



ACADEMIC RESEARCH and REVIEWS in HEALTH SCIENCES

EDITORS

Assoc. Prof. Gülşen GONCAGÜL Ph.D.

Assoc. Prof. Elçin GÜNAYDIN Ph.D.



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Academic Research and Reviews in Health Sciences

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– Chapter-1 –

DEVELOPMENT OF ELISA AND DOT-ELISA FOR DETECTION OF NATIVE BOVINE ROTAVIRUS (BRV) STRAIN¹

Serpil Yanbakan^{2,3}

Atilla Şimşek⁴

1 Bu çalışma, Serpil YANBAKAN 'ın “Türkiye’deki yenidoğan diyareli buzağılarda bovine Rotavirus (BRV) antijen varlığının araştırılması amacıyla ilk monoklonal ve poliklonal antikor temelli Enzyme-Linked Immunosorbent Assay (ELISA) ’nın geliştirilmesi” başlıklı Doktora Tezinin bir kısmından özetlenmiştir.

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Introduction

Rotaviruses that belongs to *Reoviridae* family are responsible from diarrhea of newborns include in human and different animal species. According the following reports, bovine rotavirus (BRV) is an primary agent of neonatal calf diarrhoe in all over the world include Turkey (Alkan et al., 1992; Burgu et al., 1995; Çabalar et al. 2000, Kapikian et al., 1986; Luchelli et al.,1992; Saif, 1991). Bovine rotavirus is the most important cause of viral gastroenteritis because of significant economic losses in cattles worldwide so the rapid test techniques should be delivered as early as the first few days of newborn life. There are several assays can be performed for the diagnosis of BRV in stool samples but a little of these can be used for routinely and process a lot of samples at the same time. ELISA has been widely used in several diagnostic laboratory to identify BRV antigens in stool samples and it is reported to be performed easily, rapid, sensitive and specific diagnostic technique by several researchers (Al-Yousif Y. et al., 2000; Kelkar et al., 2004; Villegas et al., 2002). Diagnosis of BRV antigen in stool samples has been performed by commercially available BRV ELISA kits in Turkey (Alkan et al., 1992; Burgu et al., 1995; Çabalar et al. 2000).

The purpose of this study was to develop an antigen capture ELISA for diagnosis BRV antigen in stool samples of diarrhetic calves in Turkey. ELISA that was performed in the present study could be used an alternative test to commercial ELISA kit for the diagnosis of BRV in stool samples. Rapid identification of BRV antigen in calf stool samples by routinely used diagnostic assays as ELISA can decrease the economical loses. This is the first report of devoloped antigen capture ELISA for diagnosis BRV antigen in stool samples of diarrhetic calves in Turkey.

Materials and Methods

Propogation of BRV isolate in cell culture

African green monkey kidney cell line (MA104) was maintained for virus growth. MA104 cells were cultivated in Dulbecco's minimum essential medium (DMEM) (Biological Ind., Israel), supplemented with 10% heat inactivated fetal calf serum (FCS), antibiotics and antimicotic. The cell cultures were incubated in roller bottles in a CO₂-gased incubator at 37°C and in a 5% CO₂ atmosphere.

The tissue culture-adapted group A BRV isolate (G10, P11), kindly supplied by Gülyaz V., was originally isolated by Gülyaz et al. (2005) that performed the first BRV isolation from newborn calves with diarrhea in Turkey. Bovine Rotavirus was grown in 80-90% confluent monolayers of 3- to 5-day-old MA104 cells. Confluent monolayers of MA104 cells were infected with BRV isolate and

incubated for 1 h at 37°C and treated with 10 microgram(μg) / ml of pancreatin (Merck, Germany) in FCS free DMEM. BRV infectivity was enhanced by 1% dilution of the pancreatin (10 $\mu\text{g}/\text{ml}$) in DMEM supplement into the cell culture media every two days as reported by Gülyaz et al (2005). Cytopathic effects were read daily for one week, and two blind passages were performed. After the observation of completed CPE of BRV isolate, the BRV-infected cell suspensions were harvested into the centrifugation tubes and centrifugated at 3000 g for 30 minute. BRV supernatant was filtered through 0.22 micrometre (μm)-pore sized filtered that is adapted to syringe and stored at -80°C until it was used for first immunization schedule. A small aliquot of these BRV suspensions were set aside for further studies as polyethylene glycol (PEG) precipitation and immunization schedule for production of anti-BRV polyclonal antibody.

Polyethylene glycol (PEG) precipitation

BRV was concentrated by PEG-6000 (Merck, Germany) precipitation technique to determine concentrate and semi-purified BRV suspensions. The PEG-6000 precipitation method was used as reported by Mahy and Kangro (1996). After the last centrifugation step supernatants were derived carefully and decanted into the eppendorf tubes. This supernatants that contain concentrated BRV suspensions were preserved at -80°C until the next period.

Immunization schedule for production of anti-BRV polyclonal antibodies

Four weeks old, New Zealand white female rabbits were used to determine the anti-BRV polyclonal antibody by two different immunization protocols in accordance with Ethical Committee's decision (2009/001) of Selçuk University. The rabbits were allowed to get familiar with their new environment among two weeks for initial preparation for pre-bleed procedure before the first immunization schedule. Two weeks after the adaptation time pre-immune serum was collected from rabbits and stored frozen at -20°C in small aliquotes to use as a blank when performing ELISA optimization tests.

