12, 13).

The most significant finding of our study was that the women who were specifically educated about home accidents were taking more preventive measures. This finding is consistent with previous studies. In two studies conducted by Turan et al. (14) and Çınar (15) to find out the effect of educating mothers about home accidents, demonstrated that the knowledge level of the mothers were significantly higher after the education than before the education. King et al. (16) also conducted a study to prevent home accidents in childhood by visiting homes and providing education; the study showed that after the education in the vast majority (63%) of the participants there was an improvement in knowledge, attitude and practices about home accidents. Systematic reviews (17, 18, 19, 20) show that one of the most effective strategies to prevent home accidents is educating parents and children to make behavior change and promote safety apparatus in houses. However, having knowledge does not always make people apply it in practice. On the other hand, in this study, we investigated the specific education with a question "have you ever taken a specific education about home accidents". Therefore, it doesn't provide a comprehensive information about the type and content of the education. Further qualitative and quantitative studies may explore this information.

In our study we found no association between safety measures and mother's education level. This may be because of the lack of specific courses about home accidents within the national educational curricula in Turkey. Although there are some chapters regarding the first aid after some types of accidents in the lecture of "Health Knowledge and Traffic Culture" in national high school curriculum, there is no specific and comprehensive education about home accidents (21).

We found a weak association between taking preventive actions and family's income; since higher income level can be a reflection of general higher socio-economic status, these families might be more aware of home accidents; or for them, taking preventive measures might be more affordable (22).

We also found a weak negative correlation between the scale score and child's age; on the other hand, we found that frequency of home accidents increase with age. This might be explained by the tendency of mothers to take less preventive measures when their children have grown. However, we cannot make a temporal inference from these associations. Since we don't know whether the accidents are more frequent because mothers take less preventive measures, or because mothers take less preventive measures the accidents happen more frequently.

The trends we found between the age of child and the type of the accident can be explained by the neurodevelopmental stages of the child (23). As the children develop more motor skills, they tend to explore their surrounding environments and thus the frequency of most accident types increases. The dramatic increase of falling, crash and finger jam from age 1 to age 2 can also be explained by the neurodevelopmental process of the child; after the first year of age when they start to walk they might face more accidents. Particularly serious accidents, such as poisoning, electric shock start at older ages when they gain more control over their extremities and acquire ability to grasp objects; also, as their height increase they might be able to reach the objects in higher places such as shelves, drawers, electric sockets (24).

In a qualitative study conducted with mothers in Wales (25) it was found that fathers also have a role in prevention of home accidents and related injuries. As our study was conducted only among mothers, there is not adequate information about fathers' roles. Therefore in the future, a study that includes the fathers will give a more comprehensive information.

Also, since this study was conducted among the mothers who referred to family health centers there might be a referral filter bias. These mothers may be more aware of health related issues compared to those who didn't refer to the health centers; therefore, the status of taking preventive measures among those who didn't refer to health centers may be worse. Furthermore, the participants might have reported preventive measures more than they actually do. This can be an outcome of social desirability bias. Therefore, the scale scores we have found in this study might be an over-estimation of true preventive measures. Moreover, our study population had a higher socio-economic status than Turkey's average; therefore, the general situation regarding preventive measures taken by parents in Turkey probably is worse than our findings.

5. CONCLUSION

We concluded that, not the formal education but taking a specific education about home accidents increase preventive measures against home accidents. Therefore, a structured education specifically addresses home accidents is very important to increase the quantity and quality of preventive

measures against home accidents (26). This education should comprehensively cover the most common (i.e. falls, crashes) and serious (i.e. burning, choking) home accidents considering the age of the child; and should be interactive and practice-based in addition to theoretical knowledge. This education may target current mothers, teenagers, pregnant women etc. to have a short-term outcome; or can be integrated to curriculum of secondary schools or universities in a continuous fashion for a sustainable long-term outcome. We didn't investigate the source of information about home accidents in our study, however, previous studies (27,28) found mass media as an important source of information; therefore mass media can also be used in raising awareness about home accidents.

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Clinical and Experimental Health Sciences

Evaluation of Nurses' Knowledge about Risk Monitoring and Risk Prevention for Pressure Ulcers

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ABSTRACT

Objective: The aim of the study was to evaluate the levels of nurse's knowledge on prevention of pressure ulcers and its associated factors.
Methods: This is a cross-sectional, descriptive study. The research sample consisted of 250 nurses who worked at a training research hospital from 1 September to 1 December 2016. The research data were collected using the "Nurse Information Form" and "Pressure Ulcer Prevention Knowledge Survey" prepared in light of the literature.
Results: The sample was mostly undergraduate (70.0%) and the mean age was 26.11±5.33 years. Nurses (98.8%) indicated that "advanced age" has a significant influence among risk factors that cause pressure ulcers. The item on the "Pressure Ulcer Prevention Knowledge Survey", that was answered incorrectly most often (92.8%) was "when conscious patients with learning ability sit on chairs, they should be informed that they should shift their weight every 15 minutes," in the sub-dimension of "Nursing Interventions for Preventing Pressure Ulcers". There was a statistically significant difference between the knowledge level scores of nurses with respect to nurses' age, education level, working unit and pressure ulcer education ($p<0.05$).
Conclusion: Nurses' knowledge level scores for prevention of pressure ulcers were above the average value. It is important to organize continuous education programs to increase nurses' knowledge about the risk factors for pressure ulcers and their prevention.
Keywords: Pressure ulcer, nursing care, risk factors, risk assessment, training programs

1. INTRODUCTION

Pressure ulcers that cause serious health problems in long-term care at home and in all types of health care settings, still occur due to difficulties in care and treatment which result in increased costs (1-4). Pressure ulcers can occur in any skin area that is exposed to pressure (5, 6). Patients confined to bed or chair with impaired sensory function, impaired mobility, impaired feeding, and immunodeficiency and elderly individuals are in the risk group for pressure ulcer development (2, 7). Intrinsic and extrinsic factors influence the development of pressure ulcers. Intrinsic risk factors in the development of pressure ulcers are diabetes, smoking, malnutrition, immunosuppression, vascular diseases, spinal cord injuries, contractures and prolonged immobility. Extrinsic risk factors for development of pressure ulcers are lying on hard surfaces, staying at nursing homes, poorly fitting prostheses, poor skin hygiene, physical restraints and medical devices (8).

Most pressure ulcers are due to preventable causes. Maintaining the integrity of the skin is one of the important objectives during the care provided for pressure ulcers (6, 9). The main way to prevent pressure ulcers is to minimize the body parts that are under pressure for long periods of time (8). Prevention and management of pressure ulcers consists of identifying persons in the risk group, eliminating or reducing risk factors, and applying specific preventive measures (10-12). The first step in identifying risk factors for pressure ulcers in individuals and planning nursing intervention to prevent pressure ulcers is the use of risk assessment scales. The risk assessment should be carried out on admission to healthcare setting and should be regularly performed according to a schedule or in line with changes in the health status of the patient (13, 14). It is important to gain knowledge and skills of preventing, evaluating, diagnosing, and treating pressure ulcers (4, 13).

Pressure ulcers are regarded as a sign of inadequate nursing care, negligence in preventive practices, and inadequate quality of care (15-17). Their prevention and treatment require a multidisciplinary team approach with holistic care, and nurses have significant responsibilities in this regard (18, 19). Nurses should ensure early prevention of pressure ulcers by regularly assessing risk for every patient admitted to the hospital. After determining the risk level of the patient, a suitable nursing care should be planned with the patient in line with the obtained data (3, 4, 20)

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The National Pressure Ulcer Advisory Panel (NPUAP), the European Pressure Ulcer Advisory Panel (EPUAP), and the Pan Pacific Pressure Injury Alliance (PPPIA), which were established as organizations for the prevention, care, treatment, and studies of pressure ulcers, prepared jointly a document entitled "Prevention and Treatment of Pressure Ulcers: A Quick Reference Guide (2014)". The aim of this cooperation is to provide evidence-based recommendations about the prevention and treatment of pressure ulcers for healthcare professionals throughout the world (21). Whatever the healthcare needs or diagnosis, nurses can use this guide while providing care for all patients and vulnerable people who are at risk of developing pressure ulcers, whether in a hospital, long-term care center, or living with help at home or elsewhere (18, 22). These guidelines form the basis for the development of training strategies for the prevention and management of pressure ulcers by contributing to evidence-based healthcare practices (15).

Pressure ulcers are an important complication, which is very common despite being preventable with appropriate precautions. Pressure ulcers are an indicator of deficiency in nursing care, negligence in preventive practices and inadequate quality of care. Nurses have very important responsibilities regarding pressure ulcers. Evidence-based practices reduce the incidence of pressure ulcers and improve the quality of care (23). Therefore, determining nurses' knowledge about, skills in and practices for preventing pressure ulcers is important. In Turkey, there are no valid and reliable measurement tools for assessing the nurses' knowledge levels related to pressure ulcer prevention. The number of national and international studies assessing nurses' level of knowledge about preventing pressure ulcers is limited. This study will provide an insight into further studies to be conducted on this topic.

The aim of the study was to evaluate the levels of nurse's knowledge on prevention of pressure ulcers and its associated factors. The research questions were as follows:

- What are the nurses' knowledge levels about preventing pressure ulcers?
- What are the knowledge of the nurses regarding risk factors of pressure ulcers?
- Are there any differences between the nurses' knowledge levels about preventing pressure ulcers according to their sociodemographic and occupational characteristics and training and practice related to the pressure ulcers?

2. METHODS

2.1. Design

This study is a descriptive, cross-sectional research design.

2.2. Setting

The research was conducted in a training and research hospital in Istanbul. It serves for many specialties by combining its academic activities with health services.

2.3. Sample

The research population consisted of 350 nurses working in the hospital between September 1 and December 1, 2016. This study attempted to include all the nurses in the study population in its sample. A total of 250 (71.4%) nurses were included the study. Nurses who did not agree to participate in the study or could not be reached for various reasons (annual leave, rest, maternity leave, etc.) were not included in the survey.

2.4. Ethical considerations

Ethical approval was obtained from the IBU Ethics Committee of Clinical Investigations (Decision No: 16.08.2016/53-15) before the study was conducted. In addition, permission was obtained from the management of the hospitals where the study was conducted. The nurses who participated in the research signed an Informed Volunteer Consent Form that explained the aim of research. They were informed that the data from the questionnaires would be kept confidential so that their anonymity was guaranteed.

2.5. Data collection

The data collection forms were prepared by the researchers based on the literature review (4, 13-15, 21). "Nurse Information Form" and "Pressure Ulcer Prevention Knowledge Survey" were used as data collection tools in the study. After the nurses were informed about the study, the forms were distributed to those who agreed to participate in the study. The nurses were asked to fill out the questionnaire after the information was given.

2.6. Instruments

Nurse Information Form: This form has 16 questions in two sections. The first section has questions about socio-demographic (age, gender, marital status, educational level) and occupational characteristics (professional experience, unit working time, position, unit). The second section has questions about nurses' training and practice characteristics regarding pressure ulcers (average number of patients with pressure ulcers given care, training about pressure ulcers, training needed for assessment and prevention of pressure ulcers, etc.).

Pressure Ulcer Prevention Knowledge Survey: The form was developed to assess the knowledge level of nurses about risk monitoring, evaluation, and prevention of pressure ulcers. This form has 5 sections: (1) Risk factors for pressure ulcers (16 items), (2) Medical interventions that cause pressure ulcers (10 items), (3) Evaluation of skin care (7

items), (4) Stages of pressure ulcers (5 items) and (5) Nursing interventions for preventing pressure ulcers (28 items). The items were answered according to the True/False format. Correct answers were scored 1 while incorrect answers were scored as 0. The lowest possible score that can be obtained from this form was "0" and the highest possible score was "66". An increase in score indicates an increase in the nurses' knowledge level about preventing pressure ulcers.

To evaluate the items in the questionnaire in terms of wording, understandability and content validity, expert opinions were obtained. The panel of experts consisted of five specialists: two in the fundamentals of nursing, two in surgical nursing and one in internal disease nursing. They expressed their opinions by scoring each item on three-point scale, ranging from one to three (1=not understandable and not relevant, 2=relevant with rewording, 3=understandable and relevant). The acceptable score for each item was two or more, and there was no item removed from the scale. According to the views of specialists, the scale's Content Validity Index (CVI) was .91. A pilot study was also conducted to determine whether the items on the questionnaire were understandable or not. Before the study was conducted, the questionnaire was administered to 15 nurses. In accordance with their recommendations, some minor revisions were made, and the final form of questionnaire was obtained.

2.7. Statistical analysis

Data were analyzed using the Statistical Program for Social Sciences (SPSS) 21.0 package program. The nurses' knowledge level about pressure ulcer prevention was the dependent variable. The nurses' sociodemographic and occupational characteristics and their training and practice related to the pressure ulcers were the independent variables. Frequencies, arithmetic means, standard deviations and percentages were used for descriptive statistics. Chi square test was used for comparing categorical variables; whereas Student's t test and one-way ANOVA tests were used in comparing the means. The relationship between the variables was examined using Pearson's correlation analysis. The results were evaluated at a confidence interval of 95% and a significance level of $p<0.05$.

3.RESULTS

3.1. The nurses' sociodemographic and occupational characteristics and training and practice related to pressure ulcers

The mean age of the nurses was 26.11±5.33 years old. More than eighty percent (81.2%) of the nurses were women, and 70.0%" had an undergraduate education. Less than one quarter of the nurses (23.6%) worked in the intensive care unit. The mean duration of professional experience of the nurses in this study was 63.80±63.80 months (Table 1).

Table 1. *Distribution of nurses according to sociodemographic characteristics (n=250)*

Characteristic	Category	n	%
Age	*Mean*: 26.11±5.33 (*Range*: 18-45)		
Age group	18-19 years	18	7.2
	20-29 years	187	74.8
	30-39 years	35	14.0
	40 years and over	10	4.0
Gender	Female	203	81.2
	Male	47	18.8
Marital status	Married	50	20.0
	Single	200	80.0
Education level	Health vocational high school	50	20.0
	Associate degree	9	3.6
	Undergraduate	175	70.0
	Graduate	16	6.4
Professional experience (months)	*Mean*: 63.80±63.80 (*Range*: 1-324)		
Professional experience (years)	0-1 years	62	24.8
	2-5 years	99	39.6
	6-10 years	52	20.8
	11 years or over	37	14.8
Unit working time (month)	*Mean*: 39.09±42.40 (*Range*: 1-264)		
Unit working time	0-1 years	93	37.2
	2-5 years	108	43.2
	6-10 years	39	15.6
	11 years and over	10	4.0
Position	Service nurse	87	34.8
	Service responsible nurse	7	2.8
	Intensive care unit	59	23.6
	Operating room nurse	20	8.0
	Emergency nurse	25	10.0
	Other (nursing instructor, nursing polyclinics, supervisor nurse, angiography nurse, endoscopy nurse, etc.)	52	20.8
Unit	Intensive care unit	59	23.6
	Internal medicine service	21	8.4
	Surgical service	19	7.6
	Mixed service (internal diseases, surgery, gynecology)	54	21.6
	Operating room	20	8.0
	Emergency	25	10.0
	Other (angiography, outpatients, etc.)	52	20.8

Nearly sixty percent (58.4%) of the nurses stated that they were working in a hospital and provided care for patients with pressure ulcers, 83.6% had been educated about pressure ulcers, and 63.2% had received this education during their nursing education. Only 34.4% of the nurses in the sample group indicated that they needed education about the evaluation and prevention of pressure ulcers and that they wanted most to receive education about risk factors and risk assessment (21.2%) and causes of pressure ulcers (23.6%) (Table 2).

Table 2. *Distribution of nurses according to professional qualifications regarding pressure ulcers (n=250)*

Characteristic	Category	n	%
Providing care to pressure ulcer patients	Yes	146	58.4
	No	104	41.6
Average number of patient with pressure ulcers given care	Never	106	42.4
	1-2 patients	127	50.8
	3-4 patients	14	5.6
	5 patients or over	3	1.2
Received any training about pressure ulcers	Yes	209	83.6
	No	41	16.4
Where training about pressure ulcers was received	Within the curriculum of nursing education	158	63.2
	In-service training program	86	34.4
	Courses, seminars, and symposiums	42	16.8
Information sources used to prevent pressure ulcers	Information received during nursing education	150	60.0
	Practices of experienced nurses working together	69	27.6
	Physician recommendations	34	13.6
	Magazines, books, etc. professional spreads	26	10.4
	Internet, newspaper, or TV	16	6.4
Training needed for assessment and prevention of pressure ulcers	Yes	86	34.4
	No	164	65.6
Training subjects needed for assessment and prevention of pressure ulcers	Etiology and pathology	20	8.0
	Risk factors	59	23.6
	Risk assessment	53	21.2
	Skin evaluation	48	19.2
	Skin care	37	14.8
	Selecting and using pressure distributing-reducing support surfaces	24	9.6
	Position changes to reduce pressure, friction, and tears	15	6.0
	Management of pressure ulcers and understanding nursing roles and responsibilities in the multidisciplinary team	29	11.6
	Policies and procedures	11	4.4
	Education of patients and their relatives	12	4.8
	Recording	11	4.4

3.2. Pressure ulcer prevention knowledge survey scores

The mean score on the "Pressure Ulcer Prevention Knowledge Survey" was 52.95±5.78 (ranging from 28 to 63) (Table 3). The nurses' knowledge level scores for the prevention of pressure ulcers were above the mean value.

Table 3. *Pressure ulcer prevention knowledge survey score distribution (n=250)*

	Potential Distribution	Mean	±SD	Min	Max
Pressure Ulcer Prevention Knowledge Survey	0-66	52.95	5.78	28	63

The majority of nurses (98.8%) selected "advanced age" among the risk factors leading to pressure ulcer development, 89.2% selected the maximum pressure ulcer risk for "compression sleeves". Among the factors that nurses should pay attention to when evaluating the skin condition for pressure ulcers, the most accurate answer (99.2%) was "skin assessment should be started on the day the patient is hospitalized," whereas the most selected wrong answer (11.6%) was "apart from bone spurs, tissues should also be assessed because pressure ulcers develop on these areas particularly due to external pressure caused by medical tools". More than half of the sample (67.6%) correctly answered the definition of "Stage I" regarding the stages of pressure ulcers. Nurses (98.8%) demonstrated they knew the correct intervention to prevent pressure ulcers "when the skin of a patient with incontinence gets wet, it should be cleaned immediately and at certain intervals" and "the mobilization and transfer of fully bedridden patients should be performed by two or more people". It should be noted many nurses (92.8%) also selected that "when conscious patients with learning ability sit on chairs, they should be informed that they should shift their weight every 15 minutes" (Table 4).

3.3. Comparison of the nurses' knowledge level scores for pressure ulcer prevention according to their sociodemographic and occupational characteristics and training and practice related to pressure ulcers

We did not find statistically significant differences between Pressure Ulcer Prevention Knowledge Survey scores with respect to nurses' gender, marital status, occupation or professional experience (chi square test; p>0.05).

According to the results of the analysis, the Pressure Ulcer Prevention Knowledge Survey scores of nurses in the age groups of 20-29 years, 30-39 years, and 40 years or older (53.41±5.66, 53.23±4.65, and 54.50±4.20, respectively) were significantly higher than those of nurses aged 18-19 years (46.78±6.43). Considering the educational levels of the participants, the knowledge scores of the participants with associate, undergraduate and post-graduate degrees (51.56±4.50, 54.81±4.07 and 55.25±3.40, respectively) were significantly higher than those of the graduates of vocational health high schools (45.96±6.29).

Tablo 4. *Pressure Ulcer Prevention Knowledge Survey (n=250)*

Item	True		False	
	n	%	n	%
(1) Risk Factors for Pressure Ulcers				
1. Advanced age	247	98.8	3	1.2
2. Disturbance in sensory perception	153	61.2	97	38.8
3. Changes in states of consciousness	157	62.8	93	37.2
4. Malnutrition	204	81.6	46	18.4
5. Dehydration	210	84.0	40	16.0
6. Obesity/Cachexia	243	97.2	7	2.8
7. Hypotension	166	66.4	84	33.6
8. Immobility	239	95.6	11	4.4
9. Edema	246	98.4	4	1.6
10. Wet skin	215	86.0	35	14.0
11. Anemia	171	68.4	79	31.6
12. Hypodermia/Hyperthermia	63	25.2	187	74.8
13. Medicines	236	94.4	14	5.6
14. Pressure (duration, intensity)	242	96.8	8	3.2
15. Raising the head of bed 30 degrees more	62	24.8	188	75.2
16. Comorbid diseases (diabetes mellitus, cardiovascular, etc.)	241	96.4	9	3.6
(2) Medical Interventions that Cause Pressure Ulcers				
1. Contact with nasogastric catheter or oxygen cannula	157	62.8	93	37.2
2. Lips connected to an endotracheal tube	176	70.4	74	29.6
3. Ears in contact with oxygen cannula or pillow	165	66.0	85	34.0
4. Drainage tube	177	70.8	73	29.2
5. Foley catheter (generally inner face of the thigh)	168	67.2	82	32.8
6. Physical detection (wrists)	218	87.2	32	12.8
7. Contact zones of orthopedic devices, splints, positioning tools	220	88.0	30	12.0
8. Compression sleeves	223	89.2	27	10.8
9. Anti-embolism stocking	216	86.4	34	13.6
10. Central catheter	100	40.0	150	60.0
(3) Evaluation of Skin Care				
1. Skin assessment should be started on the day the patient is hospitalized.	248	99.2	2	0.8
2. The skin of a patient at risk should be observed for pressure ulcer development.	243	97.2	7	2.8
3. Skin should be assessed in terms of color change, temperature, turgor, humidity and bubbles.	242	96.8	8	3.2
4. Since pressure ulcers are generally observed on bone spurs, the assessment should focus on these areas first.	234	93.6	16	6.4
5. Apart from bone spurs, tissues should also be assessed because pressure ulcers develop on these areas particularly due to external pressure caused by medical tools.	221	88.4	29	11.6
6. All hospitalized patients should be assessed using the Pressure Ulcer Risk Assessment Scale.	230	92.0	20	8.0
7. Patients and caregivers should be provided with training for skin assessment.	244	97.6	6	2.4
(4) Stages of Pressure Ulcers				
1. There is a skin loss in the dermis layer. There is a superficial ulcer. The wound bed is red or pink, and it does not have necrosis (Stage II)	111	44.4	82	32.8
3. There is no open wound. There is a redness which does not fade after pressing on it. It may be the sign of ulceration (Stage I)	169	67.6	42	16.8
4. There is a deep ulceration which is followed by bone, tendon or muscle involvement. There is necrosis tissue on the wound bed (Stage IV)	76	30.4	120	48.0
5. There is a full-thickness ulcer. Subcutaneous fat tissue is observed. There is no bone, tendon or muscle involvement. There may be necrosis (Stage III)	77	30.8	112	44.8

Tablo 4. *Pressure Ulcer Prevention Knowledge Survey (n=250) (continued)*

Item	True		False	
	n	%	n	%
(5) Nursing Intervention for Preventing Pressure Ulcers				
1. Position should be changed regularly every two hours.	227	90.8	23	9.2
2. Pressure areas should be observed with every position change.	241	96.4	9	3.6
3. Skin should be kept dry and clean.	243	97.2	7	2.8
4. Friction and damage to the skin should be prevented.	236	94.4	14	5.6
5. The position of bedridden patients should be changed regularly every three hours.	150	60.0	100	40.0
6. It should be noted that bed linen is clean and stretched.	241	96.4	9	3.6
7. Skin protection creams should be used for patients with incontinence.	226	90.4	24	9.6
8. Protein and calorie intake of patients appropriate to their needs should be maintained..	238	95.2	12	4.8
9. Sufficient fluid intake of patients should be ensured.	237	94.8	13	5.2
10. Bone spurs on which redness has occurred should be massaged.	174	69.6	76	30.4
11. Patients should be enabled to perform active-passive exercises in the bed.	239	95.6	11	4.4
12. Protruding and pressure zones should be massaged.	215	86.0	35	14.0
13. Special protective pillows should be used for heels and elbows.	223	89.2	27	10.8
14. Supporting surfaces such as inflatable mattresses that distribute and reduce pressure, silicone beds, pillows, foams (recommended tools and materials for the prevention of pressure ulcers) should be used.	238	95.2	12	4.8
15. Ring-shaped cushions should be used to prevent pressure ulcers.	175	70,0	75	30.0
16. The blood sugar, hemoglobin and hematocrit values of patients should be checked.	213	85.2	37	14.8
17. The head of the bed should not be elevated more than 30 degrees in accordance with the clinical status and medical recommendations.	202	80.8	48	19.2
18. When conscious patients with learning ability sit on chairs, they should be informed that they should shift their weight every 15 minutes.	18	7.2	232	92.8
19. Heels should be kept high to reduce pressure on them.	230	92.0	20	8.0
20. Pressure should be alleviated by putting a water-filled glove on the heel of the foot.	203	81.2	47	18.8
21. Sheets or bed linens should be used to move or transfer patients.	231	92.4	19	7.6
22. Cushions should be used for patients sitting on chairs.	235	94.0	15	6.0
23. Changes that occur to decubitus ulcers should be recorded.	234	93.6	16	6.4
24. When the skin of a patient with incontinence gets wet, it should be cleaned immediately and at certain intervals.	247	98.8	3	1.2
25. The skin of individuals at the risk of pressure ulcers should be assessed at least once a week.	192	76.8	58	23.2
26. The mobilization and transfer of fully bedridden patients should be performed by two or more people.	247	98.8	3	1.2
27. Hot water and soap should not be used because they dry out the skin and increase the risk of pressure ulcers.	206	82.4	44	17.6
28. Patients and their families should be informed about the development, risk factors and causes of pressure ulcers.	235	94.0	15	6.0

When the nurses' knowledge level scores for pressure ulcer prevention are examined according to the unit they were working, the Pressure Ulcer Prevention Knowledge Survey scores of the nurses working in internal medicine, surgical service, and the operating room (53.57±4.69, 53.68±4.73, and 57.55±3.55, respectively) were higher than those working in the emergency unit and other units (outpatient clinic, electrocardiography, x-ray, blood collection department, etc.) (44.24±5.85 and 50.12±5.26, respectively). The knowledge scores of the nurses working in the intensive care unit (57.08±3.13) were statistically higher than those of the nurses working in medical wards or units, surgery, mixed service, emergency nursing, and other departments.

The scores of the nurses who received any education about pressure ulcers (54.43±4.38) were higher than those of the nurses who were not educated about the pressure ulcers (45.44±6.22). According to the analysis, the scores of the nurses who did not need any training for the evaluation and prevention of pressure ulcers (54.54±4.34) were significantly higher than those of the nurses who need education about the prevention of pressure ulcers (49.92±6.90) (Table 5).

Table 5. *Comparison of pressure ulcer prevention knowledge survey scores with practice and training characteristics of nurses for pressure ulcers (n=250)*

Practice and training characteristics of nurses for pressure ulcers		n	Knowledge level score		*t/F* p
			Mean	±SD	
Providing care for pressure ulcer patients	Yes	146	54.85	4.16	t=6.668* p=0.000
	No	104	50.29	6.64	
Average number of patients with pressure ulcers given care	[a]Never	106	50.32	6.60	F=15.010* p=0.000
	[b]1-2 patients	127	54.89[(a)]	4.22	
	[c]3-4 patients	14	54.50[(a)]	3.94	
	[d]5 or over	3	56.67	2.31	
Received any training about pressure ulcers	Yes	209	54.43	4.38	t=11.131* p=0.000
	No	41	45.44	6.22	
Training needed about assessment and prevention for pressure ulcers	Yes	86	49.92	6.90	t=-6.490* p=0.000
	No	164	54.54	4.34	

*t: t-test, F: one-way ANOVA, *p<0.001*

4. DISCUSSION

Prevention of pressure ulcers is an indication of the care quality (4, 24). The development of preventive activities specific to health personnel, hospital, family education, and the institution is the basis of effective prevention programs (17, 19). For the prevention of pressure ulcers, it is important to determine the knowledge level of nurses and to develop action plans for the patients by identifying possible risk groups (15).

Several causes contribute to the risk of pressure ulcer development. In this study, a significant number of nurses stated that the most important risk factor for developing pressure ulcers was "advanced age". Due to old age, some changes occur in the skin (3, 25). A study conducted by Katran (26) found that 31.4% of the patients in the age group of 75 years and over developed pressure ulcers and there was a significant relationship between age and pressure ulcer development. Similarly, some research (27,28,29) have reported a significant relationship between the age of the patients and pressure ulcer development.

Medical tools (nasal cannulae, oxygen masks, intubation tubes, nasogastric catheters, urinal catheters, blood pressure cuffs, splints, etc.) used for the purposes of diagnosis and treatment improve the quality of life of patients and causes medical tool-related pressure ulcers, which threatens patient safety. As a result of the external pressure caused by medical devices fixed on tissue, blood and lymph circulation is impaired, which causes pressure ulcers (28, 30). Approximately half of the nurses in this study reported that the pressure ulcer was seen only in bedridden patients and that pressure ulcers associated with medical devices were most often caused by a compression sleeve. A study conducted by Black et al. (30) found that the most common region of pressure ulcers due to medical devices did the ears, which is caused by the oxygen cannula. A study conducted in the intensive care unit of a university hospital (31) reported that the answer for the item "the pressure ulcer is only seen in bedridden patients" was 39.6% for pre-training and 43.8% for post-training. Therefore, it will be useful to raise the awareness of nurses to prevent pressure ulcers caused by medical devices and to develop policies and procedures in this direction. It is the responsibility of nurses to prevent the pressure ulcers associated with medical devices and to detect any ulcers early. This requires nurses to evaluate and care for the skin and mucous membranes under and around the medical device.

It is very important to use risk diagnostic tools to prevent pressure ulcers. It is also very important to use valid and reliable risk assessment scales and perform evidence-based practices to improve and standardize the quality of patient care (32). Skin assessment provides information for practices intended to minimize risk and evaluating their consequences. For this reason, daily skin assessment should be performed for all patients and a care plan should be prepared for each patient. All the areas of the skin should be examined in every position, and special attention should be paid to skin over bone protrusions (33). Health professionals should have complete knowledge about how to perform a comprehensive skin assessment (34). One study (35) reported that the pressure ulcer was assessed on the first day of hospitalization, almost immediately, in the risk intensive care unit. The point about skin condition assessment emphasized most by the nurses (99.2%) was that it should be carried out as soon as the patient is hospitalized.

The National Pressure Ulcer Advisory Panel and the European Pressure Ulcer Advisory Panel, as part of the guideline development process, have developed an international general definition of pressure ulcers and a classification system. After a joint study, it was concluded that skin-tissue damage occurs at four levels (21, 22). Once a pressure ulcer is identified, the stages and size of the wound should be carefully documented (8). Staging of pressure ulcers is very important in terms of the diagnosis of pressure ulcers and appropriate treatment and care interventions according

to wound type. The examination of skin areas developing pressure wounds and their stages showed that the pressure wounds developed most in the sacrum area and the pressure wounds in this region were mostly in Stage II (25, 28, 36). The correct answers were below the mean score in the study (37) in which nurses' knowledge and practice related to deep tissue injury and Stage I pressure ulcer prevention and management were assessed. More than half (67.6%) of the nurses in this study responded correctly to the definition of Stage 1 in the pressure ulcer classification. This result shows that most nurses have the knowledge to take measures to prevent the development of pressure ulcers. In addition, the nurses should have adequate experience and equipment when the ulcers are correctly staged.