In first immunization protocol 5 ml of BRV cell culture supernatant antigen was used for injection of one rabbit in day 1, 3, 5 and it was continued with a similar schedule of alternating boost in day 7, 15, 21 with 2 ml of PEG concentrated BRV into each four subcutaneous sites on his back sites. And the rabbit was bleed one month after the last immunization schedule and each post immunization rabbit sera were collected and stored at -20°C in small aliquotes. In second immunization protocol BRV cell culture supernatant antigen was prepared by injecting 500 microliter (μl) of antigen solution into the 500 μl of Freund's complete adju-

vant (Sigma, USA) and mixed to get a good suspension for injection of the other rabbit and 1 ml of immunogen (1:1 antigen:adjuvant mix) was injected into each four subcutaneous sites on his back sites. The injections were boosted with an equivalent amount of immunogen in Freund's incomplete adjuvant in day thirty. One week after post immunization the rabbits were boosted with an inoculation of the viral suspension in phosphate buffer saline (PBS) (1:1). And the rabbit was bleed 14 days after the last immunization schedule and each post immunization rabbit sera were collected and stored at -20°C in small aliquotes. Both of the antisera were used as capture antibody in antigen capture ELISA optimization tests after ammonium sulphate precipitation and dialysis procedures.

Ammonium sulphate precipitation

Ammonium sulphate (Sigma, USA) precipitation was used for purification of polyclonal antibodies from rabbit anti-sera against BRV. Both of the post immunization rabbit sera were concentrated with ammonium sulphate precipitation and dialysis to determine polyclonal antibodies (anti-BRV antibodies) that belongs to BRV isolate in antigen capture ELISA. Ammonium sulphate precipitation and dialysis process was performed as described by Arda and Ertan (2004). The amount of saturated ammonium sulphate solution was calculated to obtain 70% saturation. The saturated solution was slowly added into the serum and the serum was transferred into a large beaker in an ice bath on a magnetic stirrer and mixed for 1 hour (h). The solution was centrifuged at 10000 g for 10 minutes and the supernatant was discarded. The pellet was suspended in PBS. Thereafter antibody solutions were dialyzed in dialyse tube (Sigma, USA) overnight against PBS, divided into aliquots and stored at -20°C. Ammonium sulphate concentrated and dialyzed anti-BRV polyclonal antibody was used as capture antibody in antigen capture ELISA.

Stool samples

In the present study, one hundred stool samples of less than one year old calves with acute diarrhea originated from farms located in Konya region of Turkey were collected from 2008-2009 during spring and autumn seasons. The samples were stored at -20°C until they were tested in ELISAs.

Antigen capture ELISA procedure

Checkerboard titration test was developed in tissue culture 96 -well flat bottom microplate (Greiner, Bio-one, Germany) wells as described by Crowther (2009) to determine the optimum dilution of each BRV antigen, monoclonal antibody

(Mab rotavirus from ascites, anti-major inner capsid protein VP6 antibody, clone 2B4, Abcam, USA) and post immunization rabbit sera to monitor if it was provided a satisfactory antibody response by ELISA. During the optimization process of the monoclonal and polyclonal antibody titer that belongs to BRV suspension it was continued until it was observed a maximal absorbance in ELISA reader.

ELISA microplate wells were coated with 50 μ l/well of a predetermined concentration of antibodies in carbonate-bicarbonate buffer (Na_2CO_3 , NaHCO_3 [pH 9.6]), at an optimum dilution. Bovine sera albumin (BSA) was used as blocking solution (1% BSA in Tris, NaCl) was used negative control and 50 μ l/well of BSA solution were bound to appropriate columns of microplate wells and incubated during 2 hours at 37°C. When the time is over, the unbinding material was discarded and removed by washing thrice with washing buffer (0.05% Tween-20, Tris, NaCl). To block the unreacted sites on the microplate wells, 200 μ l of 1% BSA blocking solution was used and incubated during 1 h at 37°C. The unbinding material was removed by washing thrice with washing buffer. After the washing process two of microplate wells were separated for PEG concentrated BRV as used positive control antigen. Thereafter 50 μ l/well optimum dilution of stool sample that prepared in 1% BSA blocking solution was added to coated microplate wells and incubated during 1 hour at room temperature. Tween-20 washing solution (0.05%) was added to wells to remove the nonspecifically bound test material. Anti-bovine Nebraska calf diarrhea virus horseradish peroxidase conjugate (ViroStat, USA) 1:500 (recommend dilution by manufacturer's) diluted in blocking buffer was added to wells (50 μ l). After the incubation period for 30 minutes the microplate wells were washed 3 times with washing buffer. Fifty microliter of 3, 3', 5, 5' - Tetra methyl benzidine (TMB, Sigma, USA) substrate was added after washing. Colour development was observed as soon as transferring the substrate. After for 10 minutes incubation time in the dark reaction was stopped with addition 50 μ l/well of 1 molar (M) H_2SO_4 acid stopping solution. The results were read on an ELISA reader at 450 nanometre (nm) wavelength to measure the antigen concentration. Antigen capture ELISA results were shown as the mean absorbance of replicate samples detected at 450 nm wavelength.

A total of 100 stool specimens were tested in parallel with the optimized monoclonal and polyclonal antibody based antigen capture ELISA and commercially available ELISA (Bio-x diagnostics, Belgium). The commercial ELISA was used according to the manufacturer's instructions.

Calculation of the ELISA cut-off value

ELISA cut off value was calculated as described by Frey et al. (1998) as the mean absorbance from the negative coating wells plus 3 standard deviations. The positive result was judged if the optical density (OD) value of the sample was higher than that of the cut off value determined by ELISA. The following formula was used to calculate cut off value: Cut off = Mean absorbance value of the negative control ODs + 3 × standard deviation of the negative control ODs. Test samples with absorbances of OD sample- Negative control OD sample value higher than the cut off value were considered positive, samples with absorbances below the cut off value were considered negative for BRV antigen.