Among the practices of nurses to prevent pressure ulcers in this study, the most accurate answers were "when the skin of a patient with incontinence gets wet, it should be cleaned immediately and at certain intervals" and "the mobilization and transfer of fully bedridden patients should be performed by two or more people." It should be pointed out that "when conscious patients with learning ability sit on chairs, they should be informed that they should shift their weight every 15 minutes" is the most incorrectly answered item by the nurses. A study examining the knowledge levels and attitudes of nurses in a nursing home in Belgium (15) found that the highest score obtained by the participants was related to risk assessment. Only 16% of respondents stated that it is important to shift position regularly while sitting on a chair. Another study (38) showed that more than half of the participants (54.4%) had appropriate knowledge for the prevention of pressure ulcers, but the remaining participants (45.6%) did not. In a study conducted by İnan and Öztunç (28), 98.8% of the nurses stated that the incontinent patients should be cleaned immediately and at regular intervals when the skin gets wet and two or more people should perform the mobilization and transfer of fully dependent patients. In another study (39), 9% of nurses stated that massage of bone protrusions and the use of inflatable rings were effective protective measures, although nurses correctly identified many strategies to prevent pressure ulcers.

This study found that there were significant differences between the nurses' knowledge level scores and their age, educational level, providing care for a patient with a pressure ulcer, and prior education regarding pressure ulcers.

This study also found that nurses in the age group of 18-19 years had the lowest level of knowledge. This may be related to the fact that nurses at the ages of 18 and 19 do not have much experience in caring for patients with pressure ulcers. Moreover, since these nurses graduated from health vocational high schools, pressure ulcer prevention may not have been emphasized within the scope of their education. Similarly, a study conducted by Doğu (31) found that there was a statistically significant difference by age in nurses' knowledge level scores about pressure ulcers and caring for them. Another study (40) reported no significant relationship by age in nurses' knowledge levels about managing pressure ulcers.

In the present study, the knowledge level scores of the nurses who had associate, undergraduate, and graduate educational levels were higher than those of the nurses who graduated from health vocational high school. According to these results, the training and practices of undergraduate nurses for 4 years are effective and sufficient. A study (41) conducted with 740 nurses to determine their knowledge levels about the prevention of pressure ulcers found that knowledge levels of nurses with bachelor's degrees were 80.3%, and that those of nurses with associate's degrees were 71.7%. Another study (38) found a significant difference between the educational level of nurses and their knowledge level about prevention of pressure ulcers. Thus, the pressure ulcer knowledge levels of nurses with bachelor's degrees were 2.4 times higher than those of the nurses with a high school diplomas.

Patients admitted to the intensive care unit are individuals who are at high risk of developing pressure ulcers due to their vulnerability to widespread systemic effects from the nature of their health problems, having lost their ability to perceive and act on stimuli, the treatment options used, and the intensive care environment (11, 42). In this study, the knowledge level scores of the nurses working in the intensive care unit were significantly higher than those of the nurses working in the internal medicine service, surgical service, mixed service, emergency service, and other units. Karadağ Aydin and Karadağ (37) reported that nurses working previously in a service with pressure ulcer patients had a higher level of correct response scores for prevention/treatment of pressure ulcers than those not working in these services. Another study (40) found no significant relationship between the unit where nurses were working and their knowledge levels about managing pressure ulcers.

There were no statistically significant differences between knowledge level scores by professional experience and unit. A study conducted by Nuru et al. (38) found that there was a significant difference by work experience in nurses' levels of knowledge about preventing pressure ulcers. Nurses with 11-20 years of work experience had a 4.8-fold higher level of knowledge than those with less than 10 years of work experience. Another study (41) conducted with nurses in Spain on the clinical practice of information and pressure ulcer care revealed that the longer the work experience, the more knowledge nurses gained. The reason for this is that nurses with more working experience may have benefited from the knowledge and skills gained by working with other team members. While Karadağ Aydin and Karadağ (37) found a significant difference between the knowledge level of nurses and previous experience on pressure ulcer management, there was no statistically significant difference between working period and knowledge scores in the study conducted by Doğu (31).

This study found that nurses trained in preventing pressure ulcers had significantly higher scores than non-educated

nurses. Of the participants, 83.6% received training on pressure ulcers and 63.2% stated that they received this training within the curriculum of nursing education. In another study (38), nurses who received formal training in pressure ulcers had a 4.1 times greater knowledge level than those who were not trained on pressure ulcers. A study (14) conducted by Swedish nurses to assess the knowledge level, attitudes, and practices related to pressure ulcer prevention showed that nurses participating in the post-graduate training course were significantly better at all parts of the applied knowledge test than those not taking the course. Another study (17) found that there was a significant difference between nurses' knowledge levels and their participation in in-service programs, and that continuous education after graduation changed their knowledge and attitudes. Similarly, a study conducted Acaroğlu and Şendir (39) showed that nurses needed training in pressure ulcers to support blood-based practices and to reduce the use of ineffective strategies. A study conducted by Unver et al. (43) found that nurses who had received any education about pressure ulcers had better attitudes towards the prevention of pressure ulcers.

The data obtained in this study were limited to the nurses who were working at a Practice and research hospital affiliated with a foundation university in Istanbul during the period when the study was conducted and agreed to participate in the study. Further studies should be conducted with nurse groups working in different types of hospitals to obtain detailed information about nurses' knowledge levels regarding pressure ulcer prevention and to generalize the results.

5. CONCLUSION

In this study, nurses' knowledge level scores for prevention of pressure ulcers were above average. This study found that the knowledge levels of nurses whose educational levels were high, who participated in in-service training programs, courses etc. and who provided care for patients with pressure ulcers were higher. The knowledge levels of nurses working in intensive care were higher, and the nurses working in the emergency department were the lowest. The knowledge level scores of nurses whose had less experience and who were recent graduates were lower.

A high incidence of pressure ulcers in an institution may result from the fact that nurses working in clinics do not have adequate levels of knowledge. When nurses are educated and have knowledge about the prevention of pressure ulcers, nursing practices can be improved. Therefore, the knowledge levels of nurses working in all units regarding the prevention of pressure ulcers and practices related to them should be assessed periodically. Their lack of knowledge about this topic can be overcome by obtaining evidence-based data and correcting misinformation. Supporting the continuous participation of nurses in training programs such as courses, workshops and in-service training programs, etc. is very important to ensure the continuity of care and increase nurses' awareness about pressure ulcers. These continuous training programs should be planned in accordance with changes in information and technology and use international guidelines about evidence-based practices for pressure ulcers. These training programs should be included in the in-house orientation training programs planned for nurses who are starting work. Patients' quality of life can be improved by enabling nurses to provide care in accordance with the evidence-based practices for the prevention of pressure ulcers.

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Clinical and Experimental Health Sciences

Evaluation of Genotoxicity Risk in Health Care Workers Exposed to Antineoplastic Drugs

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ABSTRACT

Objective: DNA damage that can be caused by workplace exposure to antineoplastic drugs in health workers has been shown in many scientific studies. It is aimed to evaluate whether the risk of genotoxicity in health workers decreases after the regulations and measures taken by national and international health authorities in our work.

Methods: For this purpose, DNA damage was assessed by using alkaline comet technique in lymphocytes isolated from blood samples of health workers (n=29) who were involved in preparing and / or administering antineoplastic agent at Trakya University Health Research and Application Center and compared with the control group (n=30). Also, those who prepare and/or administer antineoplastic agents; (n=16) and manual (n=13) preparations.

Results: As a result of the evaluation, there was no statistically significant difference between health personnel and control group in preparing and / or administering antineoplastic agent (p>0,05, Mann-Whitney U) and there was no difference in the genotoxic risk between preparation forms. Furthermore, when the exposed control group was assessed for DNA damage as smokers and nonsmokers, there was no statistically significant difference in terms of DNA damage (p>0.05).

Conclusion: At the center where our samples were taken, the resulting measures resulted in the control of the risk of genotoxicity due to occupational exposure to antineoplastic agents.

Keywords: Alkaline Comet Assay, Genotoxicity, Antineoplastic, Occupational exposure, Occupational health safety

1. INTRODUCTION

Antineoplastic agents are drugs that are used in the treatment of cancer and have mutagenic and carcinogenic properties which affect healthy cells because of their low selectivity to cancerous cells. Health workers are exposed to contaminants such as tears, saliva, sweat, and contact with body wastes such as urine, feces, vomit, etc. during preparation and administration of these drugs during the cleaning of dusts and spillages caused by breakage of tablets (1).

Studies have shown that workplace exposure to antineoplastic medicines causes DNA damage in health workers (1). This poses a risk for the fetus if it is risky for health workers and if the health worker is unaware of the fact that she is pregnant (2). It is important to note that the duration of exposure and the precautions specified in the safe use standards of antineoplastic medicines published by the Ministry of Health (such as the use of gloves and goggles, preparation in biological safety cabin) are significant during this risk (3).

Since they are mutagenic and carcinogenic, a dose that can be considered safe for exposure to these drugs can not be determined. The assessment of genotoxicity risk is very important in terms of protection of the health of the health care workers, because this exposure is reduced as much as possible and at low doses, because of the possibility of continuous exposure to these drugs. Recently, robotic drug preparation units have been used to reduce occupational exposure and minimize errors in drug preparation. The aim of our study is to evaluate the current status of the genotoxicity risk reported in previous studies in the health care workers working in the preparation unit of antineoplastics such as doxorubicin, 5-fluorouracil, docetaxel, paclitaxel and cyclophosphamide by using alkaline comet technique.

2. METHODS

2.1. Chemicals and Reagents

The chemicals used were the following: disodium ethylenediaminetetraacetic acid (Merck 324503), low melting agarose (LMA) (Sigma A4018), high melting agarose (HMA) (Sigma A7174), sodium hydroxide (Sigma 06203), sodium chloride (Merck 106404), Tris (Sigma T6066), Histopaque 1077 (Sigma 10771), Ethidium Bromide (Sigma E8751), Hydrochloric Acid (Sigma 320331), Triton X-100 (Fisher BioReagents bp151-100), ethanol (Merck 100983)

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2.2. Collection of Working Group and Blood Samples

Between the years 2015-2017; health workers (Exposed group, n = 29) taking part in preparing and/or administering antineoplastic agents such as doxorubicin, 5-fluorouracil, paclitaxel and cyclophosphamide were included in Health Research and Application Center of Trakya University for at least 3 months and health workers (Exposed group, n=30) were compared in the same hospital with no antineoplastic agent and with similar demographic characteristics (age, gender, alcohol, smoking, etc.). Also, those exposed to antineoplastic agents are evaluated as robotic (n = 16) and manual (n = 13) preparations. The suitability of the study for the Helsinki declaration was approved by the Scientific Research Ethics Committee of the Faculty of Medicine of Trakya University (Decision No: TÜTF-GOKAEK 2014/107). Individuals were informed about the study first, and 2 consecutive venous blood samples were collected in heparinized tubes after the consent form and questionnaire were filled out voluntarily from those who agreed to participate in the study. Pregnants and those who received x-ray radiation in the last 6 months and those who did heavy workouts in the previous 3 days were not included in the study.

2.3. Lymphocyte isolation

Blood, which was brought to the laboratory rapidly after it was received, was centrifuged with histopaque 1077 to isolate lymphocytes (250g, + 4°C, 10').

2.4. Alkali Comet Technique

Alkali comet technique developed by Singh et al and adapted to our laboratory was used to determine DNA damage in isolated lymphocyte samples (4). The slides were covered with 0.65% high boiling grade agar (HMA) 1 day prior to the experiment. Stock lysis solution (2.5M NaCl, 100 mM Na2EDTA, 10 mM Tris, pH10), 10M NaOH solution, 0.2 M EDTA solution and neutralization buffer (0.4 Molar Tris, pH 7.5) were prepared overnight and stored at + 4°C.

Two specimens were used for each sample. 100 µL of the isolated lymphocyte suspension and 0.65% low boiling-point agar (LMA) (37 ° C) were spread on the slide and covered with lamellae. The slides were left in the cold for 30 minute to solidify the agar and cell suspension and then lysed overnight at + 4°C in a freshly prepared lysis solution (stock lysis solution, Triton X-100 and DMSO; 89%: 1% 10%) to lyse lymphocyte cells.

2.5. Electrophoresis and dyeing

The laminates removed from the lysis buffer were left in the electrophoresis solution [300 mM NaOH, 1 mM EDTA pH13] for 20 min to open the DNA helix. Subsequently, the electrophoresis was placed in a horizontal electrophoresis tank and subjected to electrophoresis for 20 minutes at 15 volts at 300 mA. All post-lysis procedures were performed in the dark and at + 4°C to avoid additional DNA damage. The slides removed from the electrophoresis were neutralized in neutralization buffer [0.4 Molar Tris, pH 7.5] 3 times for 5 minute. Lastly, 50%, 75%, 100% alcohol was held for 5 minute at + 4°C, and the slides were fixed and dried. Each slide was examined by staining with 50 µL Ethidium Bromide (EtBr – 20 µL/mL).

2.6. Microscopic Analysis

The fluorescence attenuated microscope (Axio Observer Z1, Carl Zeiss, Germany) scored comet in 100 cells per well with 40x magnification. Scoring; according to the traction of the comet tail in the electric field, it was classified into 3 groups as non-immigrant, less immigrant, and immigrant. Total comet score is calculated with 0x (non-migrated comet) + 1x (few comet) + 2x (comet with high migration) formula (5). For each slide, the damage was scored from 0 (no damage) to 200 (maximum damage).

2.7. Statistical analysis

It was calculated that when trying to find a significant difference of 0.04 in the groups, 99% of the effort and 0.01 of the α error level were found, 28 participants were required in each group. Groups were followed by 29 control groups and 30 study groups. Statistics were expressed as descriptive variables, mean and ± standard deviation, median, percentile. Categorical variables were compared with chi-square and fisher tests. Shapiro-Wilk's test is used to assess normality of the variables. Student's T test is used for variables that follow normal distribution and Mann-Whitney U test is used for variables that does not follow normal distribution. A value of $p < 0.05$ was considered statistically significant.

3. RESULTS

As shown in Table 1, there was no statistically significant difference between the distribution of demographics and life habits in the study and control groups ($p > 0.05$). There was no statistically significant difference in total Comet Score that was a DNA damage parameter in peripheral blood lymphocytes, when compared between health personnel and control group taking part in preparing and/or administering antineoplastic agent (Table 2, $p>0.05$). The exposed group was divided into two subgroups in order to assess the effect of the preparation on the risk of genotoxicity. First manual subgroup is formed from workers who prepare the drug manually; and/or health-care workers who apply the manually prepared medication to the patient. The second is the robotic subgroup; a robotic unit, and a healthcare worker who prepares a medicine or applies a medicine to a patient who is prepared in a robotics unit. There was no statistically significant difference between Total Comet Score manual subgroup and robotic subgroup (Table 2, $p> 0,05$).

Furthermore, when the effect of DNA damage was assessed in smokers in the groups, no statistically significant DNA

damage results were found with non-smokers (Table 2, p> 0.05).

Table 1. *Demographic characteristics and lifestyle habits of the groups*

Groups			Control group	Exposed group	*p* value
n			30	29	
Age mean (±SS) (year)			34.67±8.65	32.28±7.41	0.260*
Body mass index (±SS)			24.7707±4.69	23.43±3.39	0.213*
Gender	Woman		2 6(86.7%)	24 (82.8%)	0.731+
	Man		4 (13.3%)	5 (17.2%)	
Smoking	Smoker (piece/ day)	1-10	4 (13.3%)	5 (17.2%)	0.306+
		11-20	8 (26.7%)	4 (13.8%)	
		≥21	2 (6.7%)	0 (0%)	
	Non-smoker		16 (53.3%)	19 (68.4%)	
Alcohol consumption	Yes		9 (30%)	4 (13.8%)	0.209+
	No		21 (70%)	24 (82.8%)	
	Quitter		0 (0%)	1 (3.4%)	

*+: Student's T test; *: Fisher's exact test; exposed group against control group*

Table 2. *DNA damage (TCS)* according to control and study groups and preparation patterns*

Groups		n	Median (25th percentiles – 75th percentiles)	*p*§
Control Group		30	0.00 (0.00 – 2.25)	0.140+
Exposed group		29	2.00 (0.00 – 3.00)	
Control Group	Smoker	14	0.5 (0.00 – 3.25)	0.322+
	Non smoker	16	0.00 (0.00 – 1.75)	
Exposed group	Smoker	9	1.00 (0.00 – 2.00)	0.302+
	Non Smoker	20	2.50 (0.00 – 5.25)	
Exposed group	Manuel Preparation	13	3.00 (0.00 – 6.00)	0.337#
	Preparation with Robotic Unit	16	1.00 (0.00 – 2.75)	

*(§: Mann-Whitney U test is used; +: working group against control group; #: Preparation with robotic unit subgroup against preparation manual subgroup; *: TCS (Total Comet Score) = 0x (number of non-migration comet) + 1x (few comet) + 2x (high migration number comet)*

4. DISCUSSION

The deterioration of working health after occupational exposure is a major problem both in terms of public health and the health economy. Today, health and work authorities take various measures and apply sanctions for occupational health and safety. In the last 30 years, attention has been drawn to the possible exposure risk of health personnel preparing and administering antineoplastic drugs. In 2004, T.C Ministry of Health General Directorate of Treatment Services issued "Guidelines for Safe Work with Antineoplastic (Cytotoxic) Drugs" to inform relevant health personnel and provide a safe working environment (3). In our study, genotoxicity risk was assessed by alkaline comet technique after taking precautions in health personnel involved in preparing antineoplastics such as doxorubicin, 5-fluorouracil, mossataxel, paclitaxel and cyclophosphamide, and genotoxicity was not detected in control subjects exposed to antineoplastic agents. Furthermore, the preparation did not have a statistically significant role on DNA damage in the group included in the study.

The risk of genotoxicity caused by exposure during the administration and preparation of medicines in health workers has been evaluated in various studies, and it has been shown that some studies have no statistically significant risk of genotoxicity (6,7) and some studies have a statistically significant effect on DNA damage compared to the control group (5,8-17) . One of the first studies done in nurses exposed to antineoplastic drugs in Turkey has started in 1991 Sardas et al. In this study, it was reported that sister chromatid technique detected high chromatin damage in lymphocytes compared to the control group (8). Some examples of DNA and chromosomal damage reported by different techniques are presented below. El-Ebiary et al. reported higher chromosomal aberrations and microcirculation frequency in the study of chromosomal aberrations and microcirculation in healthcare personnel in preparing and administering antineoplastic drugs in a cancer hospital (1). Burgaz et al. reported a higher microcirculation rate in healthcare personnel in our country than in the control group by means of microcephaly method in our country where they detected antineoplastic drugs in urine specimens (9). In a similar study, it was reported that genetic damage was not observed with comet technique in health personnel who had antineoplastic drugs in urine specimens in America (6). In two different studies, Villiarini (10) and Rekhadevi (11) et al. reported that DNA damage was found to be statistically significantly higher in healthcare personnel who prepared an antineoplastic drug in studies evaluating exposure to urine, and that the damage was less with Villiarini and arc protective equipment. In another study that showed that protective equipment reduced the risk, Kopjar anda et al. also reported high levels of damage in the health care staff who prepared antineoplastic medication compared to the control (12). Maluf et al. reported that there was no difference in micro-nuclear parameters after a new evaluation, which was the continuation of the study after 4 years in the group they had previously performed and those who were exposed to antineoplastic agents in the work environment, found that the frequency of DNA damage was significantly higher than that of control (13).

When the results of the studies are examined, it is seen that individual factors such as age, drugs used, life style, smoking and alcohol use, it is seen that method-dependent variables such as exposure time, dose, application frequency and combination, accidental drug delivery, biological safety cabinets, glove, glasses and mask dependent factors such as the time taken for blood sampling, method differences in the applied comet technique, (6,10,18,19).

It is known that different antineoplastic agents exhibit different DNA damage profiles and produce synergistic effects together (20). Limitation of our work is study results cannot

be generalized, because of the differences between health care workers such as exposure time, application frequency and safety precautions. The alkaline comet technique, which we use in our study, is a technique that is frequently used in human biosimulation studies and accepted as correct (21,22).

In the first study conducted in 1998 with the alkaline comet technique in our country for the evaluation of genotoxicity in nurses who prepared antineoplastic medicines, Undeger et al emphasized that the genotoxicity risk observed in our country was due to the lack of guidelines to provide awareness of health personnel in our country (14). In another study conducted in our country, Izdes et al reported the risk of DNA damage in nurses exposed to antineoplastics (5). In our study, in the health personnel included in the study, the results were not statistically significant but the total comet score average was found to be lower when working with the robotic unit. In the robotic drug unit, the medicines are prepared automatically and the prepared health care practitioner applies to the patient. The risk of exposure to the robotic unit is therefore reduced. In the study conducted by Sessink et al., low level surface contamination was detected in some vials due to spillage in the robotic drug preparation unit, but due to the wearing of two layers of gloves, it was shown that no contamination of workers' hands and no cyclophosphamide in their urine (23).

5. CONCLUSION

As a result, it has also been observed in our work that the use of protective equipment such as gloves, masks, goggles, cabin, and the necessity of working with a robotic drug unit (10,14,17,24). As emphasized in other studies (1) occupational exposure determination and risk assessment studies are specific to the population in which they are conducted and are not realistic to compare with each other.

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Clinical and Experimental Health Sciences

Effects of Water Samples in Polyethylene Terephthalate Bottles Stored at Different Conditions on Zebrafish Embryos with Relevance to Endocrine Disrupting Chemical Migration and Adenomatous Polyposis Coli Tumor Suppressor Gene

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ABSTRACT

Objective: Polyethylene terephthalate (PET) is a material that is most commonly used for production of clear plastic bottles. Adenomatous polyposis coli (APC) and β-catenin have been related with cancer. Aim was to investigate the effects of PET bottled water samples that were exposed to sunlight and hot water on zebrafish embryos. Moreover the effects of these water samples on APC knockdown zebrafish embryos were also evaluated.
Methods: Phthalate concentrations in water samples were determined using ELISA. Immunohistochemical method and RT-PCR were used to analyse the expressions of proliferative cell nuclear antigen (PCNA), β catenin, Wnt 3a and Gsk3β. Biochemical parameters were measured using spectrophotometric methods. Vitellogenin concentrations were measured using ELISA and apoptotic cells were evaluated by Acridine Orange staining.
Results: Increased PCNA, β-catenin, Wnt 3a, Gsk3β expressions, vitellogenin, nitric oxide, apoptosis and impaired oxidant-antioxidant balance were observed in the exposure groups with these increases being more profound in APC knockdown groups.
Conclusion: APC knockdown embryos were more prone to the deleterious effects of water samples used in this study.
Keywords: Polyethylene terephthalate, phthalates, Wnt/β-catenin signaling, adenomatous polyposis coli

1. INTRODUCTION

The issue on the potential effects of endocrine disrupting chemicals (EDCs) on public health revealed the need for new research into the mechanisms of their effects in case of exposure. EDCs are defined as synthetic or natural molecules in the environment, they can impair endocrine functions and they are suspected carcinogens. EDCs can be detected in different products such as bottles, canned waters, storage boxes as well as treated waste water and they can be categorized as pesticides, plasticizers, industrial side products, pharmaceuticals, flameretardants, phytoestrogens, or heavy metals. EDC exposure during development is a serious and major health concern and may lead to permanent or long-lasting defects (1-3).

Polyethylene terephthalate (PET) is a widely used material for the production of clear plastic bottles to sell water. They are also used to produce soda beverages, sports drinks, vinegar containers and for cosmetic products packaging. On the other hand the potential of plastic materials from packagings to migrate EDCs into foods and beverages has been a neglected isssue for long (4). Phthalates are a group of chemicals that are used to provide flexibility and durability to plastics and chemically they are the diesters of 1,2-benzenedicarboxylic acid, known as phthalic acid. Phthalates have been related with different adverse outcomes including adiposity and insulin resistance (5,6), anogenital distance decrease (7) and alterations in sex hormone levels (8). Other consequences of phthalates have been reviewed by Hauser and Calafat (9). Being as the most commonly used plasticizer di-[2-ethylhexyl]-phthalate (DEHP) has been reported to lead to reproductive and developmental toxicity (10). Migration is defined as leaching of chemicals from food packaging into food. Although this is systematically checked by market authorizations storage conditions and the effects of acidic or alkaline foodstuffs, UV light, and heat may degrade polymers. Leaching of monomers as a result of this process is also known as “release”(11).

Adenomatous polyposis coli (*APC)* gene produces the APC protein which plays critical roles in many cellular processes. The roles of APC protein include its tumor suppressor function, control on cell division, cell attachments and movements. The APC protein works with beta-catenin through Wnt/β-catenin pathway in association with other proteins (12). Mutations in the *APC* gene has been shown to lead to uncontrolled proliferation in intestinal epithelial cells and are related with the earliest colorectal carcinogenesis stages (13). On

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the other hand although the role of Wnt/β-catenin signaling in embryonic development and tissue homeostasis has been evaluated in some studies, the relationship between abnormalities in Wnt ligands and tumorigenicity has not yet been clarified (14).

In recent years zebrafish embryo has become a popular model due to its external and rapid development, small size, high level of fecundity and optical transparency (15). In the current study we tested the hypothesis that *APC* knockdown zebrafish embryos are more susceptive to the deletious effects of water samples that had been heated in PET bottles to simulate the release of chemicals due to storage conditions. Accordingly expressions of Wnt/β-catenin pathway proteins, vitellogenin levels, apoptosis and oxidant-antioxidant status of zebrafish embryos have been evaluated.

2. METHODS

2.1. Maintenance of zebrafish

Wild type AB/AB Strain were maintained in apparently disease-free conditions, kept in the aquarium rack system (Zebtec, Tecniplast, Italy) at 27 ± 1 °C under a light/dark cycle of 14/10 h. Zebrafish were fed twice a day with commercial flake fish food supplemented with live Artemia. Reverse osmosis water that was added 0.018 mg L^{-1} Instant Ocean™ salt was used for all experiments. After natural spawnings, embryos that were fertilized were collected cultured, and staged by developmental time and morphological criteria as described previously (16). This study was approved by the Marmara University Animal Experiments Local Ethics Committee (138.2013.mar; 28.04.2014).

2.2. Preparation of water samples

Commonly used bottled water samples were randomly selected from supermarkets in Istanbul, Turkey. The first group consisted of PET bottles that were kept under sunlight for 30 days in July. The second group consisted of PET bottles that were filled with 100 ^{0}C boiled water and allowed to cool in them. Water samples from these bottles were used for the exposure groups in petri dishes (volume: 40ml). Embryos were added to each dish and placed into the incubation chamber and examined for 120 hours.

2.3. Embryo exposures

For the exposure experiments, embryos were exposed to the water samples in well plates for 120 hours after fertilization (hpf). In order to evaluate development, mortality and hatching parameters the group were prepared as three replicate wells. Each group contained 20 embryos. The exposure solutions were prepared every day as fresh solutions. When the exposure period ended, the embryos were washed with embryo medium for several times and they were allowed to develop until 120 hpf. A stereomicroscope (Zeiss Discovery V8, Hilden, Germany) was used for the detection of developmental parameters. Malformation images were recorded. The rates of mortality and hatching were determined for every 24 h. The hatching rate is defined as the ratio of hatching embryos to the living embryos in a well.

2.3. Phthalates Analyses in Water Samples

Phthalates were measured using the phthalates Elisa kit (Abraxis Phthalates ELISA, Microtiter Plate, Katalog No: 530050, Railroad Drive, Warminster,USA) which is a direct competitive ELISA method that is based on the recognition of total phthalates by antibodies. The concentrations of phthalates in the samples are evaluated by interpolation using the standard curve constructed with each run. Using the absorbances at 450 nm, a dose-response curve was obtained from known concentrations of phthalates standards and the BPA concentration in the samples (n=7) were calculated using the absorbances obtained from the standard curve.

2.4. Morpholino Microinjections

Morpholino oligonucleotides were maintained from Gene Tools LLC. APC and (5'-TAGCATACTCTACCTGTGCTCTTCG-3') the control morpholino (5'-CCTCTTACCTCAGTTACAATTTATA-3') were dissolved in 1 mM in 1× Danieau buffer. 0.5 mM morpholino was injected into wild type embryos that were at one – four cell stages for the microinjections (17,18).

2.5. Expression Analyses

2.5.1. Whole Mount Immunohistochemistry

For whole-mount immunohistochemical expression of proliferative cell nuclear antigen (PCNA), β-catenin and Wnt 3a zebrafish embryos were fixed. Pronase (2.0 mg/ml, in E3 medium; 5 mM NaCl, 0.17 mM KCl, 0.33 mM $CaCl_2$, 0.33 mM $MgSO_4$) was used to dechorionate embryos for 3 to 5 min and then they were rinsed five times in E3 medium. They were incubated for 1 hour in 4% paraformaldehyde and Anti-PCNA antibody, Anti-β-Catenin antibody, Anti-Wnt 3a antibody (abcam ab28472; abcam ab6302 and abcam ab29 respectively) were used as primary antibodies.

2.5.2. Reverse Transcription (cDNA synthesis) and Quantitative Real-Time PCR

Rneasy Mini Kit and Qiacube (Qiagen, Hilden, Germany) were used for the isolation of RNA from the embryos according to the manufacturer's instructions. After that single-stranded cDNA was produced from 1 µg of total RNA using RT^2 Profiler PCR Arrays (Qiagen). DNA Master SYBR Green kit (Qiagen) was used for PCRs. The expression of *cyclin D1*, *c-myc, β actin*, *wnt 3a* and *gsk3β* were evaluated by quantitative RT-PCR using the Qiagen Rotor Gene-Q Light Cycler instrument (Qiagen, Hilden, Germany). The average values were calculated based on the results of three experiments. DDCT method was used

normalizing the values with the house keeping gene *β actin* (19).

2.6. Determination of Vitellogenin levels

Vitellogenin levels were determined at the end of 120 hours in zebrafish embryos by the Zebrafish Vitellogenin Elisa Kit (Biosense, Prod No: V01008402,Michigan, USA). For whole body homogenates, 50 embryos were homogenized in 500 µL PBS. Then whole body homogenates were 1:500 diluted (5 µL homogenate and 2495 µL dilution buffer) according to the manufacturer's instructions. Each group was prepared as five replicates. This assay is based on the use of specific binding between antibodies and vitellogenin to measure vitellogenin in the samples.

2.6.1. Biochemical Assays

Zebrafish embryos at 72 hpf were used (n=5, 100 individuals per pool). The embryos were then homogenized in 1ml PBS, which was followed by centrifugation. The forming supernatant was used for the biochemical assays.

2.6.2. Total Protein Determination

Total protein concentrations were measured according to the method of Lowry (20). For this method, alkaline proteins were reacted with copper ions and then they were reduced by the Folin reactive. A spectrophotometer was used to evaluate the absorbance of the product at 500 nm. The results were calculated and expressed as levels per protein.

2.6.3. Lipid Peroxidation Determination

Malondialdehyde (MDA) is the end product of lipid peroxidation (LPO) and the method of Yagi (21) was used to determine MDA concentrations. The MDA results were presented as nmol MDA/mg protein using the extinction coefficient of $1.56 \times 10^5\ M^{-1}cm^{-1}$.