Specificity and sensitivity of the ELISAs

Sensitivity (%), specificity (%), overall agreement (accuracy) (%), positive and negative predictive value (%) between the tests were determined by using the commercial ELISA as a reference standard.

Results

BRV antigen-polyclonal antibody dilution ratio were determined 1:4 and 1:800 respectively and BRV antigen-monoclonal antibody dilution ratio were determined 1:4 and 1:10000 at the end of the checkerboard titration ELISA. Optimized monoclonal and polyclonal antibody based antigen capture ELISA results were used for detection of BRV in stool samples.

The results of the 100 samples tested by monoclonal and polyclonal antibody based antigen capture ELISA were given in Table 1. It was evaluated that monoclonal and polyclonal antibody based antigen capture ELISA presented 92% and 96% sensitivity; monoclonal and polyclonal antibody based ELISA presented 96% and 99% specificity, respectively.

Table 1. Comparison of monoclonal and polyclonal antibody based antigen capture ELISA results with sensitivity, specificity, predictive values and accuracy ratios.

ELISA results	Monoclonal antibody based ELISA	Polyclonal antibody based ELISA
Positive results	25	24
True positives	22	23
True negatives	73	75
False positives	3	1
False negatives	2	1
Sensitivity (%)	92	96
Specificity (%)	96	99
Positive predictive value (%)	88	96
Negative predictive value (%)	97	99
Accuracy (%)	95	98

Discussion

There are several reports that the procolytic enzymes as pancreatin and trypsin facilitates the cultivation of BRV (Almeida et al., 1978; Babiuk et al., 1977; Clark et al., 1979). As reported by several researchers (Clark et al., 1979; Gülyaz et al., 2005) treatment with proteolytic enzymes such as trypsin, pancreatin or elastin increases BRV infectivity in cell culture. In this research BRV infectivity was enhanced by pancreatin (10 µg/ml) addition into the cell culture media as described by the other researchers (Almeida et al., 1978; Babiuk et al., 1977; Clark et al., 1979).

PEG precipitation procedure in present study was previously mentioned above has been performed with good results for both bovine and human rotaviruses (Fontes et al., 2005; McNulty et al., 1977; Lewis and Metcalf, 1988). Viral precipitation with PEG was investigated that could be used as an effective procedure for obtaining viral antigen to produce polyclonal antibodies against BRV (Fontes et al., 2005). The antigenic mass obtained, the viral infectivity, and the conserved protein pattern in this research suggest that this methodology could be applied to BRV and to other viruses, reducing time or possible loss of antigens involved in viral purification.

ELISA microplate wells were coated with polyclonal antibodies against a field BRV isolate in Turkey so this ELISA in the present study is more effective for diagnosis of native BRV antigens in stool samples as compared with commercial BRV diagnosis ELISA kit that used an antibodies against to alien BRV field isolate to coat the microplate wells. Antigen capture ELISA developed in this research is performed in 2.5 h duration time with lower concentrations and considered to be highly economical assay and can be performed by any laboratory in development countries when compared with commercial ELISA kit. In the present test only a few reagents is commercially available as substrate and conjugate and the other reagents of the test is prepared in our laboratory exclude stool specimens. The polyclonal antibody coated wells of antigen capture ELISA in this research can be stored at + 4°C after for 10 months and it was observed that this long storage time isnt effective on performance of the ELISA and it was observed the same results with the same stool samples also with similar OD values.

Polyclonal antibody based antigen capture ELISA presented sensitivity (96%) and the specificity (99%) slightly was superior to monoclonal antibody based antigen capture ELISA sensitivity (92%) and the specificity (96%). The positive predictive (96%) and negative predictive (99%) values of the polyclonal antibody based antigen capture ELISA were slightly higher than the positive (88%) and negative predictive (97%) values of the monoclonal antibody based antigen capture ELISA. As a result, it is concluded that an effective, simple, economic and rapid monoclonal and polyclonal antibody based ELISA technique was developed for diagnosis of BRV with a 95% and 98% accuracy rates.

In conclusion this study is the first report of ELISA development in a laboratory for diagnosis of BRV in stool of diarrhetic calves in Turkey. This research may play an important role that load to new studings about development of improved ELISA systems for serotyping of BRV in stool samples. The results of this study indicated that the developed antigen capture ELISA is a simple, rapid, reliable, and sensitive method for the diagnosis of BRV infections in calves. At the end we can say the developed monoclonal or polyclonal antibody based antigen capture ELISA was efficient as commercially available BRV ELISA kit for detection of BRV antigens in calf stools. Further studies are however necessary to find out serological and molecular characterization field isolates of BRV and analysis the sequence BRV genes to improve our knowledge about BRV infection during an outbreak of diarrhea in bovine herds.

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– Chapter-2 –

**PAIN PERCEPTION AND MANAGEMENT OF
ONCOLOGY NURSES IN CANCER PATIENTS**

*Yasemin Özyer
Safiye Yanmış*

INTRODUCTION

Cancer rates are increasing each year in the world. Cancer is a global public health problem and an economic burden. GLOBOCAN 2018 reported an estimated number of 18,1 million new cancer cases and 9,6 million deaths due to cancer in 2018 (Ferlay and Bray, 2018). In the United States of America, there are 16 million cancer survivors (Admass et al., 2020).