2.6.4. Nitric Oxide Determination

Nitric oxide (NO) levels were assessed using the method based on reducing nitrate to nitrite by vanadium (III) chloride (22). In this method, nitrite and sulfonylamide reacts with N-(1-Naphtyl) ethylenediamine dihydrochloride in an acidic media and as a result diazonium compound is produced. The absorbance of the colored complex was measured at 540 nm using spectrophotometer and results were calculated and presented as nmol NO/mg protein.

2.6.5. Glutathione-S-transferase Determination

Glutathion-s-transferase (GST) activity was evaluated using the method based on GSH and 1-chloro-2,4-dinitro-benzenin (CDNB) conjugation and the absorbance of their product at 340 nm (23).

2.6.6. Determination of Apoptosis

Apoptosis of live embryos was determined at 72 hpf using acridine orange (Sigma, Darmstadt, Germany) staining method (24). Accordingly, live embryos that were immersed for 10 min at room temperature, in 5 µg/ml acridine orange a nucleic acid-selective metachromatic stain. After that embryos were washed in E3 medium. Then the embryos were anesthetized using Tricaine for 3 min. Embryos were visualized and imaged for less than 1 minute, apoptotic cells were determined using fluorescence microscope (Zeiss V16 Axio Zoom microscope-546 nm filter, USA).

2.6.7. Statistical analysis

One-way Anova with post-hoc Tukey's Multiple Comparision Test was used to analyse the differences between normally distributed data (Shapiro–Wilk normality test), using Graph Pad 6, A p value of ≤0.05 was considered as significant.

3. RESULTS

In order to examine the hypothesis that *APC* knockdown embryos were more prone to the possible deleterious effects of chemicals that leach from PET bottles and DEHP, we aimed to to knock down the function of APC and evaluate the effects of exposure to the water samples kept in PET bottles on both control and *APC* knock down embryos. To achieve this, a morpholino that is splice blocking specific for *APC* that targets the splicing of *APC* between exon 15 and intron 15 was designed as previously shown (25). At the one – or two-cell stage this APC morpholino was injected this into wild type zebrafish embryos. The intron-retained RNA transcript was produced as shown by the expression levels of the reported β-catenin target genes, *c-myc* (26) and *cyclin D1* (27) that are expected to be up-regulated following *APC* knockdown. We observed the malformations in the *APC* morphant embryos such as pericardial edema, tail and pigmentation defects (Figure 1A). Accordingly increased expressions of c-*myc* and *cyclin D1* were confirmed by quantitative RT-PCR (Figure 1B). Immunohistochemical results revealed the elevated cellular β-catenin staining in the neural tube, notochord and eye region which indicates clonal loss of APC function in the MO group. The expression of PCNA was evaluated as a proliferation marker and in neural tube and eye intense staining revealed elevated expression in the MO group. MO injected embryos also presented more intense Wnt 3a staining in eye, brain, neural tube, notochord, somites, dorsal, caudal and anal fins (Figure 1C).

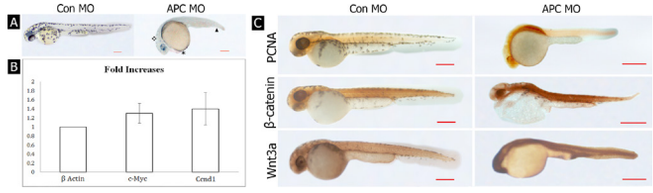

Figure 1. A) *Phenotypes of Control Morpholino (Con MO) and APC Morpholino (APC MO) *pericardial edema, ▲tail defect, □ ❖ pigmentation defect* ***B)*** *Quantitative RT-PCRwith primers specific for ϐ-actin, c-Myc, and Ccnd1 was performed on cDNAs obtained from embryos injected with control or APC morpholinos, expressed as fold increases.* ***C)*** *PCNA, ϐ-catenin and Wnt 3a expressions in Con MO and APC MO group; Con: Control, APC: Adenomatous polyposis coli, PCNA: Proliferative cell nuclear antigen*

The mortality rate increased and hatching rate decreased significantly in the APC morphant embryos compared with the Con MO group. Significant increases in mortality rates and decreases in hatching rates were observed in the 30d Sun PET and PET 100 °C groups when compared with the Con MO group. On the other hand, mortality rates increased and hatching rates decreased in both MO injected exposure groups when compared with their respective uninjected controls (Figure 2).

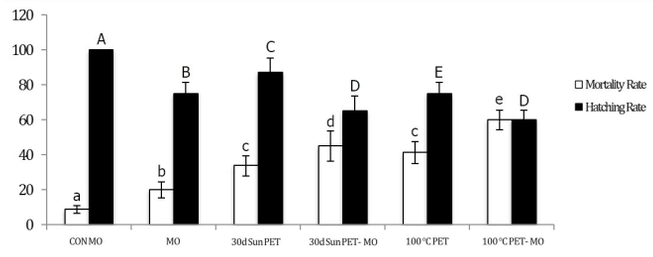

Figure 2. *Mortality rates and hatching rates of embryos, n=20, The average values were obtained from three experiments. Data presented are mean ± SD, Different letters within columns indicate statistically significant differences in the mortality rate (lower case) or hatching rate (upper case) as determined by One-way Anova followed by post-hoc Tukey's Multiple Comparision.*

Immunohistochemical analysis revealed increased intensity of PCNA in neural tube, brain and eye; β-catenin in notochord and somites, Wnt 3a in eye, brain and notochord in the 30 days sun exposed; PCNA in eye, neural tube, notochord and somites, β-catenin in eye, brain, neural tube, Wnt 3a in eye, brain, notochord and somites in the 100 ^{0}C boiled water filled PET bottles especially in the MO injected groups (Figure 3A).

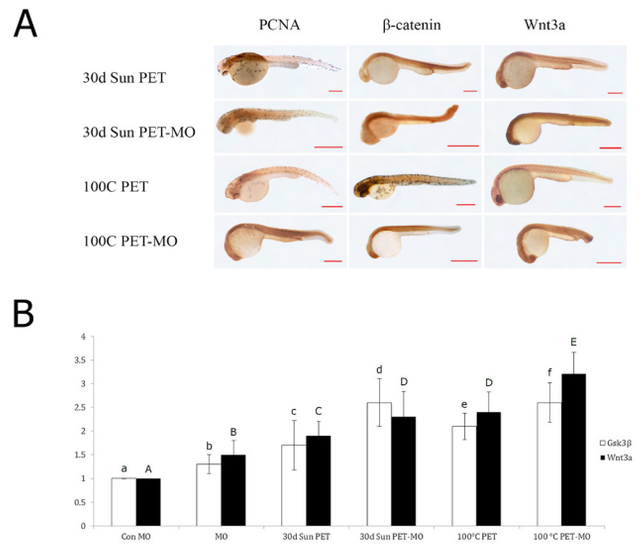

Figure 3. A) *Immunohistochemical analysis of the expression of PCNA, ϐ-catenin, Wnt 3a, Control Morpholino images are given in Figure 1.* ***B)*** *Quantitative expression of wnt 3a and gsk3ϐ expressed as fold increases in 30 days direct sun light exposed PET group (30d Sun PET), 100°C boiled water filled PET group (100^{0}C PET), and APC morpholino embryos corresponding to the exposure groups (MO). Increased expressions were observed in the exposure groups but yet increases more evident in the APC morphant embryos. Data presented are mean ± SD. Different letters within columns indicate statistically significant differences in the expressions of Gsk3ϐ (lower case) or Wnt 3a (upper case) as determined by One-way Anova followed by post-hoc Tukey's Multiple Comparision. Con: Control, MO: Morpholino, PET: Polyethylene terephthalate*

The *wnt3a* and *gsk3ϐ* expressions were found to be elevated given as fold increases with the *ϐ-actin* gene being used for normalization. Significant increases were observed in *wnt3a* and *gsk3ϐ* expressions in the MO group when compared the Con MO group. The expressions of *wnt3a* and *gsk3ϐ* in MO injected 30 d Sun PET and PET 100 °C exposed embryos increased significantly when compared with their uninjected controls (Figure 3B).

Results of total phthalates analyses in the water samples are given as the mean concentration of three replicates in Table 1. Phthalate levels in the control PET bottle was below the detection limits of the assay used in this study. On the other hand, total phthalate levels increased to the detection limit of the assay in the exposure groups, 100^0 C boiled water filled (9,63±1,3 µg/L) and 30 days direct sunlight exposed PET bottles (8,45±1,28 µg/L) (Table 1). The concentrations of vitellogenin, nitric oxide and lipid peroxidation increased significantly whereas glutathione S-transferase decreased in the exposure groups when compared with the control group (Table 2). According to the acridine orange staining results there were considerable numbers of apoptotic cells in the exposure groups mainly in the head and eye region (Figure 4).

Table 1. *Total phthalates concentrations in drinking water samples in PET and PC bottles*

Total Phytalates Concentration in PET Bottles (ng/ml)	
Control PET bottle	ND
30 days direct sunlight exposed PET bottle	8,45±1,28
100^{0}C boiled water filled PET bottle	9,63±1,3

Data presented are mean ± SD. ND: Not detected, PET: Polyethylene terephthalate

Table 2. *Vitellogenin, nitric oxide, lipid peroxidation and glutathione-S transferase levels of the zebrafish embryos*

	Vitellogenin (ng/mL)	NO (nmol/mg P)	GST (U/g P)	LPO (µmol MDA/g P)
Control	59,8±5,7	13,44±1,9	0,41±0,022	0,028±0,002
30d PET	92,6±6,3^a	21,34±3,6^b	0,23±0,01^a	0,035±0,002^d
100° PET Group	108,8±9,4^a	24,76±3,72^c	0,23±0,012^a	0,032±0,003^e

Data presented are mean ± SD. NO: Nitric oxide; GST: Glutathione-S transferase; LPO: Lipid peroxidation. Significant differences from the control group are indicated by letters, ^{a}p<0,0001; ^{b}p=0,0046; ^{c}p=0,0003; ^{d}p=0,0004; ^{e}p=0,021

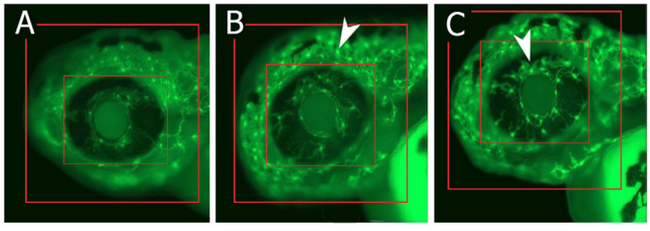

Figure 4. *Apoptotic cells were observed in the head and retina region of the zebrafish embryos.* ***A)*** *Control Group,* ***B)*** *30 d Sun Exposed PET,* ***C)*** *100 °C heated PET Group. Small square: eye region; Big square:head region, PET: Polyethylene terephthalate*

4. DISCUSSION

Use of plastic materials increased for bottled water production and PET is one of the most used polymer. But chemical migration of plasticisers and additives to water (28,29) became a major health concern. Phthalates are used to improve flexibility and phthalate migration has been shown before (30-31).

Quantitative phthalate determination is challenging as phthalates do not persist in outdoor environment. Gas chromatography mass spectrometry is the most used technique but in the present study ELISA was used. Phthalate levels were below the detection limit for control PET bottled water samples but increased in exposure groups. Increased DEHP concentrations due to poor storage conditions have been reported before (31-33).

DEHP is a potential carcinogen and toxic to reproductive organs, kidneys and liver (7,34-37). Zebrafish (*Danio rerio*) is used for studying the effects of environmental toxins (38). To examine the hypothesis that APC knockdown embryos were more prone to the effects of chemicals that leach from PET bottles we aimed to knock down APC function. Mutations in the Wnt pathway are related with birth defects, cancer and other diseases (39). Genetic mutations in APC and β-catenin way lead to activation of canonical signaling as the protein product of *APC* gene is a key component of the β-catenin destruction complex (40).

The expressions of *wnt 3a* and g*sk3β* increased significantly in the 30 days sunlight exposed and 100 ^{0}C boiled water filled PET bottle groups and increases were more profound in the *APC* knockdown groups. Mutations in APC result in the accumulation of β-catenin and stimulate proliferation genes like *c-myc* (26). In our study PCNA was evaluated as a proliferation marker and increased expressions were observed in the APC morphant exposure group. β-catenin's abnormal expression causes various diseases including cancer (41). β-catenin expression increased in exposure groups especially in *APC* knockdown groups. Acridine orange staining showed that apoptotic cells mainly accumulated in the head region which indicates possible EDC induced impairments in this region through the aryl hydrocarbon receptor (AhR) (42). Oxidant-antioxidant balance was impaired and NO levels increased in the exposure groups. There are conflicting roles of NO in proapoptotic pathways (43-45). Increased *gsk3β* expressions may be related with apoptosis through the inhibition of prosurvival transcription factors, and activation of proapoptotic transcription factors (46,47).

Vitellogenin genes are expressed in an estrogen-dependent manner therefore only mature females are able to produce vitellogenin in larger quantities. On the other hand estrogenic molecules trigger vitellogenin synthesis in males and larvae as well (48-50). In this study vitellogenin levels increased in exposure groups. DEHP's estrogenic activity is still unclear (50,51). We have previously shown that DEHP (2,5 µg/L) did not increase vitellogenin levels in zebrafish embryos (52). Increased vitellogenin levels in exposure groups may be due to higher concentration of phalates in water samples or other chemicals that may have migrated into water from PET bottles.

5. CONCLUSION

The results of this study demonstrate that poor storage conditions increase phthalate concentrations in PET bottled water samples through photolysis (53,54) and *APC* knockdown embryos were more prone to the deleterious effects of these water samples. Therefore although the determined phthalate concentrations are not yet a thread for human health, their striking effects on zebrafish embryo should be taken into account and appropriate storage conditions should be promoted for public health.

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Clinical and Experimental Health Sciences

Capecitabine Induced Hand-Foot Syndrome: A Systematic Review of Case Reports

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ABSTRACT

Objective: Capecitabine, a prodrug of 5-fluorouracil, is currently used in the treatment of metastatic colorectal and breast cancers. The aim of this study was to review the pharmacological mechanisms, treatment strategies, and documented case reports of capecitabine-induced hand–foot syndrome (HFS).

Methods: All case reports documented in the PubMed, Web of Science, and Scopus databases up to February 2018 were searched and reviewed using the keywords capecitabine, hand-foot syndrome, and case report.

Results: The database search identified 373 articles in the literature; of these, 88 articles (having 111 case reports) in the English or Turkish language having a full-text access were included in the study. The median duration of capecitabine-induced HFS was 28 (range, 7–140) days, and the daily dose of capecitabine ranged between 850 and 5000 mg/m2 in cases wherein capecitabine was applied as monotherapy(n=19). A dose reduction or treatment discontinuation, systemic or topical treatment alone or in combination, and the use of henna, vitamin E, or pyridoxine were preferred options in the treatment of HFS.

Conclusion: Health care providers and patients should be aware of developing capecitabine-induced HFS and its risk factors. Early recognition and treatment initiation for HFS are important to maintain effective chemotherapy in patients with cancer.

Keywords: Capecitabine, hand–foot syndrome, mechanism, case reports

1. INTRODUCTION

Capecitabine is used as an adjuvant treatment in colorectal cancer; as the first-line treatment in metastatic colorectal, gastric, pancreatic, and head and neck cancers; and as monotherapy or in combination with docetaxel in metastatic breast cancer (1). Although capecitabine is well tolerated by patients, hand–foot syndrome (HFS) is one of the common adverse events, which causes a significant degree of morbidity (2, 3). HFS was first described by Zuehlke in 1974 as an erythematous/malignant rash on the hands and toes of patients who received mitotane (4).