68% of adults diagnosed with cancer can live for at least 5 years. As new cases increase, the number of people surviving from cancer may continue to increase because treated individuals live longer. With advances in early diagnosis and improvement in treatment, more patients survive from cancer in the long term. Cancer treatment is made in the form of surgery, chemotherapy, hormone treatment and radiotherapy and most of the time creates undesirable long-term effects on tissues and organ systems, which disrupts the individual's health and life quality in many ways. Therefore, individuals who survive cancer have a responsibility of following and managing their health during their lives. Cancer is a life changing event (Potter and Perry, 2013).

In recent years, despite the advances in cancer treatment, survivors of cancer suffer from possible side effects of the disease and patients die due to late period cancer diagnosis and treatment-related complications. Nurses have a responsibility to implement the most up-to-date evidence based approaches to better understand the needs of cancer survivors in this period and to manage the early and late possible effects of cancer treatment. Providing comprehensive care to cancer survivors, implementing the treatment of possible effects of cancer and helping cancer survivors to perform their self-care are among the responsibilities of teachers. Pain management is also very important in this process. Cancer pain can be caused by the direct and indirect effects of the disease and the treatment (Potter and Perry, 2013).

Pain can occur as a complication of cancer and its treatment. Cancer-related pain is a common and devastating symptom that affects the patient's whole life more than the disease itself (Admass et al., 2020). Survival rates have also increased with the advancement of cancer treatment options (De santis et al., 2014). However, these advancements caused patients to experience pain and the pain to increase due to treatment options. For this reason, effective management of cancer pain is very important to optimize the quality of life in these patients (Van de beuken et al., 2008).

While pain is a serious problem, cancer related pain is one of the most serious problems (Deantre et al., 2008). It is one of the worst experiences for cancer patients and their families (Bist et al., 2011; Tsoi et al., 2017). Currently, pain is treated

insufficiently (Quadire et al., 2013). Studies conducted have reported that 38% of patients suffer from moderate and severe pain (Van den beuken et al., 2016).

Cancer prevalence is continuing to increase each year with the rapidly aging population. Pain, including cancer pain, is a personal and multi-faceted experience influenced by cultural and past experiences and coping strategies (Vallath et al., 2013). Cancer pain is a condition that leads to the patient's coming to the emergency service and continues with more hospitalization and lower patient satisfaction (Caterino et al., 2019). The treatment of pain includes a multi-faceted treatment in cancer. Pain and its treatment requires special knowledge and experience in terms of drugs and pathophysiology of pain (Kumar et al., 2011).

Knowing about and managing the treatment options of patients' cancer pain is very important for improving their quality of life (Minello et al., 2019). A study conducted showed that the knowledge and attitudes of caregiving nurses about cancer pain and its management differ from their previous experiences. This is very important because pain is influenced by sociocultural context and a different cultural structure may affect the way care is provided in patients with cancer pain (Li et al., 2019).

In a study evaluating cancer related pain prevalence, it was found that 59% of cancer patients experienced moderate and severe pain in their terminal period (Breivik et al., 2009). In a study conducted in the United States of America, Fisch et al. reported that 67% of cancer patients experienced pain and 33% received insufficient pain management for this pain (El Agual et al., 2020). Al Qadire et al. reported that 73.3% of cancer patients in Jordan experienced pain symptoms (Quadire et al., 2013). Cancer-related pain is a combination of acute and chronic pain. Pain affects life quality of patients negatively by causing psychosocial, behavioural, emotional and mental problems in addition to physical symptoms (El Agual et al., 2020).

Cancer pain may interfere with daily life activities (Breivik et al., 2009). It may affect the psychosocial health of patients by increasing thoughts of anxiety, depression and suicide. At the same time, it decreases social interaction and increases the care burden of the family (El Agual et al., 2020). Nurses may generally think that a patient not complaining about pain is not suffering. For this reason, the pain of a patient dealing with pain quietly and with strength may be ignored. In order to prevent this, nurses should be sensitive to signals of discomfort such as holding the area with pain or applying pressure to that area, and uncontrollable, spontaneous expressions of discomfort such as grimaces and moaning. In addition, pain killer demands of patients who express their discomfort should not be evaluated as excessive persistent complaints. Pain is everything the patient says and

any complaint of pain should be evaluated carefully. Nursing care should always be individualized for the patient suffering from pain (Carol et al., 2011).

Pain is an unpleasant, organic or non-organic experience that affects the whole life of an individual. The commonly used definition of pain “pain is everything that the individual says and it is real” describes how subjective pain is. Another definition of pain which is widely accepted is “it is an unpleasant emotional experience associated with or due to tissue damage”. Three aspects of these definitions have important inferences for nurses. First of all, pain is a physical and emotional experience. Secondly, pain is a response to real or potential tissue damage; therefore, laboratory or radiographic reports may not be abnormal despite real pain. Considering that some patients are not willing to explain the presence of pain unless they are asked, nurses may not be aware of a patient’s pain until it is evaluated. In addition, it is clear that patients who cannot verbally express their pain (for example children, intubated patients, individuals with cognitive disabilities, unconscious patients) experience pain that require nursing assessment and treatment although they cannot describe their discomfort. Pain affects physical functions and life quality. Acute and chronic pain affects the whole body, causes serious health problems, increases complication risks, delays recovery and accelerates the progression of fatal diseases.