The incidence of capecitabine-induced HFS is approximately 50%–60%, and the severe (≥grade 3) form of HFS occurs in approximately 10%–70% of cases. The syndrome is dose-dependent, and its occurrence is associated with the peak drug concentration and the total cumulative doses of capecitabine (5). HFS, also known as palmar–plantar erythrodysesthesia (PPE), chemotherapy-associated acral erythema, toxic palmar–plantar erythema, or Burgdorf reaction, is one of the most frequent adverse events of cytotoxic chemotherapy (6). Although many cytotoxic drugs have been reported to cause HFS, it is more frequently observed in cases treated with 5-fluorouracil, liposomal doxorubicin, and cytarabine (7).

After the first-pass metabolism of capecitabine in the liver as a prodrug, it is transformed into an active form (known as 5-fluorouracil) by thymidine phosphorylase in tumor cells, which inhibits the thymidylate synthesis in purine synthesis and blocks DNA replication and its repairing process (Figure 1) (8). The most frequently seen adverse event of capecitabine is based on dermis, which leads to vascular degeneration of keratinocytes, apoptosis, perivascular lymphocytic filtration, and edema (9). HFS manifests as dysesthesia, palmar–plantar formication, and erythema at first, and its severity increases to a painful syndrome unless treated appropriately (4, 7).

The National Cancer Institute graded the hand – and foot-related adverse effects as mild (Grade 1), moderate (Grade 2), severe (Grade 3), and life-threatening (Grade 4). Minimal skin changes, erythema, and peeling (Grade 1); moderate skin changes, swelling, and edema (Grade 2); painful erythema and swelling in the palms and soles (Grade 3); or pain with bloating, deep peeling, and ulceration (Grade 4) can be observed in various degrees in patients (10).

The World Health Organization has classified HFS according to the symptoms, clinical appearance, and pathology. Dysesthesia and paranesthesia are accompanied by tingling in the hands and feet in Grade 1; swelling without pain in

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the hands and feet is observed and uncomfortable erythema occurs during walking and holding objects in Grade 2; painful erythema and swelling are observed in the palms and soles in Grade 3; and a significant increase in the severity of pain with bloating, deep peeling, and ulceration is observed in Grade 4 (10). Patient self-monitoring tools have been developed for the self-evaluation of HFS symptoms by patients (11-14).

The mechanism of capecitabine-induced HFS has not been identified in detail; however, many hypotheses have been suggested (Figure 1).

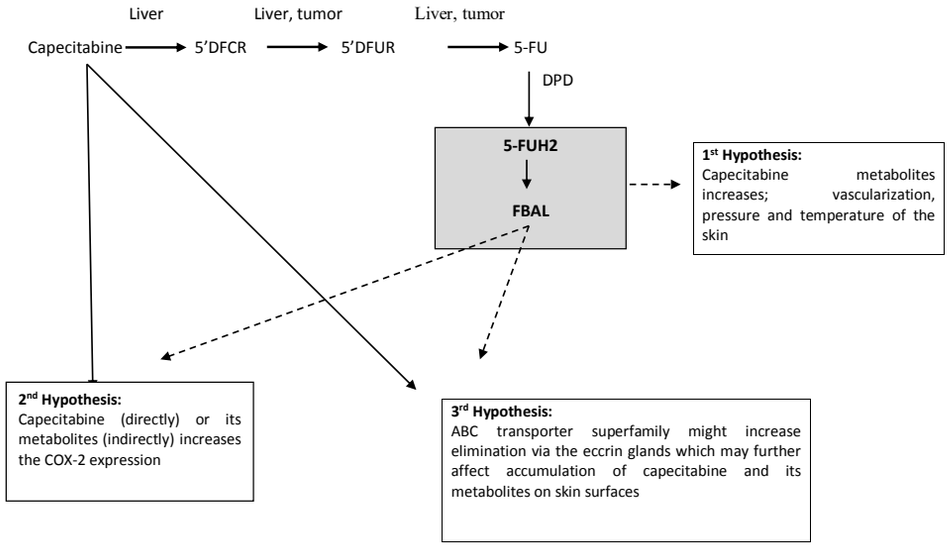

Figure 1. *Possible mechanism of capecitabine induced hand foot syndrome.*
Abbreviations: CAP, capecitabine; CD, cytidine deaminase; CES, carboxyleterase ; 5'DFCR, 5'-deoxyfluorocytidine; FBAL; α-fluoro-β-alanine; 5'DFUR, 5'-deoxyfluorouridine; 5-FU, 5-fluorouracil; 5-FUH2, 5-dihydrofluorouracil; FUPA, α-fluoro-β-ureidopropionate; TP, thymidine phosphorylase; UP, uridine phosphorylase; DPD, dihydropyrimidine deshydrogenase

One of the hypotheses states that the excretion of capecitabine by eccrine glands leads to accumulation of its metabolites. The capecitabine metabolite level is increased due to an increased thymidylate phosphorylase in the keratocytes. It is also suggested that an increased vascularization, temperature, and pressure in the hands and feet may predispose to HFS (15).

Another hypothesis suggests that HFS occurs because of palmar–plantar cyclooxygenase (COX) inflammatory-type reaction. COX-1 is found in almost all tissues and plays an important role in the protection of the gastric mucosa. COX-2 is normally found at low levels in the cells and is induced by inflammation and mutagenic stimulation; it plays a vital role in the synthesis of prostanoids (prostaglandin, prostacyclin, thromboxane, and eicosanoids) associated with pain and inflammation (16).

Moreover, it is assumed that the carrier systems affect the absorption of capecitabine. The carriers within the membrane transport system, particularly skin membrane transport system, play a crucial role in the occurrence of capecitabine-associated toxicity along with the metabolism pathways. The ATP-binding cassette (ABC) carrier family is one of the membrane transport systems comprising proteins that transfer miscellaneous drugs, xenobiotics, and endogenous compounds from the membrane. These carrier systems eliminate antineoplastic drugs from tumor cells and prevent drug accumulation in the tumor tissue, thus leading to chemotherapy failure. Many ABC carriers play an important role in the fluoropyrimide-based chemotherapeutic response by determining the drug concentration within the cell that leads to cutaneous reactions on hands and feet (17).

2. METHODS

All case reports published in English or Turkish language up to February 2018 in the Pubmed, Scopus and Web of Science databases were searched by using the keywords of 'capecitabine', 'hand-foot syndrome' and 'case report'. A total of 373 articles were identified, and of these, 75 were found in the PubMed, 252 in the Scopus, and 46 in the Web of Science databases. Case reports having full-text access and providing information regarding the following criteria were included: cancer type, patient's age and sex, dose and duration of capecitabine, and treatment options for HFS. This study is a systematic review of published case reports. Therefore, a consent form was not necessary and an ethics committee approval was not sought for the study. However, the study was conducted and written according to the principles of Helsinki Declaration. The Statistical Package for Social Science version 23 (IBM, New York, United States) program was used for statistical data analysis in the study. The patients' demographics were obtained from the case reports, and data were summarized using descriptive statistics.

3. RESULTS

Of the 373 identified articles (Figure 2), 285 were excluded due to duplicates in databases (n=90), not having full-text access (n=18), not published in the English or Turkish language (n=48), and not relevant to the scope of the study (n=129). Therefore, 88 articles (having 111 case reports) were included in this study. Although there were variations in the characteristics of diseases, patients, dose, and duration of chemotherapy and preferred treatment for HFS (18-105) in the reported cases, information regarding the cases was summarized based on the cancer type, patient's age, patient's sex, antineoplastic treatment, capecitabine dose, HFS occurrence during the capecitabine treatment (days), and treatment options for HFS in the study (Table 1).

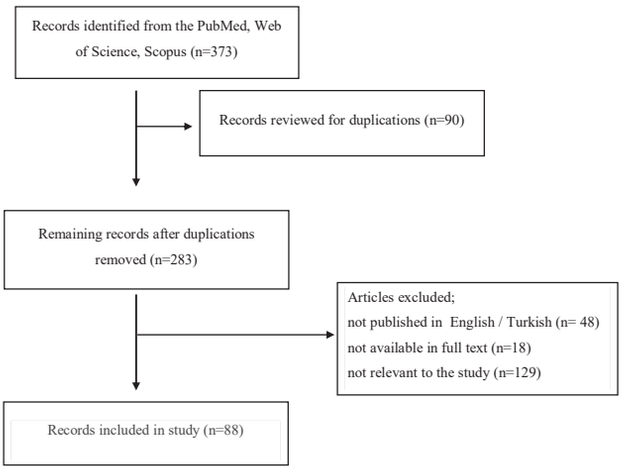

Figure 2. *Flowchart of the study methodology.*

Table 1. *Documented case reports on capecitabine-induced HFS.*

Authors, year (Reference)	Cancer type	Age (year)	Sex	Antineoplastic treatment	Capecitabine dose	Occurrence of HFS during capecitabine treatment (days)	Treatment for HFS
Capecitabine monotherapy							
Gerbrecht BM., 2003 (18)	Sigmoid colon cancer	62	F	Capecitabine	2500 mg/m2/day for 14 days then 7 days rest	After 13 and 28 days, respectively	Dose was reduced (after 28 days)
Hindenburg et al., 2003 (19)	Cervix adenocarcinoma	59	F	Capecitabine	1100 mg/m2 BID for 14 days then 7 days rest	After 7 days	Hydration and antibiotic treatment were initiated.
Schüll et al., 2003 (20)	Metastatic breast cancer	50	F	Capecitabine	2500 mg/m2/day for 14 days then 7 days rest	N/A	N/A
Jones et al., 2003 (21)	Metastatic breast cancer	47	F	Capecitabine	2500 mg/m2/day BID for 14 days with then 7 days rest	After 60 days	Pyridoxine 50 mg po TID was initiated.
LoRusso PM., 2003 (22)	Invasive ductal carcinoma and metastatic	46	F	Capecitabine	2500 mg/m2/ day for 14 days then 7 days rest	After 21 days	Pyridoxine 50 mg po TID was initiated at first. HFS ammonium lactate (Lac-Hydrin) lotion was started thereafter.
Clippe et al., 2003 (23)	Metastatic breast cancer	51	F	Capecitabine	2500 mg2/day for 14 days then 7 days rest	After 8 days	Capecitabine was discontinued.
Allen et al., 2014 (24)	Rectum cancer (early stage)	63	M	Capecitabine	1250 mg/m2 BID for 14 days then 7 days rest	After 63 days	Emolient cream was initiated. When symptoms become severe, capecitabine dose reduced at the end of 5th cycle and capecitabine dose was delayed in 6th cycle
Niemann et al., 2004 (25)	Breast cancer	61	F	Capecitabine	4000 mg/day for 14 days then 8 days rest.	N/A	N/A
Gilliam et al., 2006 (26)	Metastatic follicular thyroid cancers	49	M	Capecitabine	850 mg/m2 BID	After 25 and 180 days, respectively	Dose was reduced to 550 mg/ m2 BID
Saif et al., 2006 (27)	Advanced rectal cancer	52	M	Capecitabine	1500 mg BID for 14 days then 7 days rest	After 9 day	N/A
Inui et al., 2006 (28)	Metastatic liver cancer	88	M	Capecitabine	N/A	N/A	N/A
Saif et al., 2006 (29)	Hepatocellular carcinoma	59	F	Capecitabine	1800 mg po BID for 14 days then 7 days rest	N/A	N/A

Stubblefield et al., 2006 (30)	Metastatic breast cancer	42	F	Capecitabine	2000 mg/ m2/day	Within days of starting capecitabine	Celecoxib 200 mg po BID and gabapentin 300 mg po TID were initiated.
Vogt et al., 2006 (31)	Prostate cancer	61	M	Capecitabine	1000 mg/m2/day for 14 days then 7 days rest	After 21 days	Capecitabine was replaced by trofosfamide
Saini et al., 2007 (32)	Metastatic breast Cancer	56	F	Capecitabine	2500 mg/ day	After 10 days	Capecitabine was discontinued. Pyridoxine, intravenous fluids, non-steroidal antiinflammatory drugs and emollients were initiated.
Tavares-Bello R., 2007 (33)	Stage 3 adenocarcinoma	82	M	Capecitabine	N/A	After 35 days	Tacrolimus 0.1% ointment BID and emollients were initiated.
Sapp et al., 2007 (34)	Metastatic colon adenocarcinoma	67	M	Capecitabine	1000 mg/m2 BID for 14 days then 14 days rest	After 56 days	Capecitabine was discontinued
Lee et al., 2007 (35)	Gastric cancer	70	M	Capecitabine	2500 mg/day for 7 days then 7 days rest	After 60 days	Lotion was used.
Bosch et al., 2007 (36)	Dukes C2 sigmoid carcinoma	67	M	Capecitabine	2500 mg/m2/ day for 14 days	After 63 days	Capecitabine was discontinued.
Bianconi et al., 2007 (37)	Metastatic gestational trophoblastic neoplasia	29	F	Capecitabine	2500 mg/m2 BID for 14 days then 7 days rest	After about 210 days	N/A
Cho et al., 2008 (38)	Colorectal cancer	46	F	Capecitabine	2500 mg/m2/day for 14 days then 7 days rest days	N/A	Patients receiving 6 cycles were delayed by 2 cycles and dose was decreased by 2 cycles
Yucel et al., 2008 (39)	Metastatic breast cancer	47	F	Capecitabine	N/A	N/A	Henna was used.
	Metastatic breast cancer	48	F	Capecitabine	N/A	N/A	Henna was used.
	Metastatic breast cancer	59	F	Capecitabine	N/A	N/A	Henna was used.
	Metastatic breast cancer	73	F	Capecitabine	N/A	N/A	Henna was used.
	Metastatic colon cancer	68	F	Capecitabine	N/A	N/A	Henna was used.
Trindade et al., 2008 (40)	Metastatic sigmoid colon	56	M	Capecitabine	2000 mg/day BID	7th cycle	N/A
Vickers et al., 2008 (41)	Stage II moderately invasive adenocarcinoma	49	M	Capecitabine	N/A	After 63 days	Capecitabine dose was reduced.
	Stage III sigmoid colon cancer	58	F	Capecitabine	N/A	3rd cycle	4th cycle was delayed and the dose was reduced by 50%.
	Stage III colon cancer	54	M	Capecitabine	N/A	Before 3rd cycle	Capecitabine dose was reduced.
Surjushe et al., 2008 (42)	Adenocarcinoma of the common ble duct	50	F	Capecitabine	500 mg BID	After 2nd cycle	Topical and systemic antibiotics were initiated and capecitabine dose was reduced
Goutos et al., 2009 (43)	Colon Dukes B adenocarcinoma	71	M	Capecitabine	N/A	After 90 days	Treatment was discontinued and pyridoxine 50 mg po TID, silver sulfadiazine cream (1%) and silicone-coated nylon dressings were initiated.
Endrizzi et al., 2009 (44)	SCC	70	M	Capecitabin	1150 mg po BID	N/A	N/A
	SCC and BCC	72	M	Capecitabine	1500 mg/day	N/A	N/A
	SCC and BCC	50	M	Capecitabine	1050/m2/day	N/A	N/A