Pain management refers to minimizing and elimination of pain. Insufficient management of acute pain may cause the development of chronic pain. Chronic pain may cause constipation, hypertension, chronic stress, insomnia, weight gain or loss, and depression. Possible results may affect the daily life activities of the suffering individual. The goals of effective pain management include providing recovery, preventing complications and decreasing pain. Nurses have an active role in relieving pain, led by an advocate role. In addition to being a primary concern, pain is more than the symptom of a disease. Pain affects the patient both physiologically and psychologically for health and recovery. Acute pain is a situation that needs to be resolved urgently. Pain that starts suddenly and slowly is defined as acute pain. Chronic pain is a type of pain that lasts for more than 3 months and that negatively affects a person’s life.

Nursing management

The cause of pain differs according to different sites resulting from tumour invasion and metastasis (Admass et al., 2020). Despite the advancements and interventions in cancer pain treatment, it is known that many cancer patients in the world experience high level of pain (Admass et al., 2020). High prevalence of pain may be attributed to patients not having awareness, limited treatment

options and late treatment of patients with advanced malignancy (Admass et al., 2020). Understanding the nature of the pain and obtaining information that requires individual attitude against the patient's clinical state is essential to treat the pain in the best way (Chow et al., 2018).

Knowledge and attitudes of nurses towards cancer pain management emerges as an important factor in the management of cancer pain (Admass et al., 2020). A study conducted in Ethiopia oncology centres showed that nurses had different practices and they had negative attitude towards cancer pain. Absence of courses related with pain in undergraduate classes, role confusion, lack of in-service training and lack of motivation are among factors that affect pain management (Kassa and Kassa, 2014). In a study conducted, it was found that 77.5% of the patients had concerns about opioid-induced respiratory depression. Misinformation, attitudes and beliefs can lead to inadequacy in the treatment of cancer pain in patients.

It is important for oncology nurses to have attitude and information about cancer pain management in this process. Significant correlation was found between cancer pain management attitude, knowledge and level of education. It was found that nurses who were previously trained about pain and who had more professional experience were better in pain management when compared with nurses who were not previously trained about pain and who had less professional experience. It was found that nurses became better about pain management as their information and experience about pain increased. However, it was found that age, professional experience and undergraduate degree were positively correlated with nurses' levels of knowledge and attitude (Admass et al., 2020).

Association was found between knowledge and attitudes of nurses working in oncology centres their professional experience and about managing cancer pain (Admass et al., 2020). Correct assessment of pain is important for effective pain management. Pain is the fifth vital sign in many health institutions. Pain assessment should be performed separately for each patient. Considering that pain should be evaluated individually, pain assessment (psychological, behavioural, emotional, physiological and sociocultural) is important in providing the basis for optimum pain control. For patients experiencing acute and severe pain, nurses can focus on the severity of pain and the area where it originates and provide interventions for a more detailed assessment. Each time vital signs are evaluated, the question of pain should be repeated as the fifth vital sign. A simple question like "Are you feeling any discomfort right now?" will generally be enough. The main barriers to pain control for both nurses and patients are related to underestimation of pain and the inability to assess pain (Berman et al., 2016).

of pain in cancer patients, pain management by using pharmacological and

non-pharmacological approaches, and informing the patients and their families about the treatment plan. Sufficient experience, knowledge, and positive attitudes towards pain management are required for all these roles to be fulfilled (El Agual et al., 2020). In a study conducted, it was reported that 89% of nurses believed that physical appearance and vital signs of the patients were more reliable than their words about the pain (El Agual et al., 2020).

A study conducted on Jordanian nurses showed that about 85% of the nurses did not know that regular oral morphine administration is more effective and 90% had incorrect information about opioid administration in the management of cancer related pain (El Agual et al., 2020). Studies conducted have shown that nurses had incorrect information about opioid addiction and the effects of using placebo. Therefore, it is clear that nurses have lack of information about cancer pain management. Nurses need to focus on pharmacological and non-pharmacological information about cancer related pain management. Having information about the knowledge and attitudes of nurses about cancer related pain management will have an important role in the management of cancer related pain (El Agual et al., 2020).

Discussion

Nurses have an integral role in the assessment and management of pain since they are the leading individuals in patient care. Their roles include making a comprehensive assessment, managing assessments based on intervention and evaluating and reviewing the efficacy of pain management plan periodically; however, they are not limited to these (El Agual et al., 2020). Nurses have active roles in pain management such as determining the level of pain, preventing pain with sufficient analgesic use, and training patients and families appropriately (El Agual et al., 2020). Sufficient knowledge and positive attitude towards pain management is required to provide high quality nursing care for cancer pain. In addition, professional development, continuing training about pain assessment and management and postgraduate in-service training are important (El Agual et al., 2020).

Conclusion

Nurses have important roles in cancer pain management. Nurses have advocating roles in assessing pain, using pharmacological and non-pharmacological approaches in the treatment of pain, informing the patient and the family about the treatment, trainings about treatment plan and patient rights. However, nurses should have sufficient positive attitudes and knowledge towards pain management in order to be successful in all these roles. A training program is necessary to develop attitudes and knowledge about cancer related pain. After pain training

programs are applied, attitudes and knowledge about cancer related pain should be measured.

In general, most of the oncology nurses have a low level of knowledge and attitude towards cancer pain treatment and this increases the universal concern about insufficient knowledge and attitudes towards pain management. It was found that nurses who had postgraduate degree had effective attitudes and knowledge towards cancer pain management. For this reason, cancer pain management and revision of nursing education academic curriculum is necessary to improve the attitudes and knowledge of nurses.

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– Chapter-3 –

**THE ROLE OF STEM CELLS IN
GASTROENTEROLOGY**

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Stem Cell Biology

Adult stem cells are the progenitor precursor cells of tissues which have the capacity of continuous regeneration. They are classified due to their origin and differentiation capacity and have the functional responsibility of the development of tissues, organs and their regeneration.

Stem cells and their possible role in medical treatment have been shown interest by researchers and the developments are significant in this area. As an example, while the number of published papers in SCI database in this subject between the years 2004 and 2006 is only 600, the same number is found to be over 1500 between the years 2012 and 2014. The role of stem cells in modern medical treatment models has been increasing in the latest years. Various types of cells have taken place in up-to-date treatment protocols, such as; mesenchymal stem cells (MSCs), hematopoietic stem cells (HSCs) and adult liver stem/progenitor cells (LPCs) (1-3). Although embryonic stem cells are the most advantageous cells therotically in clinical research, ethical and legal restrictions have led researchers to focus on adult stem cells.

Two different hypothesis are valid regarding the mechanism of mesenchymal stem cells. First is the stem cell activity by producing adult cells at the region of damage and the second one is their repair effect with the secretion of anti-inflammatory factors.

Stem Cells in Gastroenterology

Similar to other areas, the role of stem cells has been increased in gastroenterology, especially in liver diseases and inflammatory or immune-related intestinal diseases. But their regeneration capacity is the most important origin of caution against carcinogenesis in their clinical usage. While stem cells can be classified as embryonic and adult stem cells, they can also be classified within gastrointestinal system such as esophageal, gastric, intestinal, colonic, hepatic and pancreatic stem cells.

Historical Background

Charles LeBlond was the first researcher who showed adult stem cell-like structures in human tissues in his study named ‘Histological localization of newly-formed desoxyribonucleic acid’ in 1948 (4).

Later, Spangrude and colleagues isolated and showed the mechanism of hematopoietic stem cells in an animal study model, forty years after LeBlond (5).

Ten years later, Thomson and his colleagues isolated embryonic stem cells from human blastocytes (6).

Another 10 years following this, Burra et al. published the first study that included the application of stem cells in gastroenterology, in their work regarding experimental hepatology (7).

Autologous Stem Cells and Tissue Repair

It is a known fact that the epithelial tissues of the liver and intestines have a high regeneration capacity. In normal circumstances, intestinal turn-over rate is known to be 2-7 days which may increase in a possible damage. This regeneration potential depends on the proliferation of progenitor cells placed in crypts.

The role and development of intestinal stem cells were shown in experimental models in 1950's. Later, Potten showed the mechanism of intestinal crypt cells more detail in 1977 (8).

Stem cells lie at the basis of the crypts on the top of Paneth cells. They migrate upwards and during this movement they transform into Goblet cells, enterocytes, neuroendocrine cells or to Paneth cells if they direct downwards. There is also a hypothesis suggesting that stem cells are placed between Paneth cells, at the same level with them.

In stomach, stem cells are places at the middle of tubules, in isthmus of gastric oxyntic glands. They can direct in two different ways from here; to mucous cells enveloping gastric surface or to transform parietal or zymogenic cells covering the base of the gland.

Esophageal stem cells are thought to be placed at the basal layer of stratified squamous epithelium. It is known that this region of the basal layer of esophageal epithelium is effective in the transformation of stem cells.

In 2007, Barker et. al showed that crypt base columnar cells among Paneth cells have a marker called Lgr5 which included a Wnt target gene (9). Lgr positive cells have a long life and act as mutlipotent cells that can transform into various intestinal epithelial cells.

Not only the intestinal stem cells, but also the mesenchymal stem cells derived from bone marrow have been shown to have role in intestinal repair and fibrosis. These cells have the capacity to transform into pericytes, endothelial cells and vascular stem cells which are essential for neoangiogenesis.

In liver, regeneration mainly depends on adult hepatocytes. These cells are differentiated cells with a long life and re-enter cell cycle with the capacity of arranging liver volume as a response to parenchymal damage. If the replication of hepatocytes are inhibited pathologically or experimentally, regeneration occurs as LPCs dependant. These cells are placed in Hering ducts and are responsible for ductal reaction which is a response to liver damage in humans. Various

studies have shown that LPCs are high degree clonogenic and bipotent cells, can transform into hepatocytes and cholangiocytes and carry hepatocyte-related antigens such as CD34 and c-kit (10-11).

Stem Cell Treatments in Intestinal Diseases

The role of stem cells has been increasing and getting more importance in the treatment of inflammatory bowel diseases, short bowel syndrome and radiation enteritis (12,13). The first hypothesis that stem cells may be beneficial in inflammatory bowel diseases was suggested when Crohn disease had regressed in the patients who had been treated with hematopoietic stem cell transplantation for hematologic malignancies which may be due to high dose of immunosuppression.

Later, the effectiveness of stem cells were shown by Oyama in 2005 and Cassinotti in 2008 as significant remission in patients with Crohn's disease and Celiac diseases (14,15). In these studies, the underlying defect is shown to be the inhibiting of T cell overactivation. In their multi-center, phase-2 clinical study, LeBlanc et al. showed that adult stem cell infusion increased the survival rate by 53% in serious and acute graft versus host disease, when conventional treatment methods were insufficient (16).

In 2009, Metzger et al. practiced successful stem cell treatment in aganglionic intestinal diseases such as Hirschprung disease and chronic gastrointestinal motility disorders (17). Stem cell application in short bowel syndrome has yet been practiced in experimental animal models (18,19).