Villalo´n et al., 2009 (45)	Metastatic breast cancer	58	F	Capecitabine	2500 mg/m2/day	4th cycle	Capecitabine was discontinued
Lopez et al., 2010 (46)	Metastatic invasive ductal carcinoma	49	F	Capecitabine	1500 mg/m2/day BID	Several days after the 2nd cycle	Emollients and topical corticosteroids were initiated and capecitabine dose was reduced to 1000 mg/m2 BID. Capecitabine was discontinued if symptoms are not resolved.
Wong et al., 2009 (47)	Metastatic nasopharyngeal carcinoma	62	M	Capecitabine	1700 mg BID for 14 days then 7 days rest	N/A	No intervention
Baena-Cañada et al., 2010 (48)	Metastatic ınvasive ductal carcinoma of breast	66	F	Capecitabine	1000 mg/m2 BID for 14 days, every 22 day	After 132 days	Dose was decreased
Disel et al., 2010 (49)	Metastatic gastric cancer	65	M	Capecitabine	1000 mg/m2/day BID for 14 days then 7 days rest	After 94 days	Capecitabine was discontinued and supportive treatment was initiated.
Gafson et al., 2010 (50)	Colon cancer	66	M	Capecitabine	1250 mg /m2 BID for 14 days then 7 days rest	After 63 days	Pyridoxine 50 mg po TID was initiated.
Vasudevan B., 2010 (51)	Adenocarcinoma of stomach	59	M	Capecitabine	2000 mg BID for 14 days then 7 days rest.	After 42 days	Topical emollient was initiated
Bayraktar et al., 2011 (52)	Breast cancer	93	F	Capecitabine	1500 mg/day	After 2nd cycle	N/A
Gordon et al., 2011 a (53)	Cecal adenocarcinoma	57	M	Capecitabine	N/A	After 2. cycle	Antibiotics was started
Serdar et al., 2011 (54)	Colon carcinoma	68	M	Capecitabine	N/A	3rd cycle	Topical steroid was initiated.
Qiao et al., 2012 (55)	Advanced rectal cancer	59	F	Capecitabine	N/A	After 9 days	Topical urea cream was initiated.
Cruz et al., 2012 (56)	Metastatic colon cancer	53	M	Capecitabine	1000 mg/m2 BID for 14 days then 7 days rest	After 21 days	Capecitabine was discontinued.
Sanghia et al., 2012 (57)	Breast cancer	30	F	Capecitabine	500 mg for 14 days then 7 days rest	After 87 days	Dose was decreased and topical emolient was initiated.
Chan et al., 2012 (58)	Colon Dukes C adenocarcinoma	42	F	Capecitabine	2000 mg BID for 14 days then 7 days rest	After 21 days	Dose was decreased to 1500 mg BID
Lipshitz et al., 2012 (59)	Sigmoid colon cancer	82	M	Capecitabine	N/A	After about 120 days	Capecitabine was discontinued
Tanaka et al., 2013 (60)	Metastatic breast cancer	62	F	Capecitabine	2400 mg/day	N/A	N/A
Marinelli et al., 2013 (61)	Hepatocellular carcinoma	53	F	Capecitabine	500 mg BID	After 30 days	Capecitabine was discontinued temporarily and emollient, urea-based creams were initiated.
Inokuchi et al., 2013 (62)	Metastatic invasive ductal carcinoma	75	F	Capecitabine	1657 mg/m2/day for 14 days then 7 days rest	After 63 days	Prophylactic pyridoxine and obetasol propionate (a superpotent steroid) were initiated. If symptoms are not resolved 0.1% adapalene gel BID was initiated.
Perri et al., 2013 (63)	Squamous cell carcinoma of the head and neck	N/A	N/A	Capecitabine	500 mg/m2 BID for 14 days then 7 days rest.	After 42 days	Capecitabine was discontinued
Mishra et al., 2013 (64)	Per ampullary carcinoma	62	M	Capecitabine	N/A	At the beginning of 3rd cycle	Pyridoxine tablet and topical steroid were initiated
Ilyas et al., 2014 (65)	Pancreas adenocarcinoma	53	F	Capecitabine	1500 mg for 14 days po BID then 7 days rest	After 42 days	Henna was used.

Prakasam et al., 2014 (66)	Advanced gastric cancer	65	M	Capecitabine	500 mg BID for 14 days then 7 days rest	After 14 days	Prophylactic antibiotics (cefotaxime and metronidazole) were initiated to prevent secondary infection of the skin lesions; topical emollients (liquid paraffin), oral steroids, Vitamin E and B complex and non-steroidal anti-inflammatory drug (diclofenac) were initiated
Parikh et al., 2015 (67)	Cutaneous squamous cell carcinoma	30	F	Capecitabine	500 mg/m2 BID for 14 days then 7 days rest.	N/A	Capecitabine dose was reduced
Elmas et al., 2016 (68)	Metastatic ductal breast carcinoma	62	F	Capecitabine	N/A	After 3rd cycle	Dose was decreased and mometazon furoate pomade and moisturizer were initiated
Li et al., 2016 (69)	Colorectal carcinoma	74	F	Capecitabine	1250 mg/m2 BID for 14 days then 7 days rest	After 21 days	Capecitabine was discontinued and mometazon furoate cream, topical retinoid cream and hydroxychloroquine (during 9 days) were initiated.
Rovere et al., 2017 (70)	Metastatic rectal cancer	47	M	Capecitabine	2000 mg/m2 /day	After about 240 days	Capecitabine was discontinued
Mazza et al., 2017 (71)	Rectal adenocarcinoma and liver metastasis	60	M	Capecitabine	N/A	After 150 days	Capecitabine dose was reduced
Combination treatment with capecitabine							
Chen et al., 2003 (72)	Breast cancer	40	F	Capecitabine and docetaxel	1250 mg/m2 BID for 14 days then 7 days rest.	After 30 days	Potassium permanganate solution (for nail disorder) and gentamicin ointment was initiated.
	Breast cancer	52	F	Capecitabine and docetaxel	1250 mg/m2 BID for 14 days then 7 days rest.	After 30 days	Potassium permanganate solution (for nail disorder) and gentamicin ointment was initiated.
	Breast cancer	50	F	Capecitabine and docetaxel	1250 mg/m2 BID for 14 days then 7 days rest.	After 30 days	Potassium permanganate solution (for nail disorder) and gentamicin ointment was initiated.
Uslu et al., 2005 (73)	Metastatic invasive ductal carcinoma	68	F	Capecitabine and docetaxel	N/A	After about 210 days	Capecitabine was discontinued. Permanganate bath, emollient cream and 500 mg/day po pyridoxine were initiated.
Kara et al., 2005 (74)	Metastatic ductal carcinoma	72	F	Capecitabine, docetaxel and zoledronate	N/A	After 2nd cycle	The treatment was stopped and vitamin E was initiated at dose of 300 mg/day.
	Metastatic ductal carcinoma	48	F	Capecitabine and docetaxel	N/A	After 2nd cycle	Vitamin E was initiated at dose of 300 mg/day.
	Metastatic ductal carcinoma	46	F	Capecitabine and docetaxel	N/A	After 3 cycle	Vitamin E therapy was started at 300 mg/day
	Invasive ductal carcinoma	40	F	Capecitabine and docetaxel	N/A	3. cycle	Vitamin E was started at dose of 300 mg/day.
	Metastatic invasive ductal carcinoma	50	F	Capecitabine and docetaxel	N/A	3. cycle	Vitamin E was started at 300 mg/day.
Gilliam et al., 2006 (26)	Metastatic FTC	41	F	Capecitabine and doxorubicin	Capecitabine 1000 mg/m2 BID	After 84 days	Capecitabine was discontinued.
Tham et al., 2006 (75)	Grade-2 ductal carcinoma	51	F	Capecitabine and whole-brain radiation	2500 mg/m2/day for 14 days then 7 days rest.	After about 400 days	Capecitabine was discontinued.

Sapp et al., 2007 (34)	Gastric adenocarsinoma	63	M	Capecitabine and oxaliplatin	1000 mg/m2 po BID for 14 days then 7 days rest	After 11 days	Capecitabine was discontinued.
Goyal et al., 2007 (76)	Metastatic hepatocellular carcinoma	50	M	Capecitabine and thalidomide	1500 mg/ day	After 60 days	All medications were discontinued. Emollients and analgesic cream were initiated.
Yucel et al., 2008 (39)	Metastatic breast cancer	49	F	Capecitabine and docetaxel	N/A	N/A	Henna was used.
	Metastatic breast cancer	33	F	Capecitabine and docetaxel	N/A	N/A	Henna was used.
	Metastatic breast cancer	50	F	Capecitabine and docetaxel	N/A	N/A	Henna was used.
	Metastatic breast cancer	59	F	Capecitabine and docetaxel	N/A	N/A	Henna was used
	Metastatic breast cancer	33	F	Docetaxel, Capecitabine	N/A	N/A	Henna was used.
Shigekawa et al., 2008 (77)	Metastatic breast cancer	44	F	Capecitabine and trastuzumab	1650 mg/m2 BID for 21 days then 7 days rest.	After 112 days	Capecitabine dose was reduced to 1800 mg/day
Saif et al., 2008 (78)	Gastric adenocarcinoma	69	M	Capecitabine and radiotherapy	1000 mg BID po for 7 days then 7 days rest	After 56 days	N/A
Karatay et al., 2008 (79)	Ductal carcinoma	55	F	Capecitabine and paclitaxel	1250 mg/m2 BID	3rd cycle	Capecitabine dose was reduced to 1000 mg/m2 BID)
Shahrokni et al., 2009 (80)	Metastatic colon cancer	55	M	Capecitabine and gemcitabine	N/A	N/A	Aggressive skin care and pyridoxine were initiated.
Mignogna et al., 2009 (81)	Breast cancer	61	F	Capecitabine, lapatinib, and zolendronic acid	2000 mg/m2 po qd for 14 days then 7 days rest days	After 28 days	Capecitabine dose was reduced.
Baretta et al., 2009 (82)	Breast cancer	59	M	Capecitabine and trastuzumab	N/A	N/A	Aloe vera was used.
Vrdoljak et al., 2010 (83)	Metastatic breast cancer	50	F	Capecitabine and ixabepilone	1000 mg/m2 BID for 14 days then 7 days rest	After 126 and 231 days, respectively	At first, capecitabine dose was reduced by 25% of the total dose. At second, 50% of the initial capecitabine dose.
Yoshida et al., 2011 (84)	Metastatic colon cancer	43	M	Capecitabine, oxaliplatin and bevacizumab	1000 mg/m2 BID for 14 days then 7 days rest	After 121 days	No intervention
Hoesly et al., 2011 (85)	Metastatic breast cancer	61	F	Capecitabine and lapatinib	1250 mg/m2/day BID	After 1094 days	Ammonium lactate cream 12% was initiated.
Akash et al., 2011 (86)	Stage-III breast carcinoma	50	F	Capecitabine, lapatinib and docetaxel	900 mg/day po	14 days after 4th cycle	Chemotherapy was discontinued and po pyridoxine, i.v ceftriaxone, i.v metronidazole, po B-vit complex, rabeprazole, iron supplements, urease cream, moisturizing cream and gentian violet paint for local application were used
Ferreira et al., 2011 (87)	Metastatic HER2 negative breast cancer	55	F	Capecitabine and bevacizumab	3000 mg/day for 14 days then 7 days rest	After 176 days	Capecitabine dose was reduced by 25%
Gordon et al., 2011 b (53)	Sigmoid colon cancer	59	M	Capecitabine, oxaliplatin and folinic acid	N/A	N/A	Topical steroid preparations was used.

Richey et al., 2011 (88)	Metastatic RCC	56	M	Capecitabine and gemcitabine	1750 mg/m2 /day for 21 days of a 28 day cycle	After about 300 days	Capecitabine dose was reduced.
Ozkan et al., 2011 (89)	Breast cancer	53	F	Capecitabine and trastuzumab	After about 4 years	N/A	Capecitabine was discontinued.
Al-Ahwal MS., 2012 (90)	Metastatic rectum adenocarcinoma	53	M	Capecitabine and oxaliplatin	Capecitabine 1000 mg/m2 BID for 14 days	After 30 days	Parasetamol, tramadol and topical emollient creams were initiated.
Sanghia et al., 2012 (57)	Adenocarcinoma colon	66	M	Capecitabine and leucovorine	N/A	After 30 days	Capecitabine was discontinued. Topical steroids and pyrodoxine injection were initiated.
Rolski et al., 2012 (91)	Metastatic breast cancer	52	F	Capecitabine and lapatinib	2000 mg/m2	After about 550 days	Capecitabine was discontinued.
Yan et al., 2012 (92)	Metastatic hepatocellular carcinoma	60	M	Capecitabine and nimotuzumab	1000 mg/m2 BID for 14 days then 7 days rest	After 98 days	N/A
Uleer et al., 2012 (93)	Breast cancer	29	F	Capecitabine and trastuzumab	N/A	N/A	Capecitabine was discontinued for 6 weeks and then started with a 50% dose reduction.
Vincent et al., 2013 (94)	Metastatic breast carcinoma	45	F	Capecitabine and bevacizumab	2000 mg po BID for 14 days then 7 days rest	N/A	Dose adjustment for capecitabine was not required.
Lal HS., 2014 (95)	Breast cancer	55	F	Capecitabine and paclitaxel	500 mg po TID for 14 days then 7 days rest	After 42 days	Emolient cream, including aloe vera and vitamin E was initiated.
Yoshida et al., 2014 (96)	Metastatic rectum cancer	62	M	Capecitabine and oxaliplatin	1000 mg/m2 BID for 14 days then 7 days rest	After 84 days	N/A
Kigen et al., 2015 (97)	Metastatic colon cancer duke C	62	F	Capecitabine and oxaliplatin (XELOX)	1500 mg BID	After 84 days	Capecitabine was discontinued and vitamin supplement was initiated.
Matsuda et al., 2015 (98)	Metastatic colon cancer	60	M	Capecitabine, oxaliplatin and bevacizumab	N/A	After 2nd cycle	N/A
Chavarri-Guerra et al., 2015 (99)	Breast cancer	65	F	Capecitabine and bevacizumab	N/A	During the 1st cycle and after 3rd cycle	Topical agents were initiated at 1st cycle and dose was delayed at 3rd cycle)
Del Re et al., 2015 (100)	HER2 positive ductal carcinoma	37	F	Capecitabine and trastuzumab	1250 mg/m2 BID for 14 days then 7 days rest	After 7 days	Capecitabine was discontinued.
Takeshita et al., 2015 (101)	Metastatic rectal cancer	66	F	Capecitabine and bevacizumab	N/A	N/A	Dose intervals of therapy was extended and capecitabine dose was reduced.
Lightowlers et al., 2015 (102)	N/A	47	M	Capecitabine and oxaliplatin	N/A	N/A	N/A
Hashidaa et al, 2017 (103)	Metastatic lung cancer and advanced rectal cancer	53	F	Capecitabine, irinotecan and bevacizumab	1600 mg/m2/day for 14 days then 7 days rest	After 121 days	N/A
Hadzavdic et al., 2017 (104)	Metastatic adenocarcinoma of colon	63	M	Capecitabine, irinotecan and bevacizumab	N/A	During 2nd cycle	A skin barrier cream, moisturized ointments and potent topical corticosteroids were initiated (but symptoms were not relieved). Then, capecitabine was discontinued.
Singh et al., 2018 (105)	Metastatic intrahepatic cholangiocarcinoma	52	F	Capecitabine and irinotecan	850 mg/m2	Five days after receiving the 2nd cycle	Capecitabine was discontinued.

N/A: Not Available; F: Female; M: Male ; i.v: intravenous ; po: per oral ; BID: 2 times a day; TID: 3 times a day; SCC: squamous cell carcinoma ; BCC: single basal cell carcinoma.

A total of 111 patients presented in the case reports were reviewed in this study, of which, 67 (60%) were female, and the mean (±standard deviation) age was 56.14±11.9 years (52.9±11.9 years in females and 61.2±9.6 years in males). The most commonly seen cancer types were breast cancer (n=48; 43.24%), colon cancer (n=23; 20.72%), rectal cancer (n=8; 7.20%), hepatocellular carcinoma (n=6; 5.40%), and gastric cancer (n=6; 5.40%).