Stem Cell Treatments in Liver Diseases

In liver diseases, stem cell applications have been suggested in various conditions such as; acute/chronical insufficiency, former to malignancy related resections as an alternative to portal vein ligation and ALPPS, HBV related cirrhosis patients and as a bridge treatment in patients waiting for liver transplantation by determining healthy tissue.

Orthotopic liver transplantation is the only curative option in end-stage liver diseases, increasing the one-year survival rate by 50-75%. Unfortunately, donor organ shortage, immunological denial, the necessity of life-long immuosuppressive drug usage and high costs are among most serious problems. Hepatocyte transplantation has been attributed great importance in the last 3 decades. Although the derived hepatocytes can not usually mimic the hepatocyte phenotype and functions completely, there are 3 methods of derivation which have been proven to be beneficial (20-22).

In another early-term clinical study in Japan, Mito et al. derived autologous

hepatocytes from 10 patients with liver cirrhosis and applied to various sites including spleen. While complete cure was obtained in one patient, hepatocytes were determined in spleen even 11 months after in another patient (23).

In another clinical study, Strom et al. determined significant recovery in liver damage and decrease in blood ammonia levels in five patients with hepatic encephalopathy and multi-organ failure after they applied allogenic hepatocytes via splenic artery. Liver transplantation was performed later in 3 patients and laboratory was normal at the end of 20 months (24).

Habibullah et al. showed that application of hepatocytes directly to the abdominal cavity was beneficial in 7 patients with fulminant hepatic failure with significant improvement in survival and encephalopathy (25). In 2 different study groups, intrasplenic and intraportal infusion of cryopreserved hepatocytes led to complete cure at the end of 12 weeks in patients with chronic liver failure in the transplantation waiting list (26,27).

Peng et al. showed significant improvement in levels of total bilirubin, PT and MELD score in 3 weeks following transplantation of mesenchymal stem cells originated from autologous bone marrow in patients with hepatitis B-related liver failure (28).

Han et al. determined biochemical and clinical amelioration in 6 months follow-up in 40 patients with HBV-related cirrhosis who had been applied hepatocytes via hepatic artery, derived from peripheral and umbilical blood (29).

The first practice of bone marrow originated stem cells was shown in patients whom were planned to perform portal vein ligation and large liver resection. The application was performed as autologous CD133+ cells intraportally (30).

Terai et al. showed significant improvement in the levels of serum albumin and Child-Pugh score in 9 patients with autologous stem cell transplantation via portal vein (31).

Stem Cell Treatment in Pancreatic Diseases

The application of stem cells in pancreas and studies so far are limited when compared to other sites of gastrointestinal system. Hussein and Theise studied stem cells in the treatment of diabetes mellitus (DM) (32).

Other treatment methods for DM are diet, insulin and oral antidiabetics for life time and none of them are effective enough for treatment. The transplantation of pancreas islet cells are better in determining the level of blood glucose. Because of the fact that donor organ is limited, bone marrow originated stem cells seem to be safer. Although there are ongoing studies regarding stem cell therapy in pancreatic diseases, the common limitation of these studies are; most of them

are at animal experiment phase, include small and limited participants and the absence of a control group.

The Relationship Between Stem Cells and Cancer

The most important danger that should be kept in mind about the application of stem cells in gastrointestinal system is that the unrestricted regeneration and proliferation capacity may lead to malign transformation.

There are 2 models defining the effect of stem cells on tumorigenesis; cancer stem cell model and clonal development model. (33,34). The hypothesis depends on the similarities between normal stem cells and cancer stem cells such as cell membrane markers, turn-over and differentiation. Alison et al. showed that intrahepatic stem cells may be factors for hepatocellular cancer or cholangiocancer (35).

Last Words

Although the developments in regenerative medicine and future study protocols regarding stem cell applications are hopeful, there are still many points to be enlightened about the biologic behaviour, the effects on immune response and oncogenic features of these cells. Today, it is not still clear that which method is better for the purification of stem cells, ideal timing or infusion method and the number of cells for application. Ethical considerations are another issue limiting the studies. The role of stem cells in medicine and gastroenterology needs numerous future multi-center studies with extended study and control groups.

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– Chapter-4 –

**LATEST ADVANCEMENTS IN THE TREATMENT
OF DUCTAL CARCINOMA IN SITU**

Turgut ANUK¹

INTRODUCTION

Ductal carcinoma in situ (DCIS) are cancers resulting from ductus of the breast, occurring on the border of the ductus of the breast and not exceeding the basal membrane(1). DCIS is expressed as 'pure DCIS' since it does not contain any invasive(2). Intraductal cancer is also entitled as non-invasive breast cancer and preinvasive breast cancer. In the USA, one-quarter of existing patients with breast cancer are diagnosed once again as a consequence of using high-resolution mammography(3). In the USA, almost 60.000 new DCIS diagnoses are established every year. For this reason, it is the fastest-growing subgroup of breast cancer(4). While the incidence of DCIS is almost at %2 in the 1980s, it has constituted %20 of all the breast cancers and %30 of all the mammographically detected breast cancers with the increasing usage of screening mammography in especially last 20-30 years(5-7). The risk factors of DCIS are the story of the first-degree kinship, increase in the age at first labor, nulliparity, excessive alcohol consumption, Afro Americans, age, age of menarche and body mass index. DCIS is accepted as the precursor lesion of invasive breast cancer. The natural behavior of DCIS varies according to tumor grade and its histological types. Although untreated low-grade ones may turn into invasive cancer after nearly 30 years, this period decreases up to 5 years for high-grade ones(8-10). When it is treated, recurrence takes place at %1-2 of the ones with mastectomy, %15 of the ones for whom lumpectomy and radiotherapy were performed and %32 of the ones for whom the only lumpectomy was performed(11). DCIS is curable cancer and ten-year survival is stated above %97. However, recurrences have affected the prognosis and posed a long-term metastasis risk at the rate of %15 (5).