Capecitabine-induced HFS occurred between 7 and 240 days of capecitabine monotherapy (n=62 cases). Among the cases receiving capecitabine monotherapy, the median (range) duration for the occurrence of capecitabine-induced HFS (n=24 cases) was 28 (7–140) days, and the daily dose of capecitabine (n=19 cases) ranged between 850 and 5000 mg/m2.

The combination of treatment strategies (n=34; 30.63%: systemic treatment ± topical treatment ± dose reduction ± treatment discontinued), capecitabine dose reduction (n=15; 13.51%), capecitabine discontinuation (n=15; 13.51%), the use of henna (n=11; 9.90%), the use of topical treatment (n=6; 5.40%), the use of vitamin E (n=4; 3.60%), and the use of pyridoxine treatment (n=2; 1.80) were observed in 111 cases. There was no information about the HFS treatment in 18 cases. Furthermore, the use of antibiotic therapy (n=1) and capecitabine replacement with other chemotherapeutic (n=1 cases) were seen, and no intervention was implemented in 3 cases.

The risk factors of developing HFS were previously indicated as advanced age, female sex, performance status, continuous chemotherapy infusion, a history of fluorinated pyrimidine administration, exposure to total body irradiation, preexisting diabetes, peripheral arterial disease and/or peripheral neuropathy, the use of tyrosine kinase inhibitors, hemoglobin level < 12 mg/dl, white blood cell counts, and the number of organs affected (106-110).

The HFS manifestations can be seen in various degrees representing differences in the occurrence of scars and time to healing. A loss of fingerprints associated with HFS has recently been reported in a male patient with metastatic nasopharyngeal carcinoma treated with capecitabine for >3 years (10).

There were no effective strategies established for the prevention or HFS treatment since the underlying mechanism is not fully elucidated in the literature. Therefore, dose reduction or cessation or postponing of therapy can be considered, particularly in patients with Grade 2 symptoms (111). The Grade 2 symptoms may rapidly progress, and symptom relief may require longer time when it reaches Grade 3. This situation can lead to the cessation of chemotherapy; therefore, an early detection of Grade 2 symptoms is crucial for dose adjustment (Table 2) (15-17; 11-14; 112).

Table 2. *Recommended dose adjustment of capecitabine in hand-foot syndrome.*

Hand-Foot Syndrome		Capecitabine dose adjustment			
Grade	Characteristics	1st occurence	2nd occurence	3rd occurence	4th occurence
1	Skin changes that not interfere with activities of daily living (eg, numbness, dysesthesia, paresthesia, tingling, erythema)	%100 dose	%100 dose	%100 dose	%100 dose
2	Pain that affects activities of daily living and skin changes (eg, erythema, swelling)	Interrupt the treatment and give the next dose of %100	Interrupt the treatment and give the next dose of %75	Interrupt the treatment and give the next dose of %50	Discontinue treatment permanently
3	Severe skin changes (eg, damp splashes, ulceration, blistering) accompanied by pain that severely affects activities of daily living	Interrupt the treatment and give the next dose of %75	Interrupt the treatment and give the next dose of %50	Discontinue treatment permanently	Discontinue treatment permanently

The treatment options for HFS were not used or were not indicated in 20 case reports included in the study. Many treatment strategies were investigated to alleviate and treat HFS symptoms including the use of antiperspirants, topical urea-lactic acid mixture, or vitamin E (113-114). Pyridoxine was used to relieve paresthesia and reduce the syndrome severity (106); however, studies showed that the use of pyridoxine as prophylaxis is not as effective as it was considered (115-116). The use of softening/moisturizing creams as a prophylactic or therapeutic option was recommended for all grades of HFS, particularly Grade 1 (117), which may prevent or delay dose reduction during the treatment. COX-2 inhibitors (6) and topical or systemic use of corticosteroids were shown to be effective in the prophylaxis and treatment of HFS; however, the effectiveness of steroids in capecitabine-induced HFS has not been proven yet (118-119) due to the risk of skin thinning and aggravation of symptoms caused by the long-term use (117). Immersing hands and feet in cold water and avoiding skin irritants and changes in temperature and/or pressure are examples of non-pharmacological treatment strategies (120).

4. DISCUSSION

Many case reports on capecitabine-induced HFS have been documented in the literature. The first case report on capecitabine-related HFS was published in 2003, and the number of cases has increased recently (22). The summary of product characteristics included information about capecitabine-induced HFS. However, there is no specific information on the occurrence and treatment of HFS (1). The case reports included in the study had diverse information regarding patient's sex, age, medical history, performance status, and dose and duration of capecitabine treatment.

Therefore, it was difficult to identify particular risk factors for developing HFS.

Female sex is recognized as a risk factor for developing HFS. In this systematic review, 67 (60%) of the 111 cases were women, emphasizing the importance of this risk factor.

It was difficult to identify any correlation between the total and/or exposed cumulative dose of capecitabine and the first occurrence of HFS during treatment since there was no detailed information regarding the capecitabine dose and duration of treatment in these cases. In addition, patients' weight, previous chemotherapy cycles, and other confounding factors could not be extracted from the case reports to conclude this finding.

It was identified that capecitabine-induced HFS occurred between 7 and 240 days of the treatment. Among the treatment strategies used for HFS, pyridoxine, vitamin E, emollient creams, and henna were likely to be effective in alleviating the symptoms. However, the effective dose and duration of these treatments have not been established (113-116).

HFS is not a life-threatening complication, but it significantly reduces the patient's quality of life. When HFS does occur, certain problems with compliance may arise, and cessation of chemotherapy may be required. Therefore, early recognition of HFS is important for maintaining the patient's quality of life and continuity of treatment. Patient self-monitoring tools have been developed for assessing HFS symptoms, which can contribute to an active patient involvement in the chemotherapy process (11-14).

5. CONCLUSION

Capecitabine-induced HFS is a cutaneous skin reaction that affects the palms and/or soles of hands and is frequently observed with the use of cytotoxic drugs, particularly 5-flourouracil, capecitabine, liposomal doxorubicin, and cytarabine.

Considering the published studies, it is difficult to indicate the best treatment options for capecitabine-induced HFS since different strategies have been used for its management. Therefore, additional data from further clinical trials and/or meta-analysis are required to establish the most appropriate treatment strategy for HFS in different patient populations.

It is essential that patients should be informed about the early signs and symptoms of HFS, and they be closely monitored by health care providers for early diagnosis and appropriate management of HFS.

In conclusion, health care providers and patients should be aware of developing capecitabine-induced HFS, its associated risk factors, and early initiation of treatment options during chemotherapy.

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Clinical and Experimental Health Sciences

A Case of an Incidentally Detected Retroperitoneal Schwannoma: Current Approaches to Diagnosis and Treatment of Schwannoma

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ABSTRACT

Schwannomas are tumors that originate from Schwann cells in the nerve sheath. They most commonly manifest in the head, neck and extremities and rarely can arise from the retroperitoneum. Here, we reported a case of an incidentally detected retroperitoneal schwannoma in a 34-year-old female and discussed the current techniques for diagnosis and treatment methods of schwannomas.
Keywords: Schwannoma, Retroperitoneal, incidental

1. INTRODUCTION

Schwannomas are tumors originating from Schwann cells in the peripheral nerve sheath. Most of the Schwannomas originate from the peripheral nerves of the face, neck and extremity, nevertheless some of them rarely originate from the retroperitoneal region(1). Retroperitoneal schwannomas add up to 0.3-3.2% (2,3) of primer schwannomas and 0.3-6% of all retroperitoneal tumors (4,5).

We aimed to investigate the diagnostic and therapeutic methods of schwannomas in the direction of a rare retroperitoneal schwannoma case.

2. CASE REPORT

In this study, the patient's informed consent was obtained that the pictures and patient information could be used in scientific content or articles.

No pathology was found on physical examination and routine laboratory examinations of a 34 year old female patient who was evaluated for complaints of dyspeptic ongoing for approximately 3 months. In abdominal ultrasonography performed to investigate the etiology of dyspepsia; a mass lesion of 24x26 mm was found between the pancreas posterior and the aorta. Tumor markers (CEA, CA 19-9) were normal. In the computed tomography; the pancreas was closely related to the portal vein and splenic venous branch in the corpus inferior compartment but without significant invasion findings, adjacent to the superior mesenteric artery and celiac truncus. Pancreas was with smooth contour and could not be selected with clear boundaries. In the arterial phase no contrast enhancement was seen and in the venous phase a solid mass lesion with peripheral contrast enhancement was observed. In the histopathological evaluation of trucut biopsy material made with computerized tomography; it was thought to be the peripheral nerve sheath tumor of the anterior segment due to diffuse and strong S-100 positivity. Because of the hypocellular and proliferative activity of the lesion was low, the mass was evaluated as benign schwannoma. First thought to be a benign schwannoma when retroperitoneal mass described in patient with follow-up and treatment options; the patient preferred to remove the mass with surgery. There upon patient was operated and mass which located postero inferior pancreatic corpus was reached in operation. (Figure 1) Mass, which was not invasive but attached superior mesenteric artery, portal vein and splenic vein, was completely excised without severe haemorrhage (Figure 2). The patient was discharged without any problems on the 7th postoperative day.

In the histopathological examination of the material; the tumor is separated from the surrounding tissue by a uniform boundary and no significant cell atypia, no mitosis or necrosis were seen. The presence of perivascular hyalinization (Figure 3) as well as diffuse and strong immunoreactivity with S-100 (Figure 4) were detected. This case was diagnosed as benign. schwannoma.

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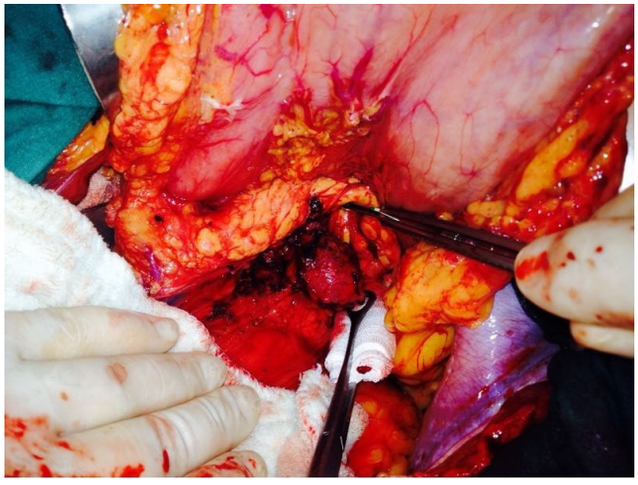

Figure 1. *Postero-inferior mass of pancreas*

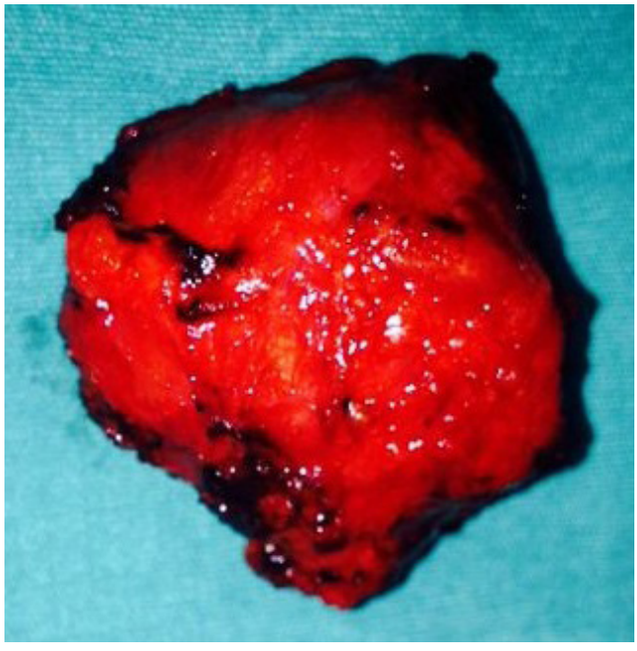

Figure 2. *Fully excised, properly limited mass*

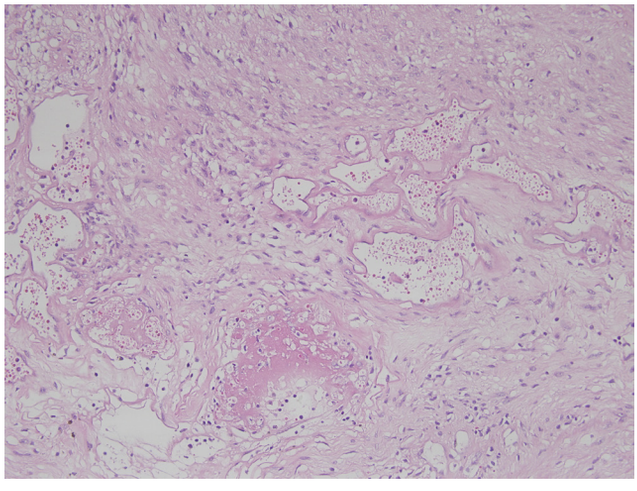

Figure 3. *Perivascular hyelinization (HEx40)*

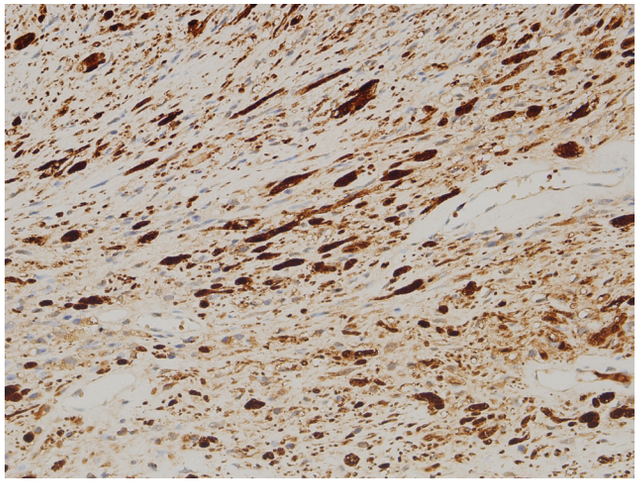

Figure 4. *Widespread and strong nuclear staining with S-100*

3. DISCUSSION

Since retroperitoneal region may be flexible, tumors developing in this area are not detected as symptom but incidentally detected without reaching large dimensions in general. Therefore, the diameter of the retroperitoneal Schwannomas causing the symptom is generally greater than 8 cm (1). While USG showed a hypoechoic mass with uniformly limited and minimal heterogeneous internal echoes in imaging, because of the low vascularity of the schwannomas, hypodense, well-defined mass is seen with contrast-enhanced CT (6). The definitive diagnosis can only be made if a strong S-100 positivity is detected after histopathological evaluation (7). In addition, the differentiation of benign or malignant schwannoma is important and necessary to determine the follow-up and treatment strategy.

There are few standard criteria for the diagnosis of malignant Schwannoma, and the size of the tumor is not sufficient to diagnose malignancy alone. First, the presence of histopathological criteria such as cellulite, nuclear atypia, and tumor necrosis increase point the possibility of malignancy (1). Especially in large schwannomas, secondary degenerative changes such as cystic degeneration, hemorrhage, necrosis and calcification can develop. In this case, imaging methods can not distinguish schwannomas from malignant retroperitoneal tumors (8,9). For this reason, surgical removal of all large retroperitoneal masses is recommended. Malignant schwannomas are generally larger than 5 cm in size, with intimal bloody or necrosis, and high Ki 67 index (5-65%), which are not well distinguished from surrounding tissues (10). The primary purpose of the treatment is to completely remove the cyst without causing damage to the nerve and causing severe haemorrhage. Benign Schwannomas do not invade vessels, but when benign tumors are large they may be involved in peripheral organs. In this case, the tumor is benign so more conservative treatment may be preferred, considering the morbidity results of surrounding tissue resection. However,

complete resection with negative margin should be targeted to malignant Schwannomas (1). In addition, some authors have reported that asymptomatic, small retroperitoneal schwannomas without histopathological malignancy findings can be followed without surgery (6).

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