CLINIC

A significant increase has been in the number of patients diagnosed asymptotically with the routine usage of mammographic screening in the last 20-30 years whereas patients apply clinically with the symptoms such as sanguineous nipple discharge, Paget's disease and a lump in the breast before the mammographic screening.

DIAGNOSIS

Mammographic evaluation is the basic approach in diagnosis. The diagnosis is mostly determined as micro-calcifications or soft tissue irregularity in mammography. As well as screening mammography is still the basic imaging method in diagnosis, digital mammography will be able to be used much more through its advantages such as image quality, sensitivity and a better

characterization of micro-calcifications. While mammographic micro-calcification is in the diagnosis of DCIS at the rate of %90-95, the diagnosis is made with the symptoms of lump in breast or nipple discharge at the rate of %10-15(4). Breast cancer-related deaths may be decreased at the rate of %30 by mammographic screening. Most of the breast calcification are benign calcifications. Nevertheless, calcifications under 1 mm are the most critical indicators of early breast cancer. %70-80 of DCIS show indications with only micro-calcifications. On the other hand, %80 of the patients for whom micro-calcification was detected apart from breast cancer are DCIS. The types of micro-calcification may be focal, pandemic, planum, and branching or gracilis granular. At present, magnetic resonance imaging come into use more frequently. It is used in the disease of DCIS through the advantages in revealing residual disease, occult invasion and multicentricity. In magnetic resonance imaging, the rates of making the diagnosis of DCIS vary between %67 and %100. The sensitivity of magnetic resonance imaging reaches up to %98. A partial consensus has been reached that magnetic resonance imaging is more superior than mammography in indicating diseased space(12-14).

PATHOLOGY

Histopathologically, DCIS is evaluated in five main subgroups called comedo, cribriform, papillary, solid, and micropapillary following structural characteristics. Instead of generally expressing all these subtypes one by one, they are generally called comedo and non-comedo types. The comedo type associates with high proliferation and increased necrosis(15-16).

PROGNOSIS

As prognostic factors, nuclear level and presence of necrosis are the most important ones. Apart from these, tumor size, surgical limit negativity, whether radiotherapy was performed or not, multiple focus, and age are the other important prognostic factors(17). Surgical limit negativity is especially a vital factor and generally over 10 mm is accepted as a safe limit(18). Seeing that the natural history of the disease is different and there are many factors affecting prognosis, various scoring systems have been evolved in the determination of prognosis. Of these systems, the most commonly used is Van Nuys Prognostic Index which was evolved by Silverstein MJ. et al(19). It took its final shape as the University of Southern California/VanNuys Prognostic Index (USC/VNPI) by adding age to this scoring system based on pathologic factors consisting of tumor size, surgical limit and degree, and necrosis (Table 1) (19). According to USC/VNPI, three different groups are identified in terms of local recurrence. The ones whose USC/

VNPI scores are 4-6 constitute low-risk group, 7-9 moderate-risk group, and 10-12 high-risk group. In these groups, ten-year recurrence-free survival is reported as %97, %73, and %34, respectively(20).

Table 1. Van Nuys Prognostic Scoring

Score	1	2	3
Size (mm)	≤ 15	16-40	≥ 41
Limit (mm)	≥ 10	2-9	<1
Pathology	No high grade	No high grade	High grade
	No necrosis	Necrosis	Necrosis
Age (Year)	> 60	40-60	< 40

SURGICAL TREATMENT

An excellent treatment for ductal carcinoma in situ is still contradictory. All the patients with the diagnosis of DCIS have to be treated. First of all, it is essential to talk to the patient clearly and in detail and include her in the decision stage. Secondly, it is obvious that there is no single treatment choice for all patients and all forms of the disease. Surgical treatment is generally recommended for patients with DCIS. It is not seen that it has an important effect on mortality. At present, the target is to treat with minimal risk of recurrence and optimal cosmetic result by conserving the breast. Even though the basic approach is surgical treatment, there are some discussions about total mastectomy and breast-conserving surgical indications. The most discussed issue is the necessity of adjuvant radiotherapy after local excision and endocrine therapy(21).

Mastectomy

The traditional treatment for DCIS is mastectomy(22). It provides a cure at the rate of %98 on an average. The risk of carcinoma after mastectomy is similar to the general female population rate. This treatment also results in local recurrence and distant metastasis by %1-2. The local recurrence after mastectomy is in two forms:

- 1- Invasive tumor is overlooked.
- 2- Cancer evolves out of the breast tissue under mastectomy flaps(23).

Reexcision in case of recurrence is a suitable decision and survival is as excellent as primary mastectomy. Another matter defended by the ones who prefer mastectomy is that DCIS is multicentric and multifocal. In addition to this, there may be some undetected hidden focus(12). MD Anderson Cancer Center prefers mastectomy because of diffuse malign calcifications in the breast, resistance limit positivity despite a resection once more after breast-conserving surgery and high-grade cancer. Cancer size is not seen as a certain mastectomy indication(12). Also, mastectomy is preferred for patients whose radiotherapy is contraindicated. Favorable constructive options have decreased the risk of recurrence. The increase in potential complications related to extensive surgery performed unnecessarily despite future intervention needs and mastectomy rates has led many various researchers to claim that more specialized prognostic indicators have to be developed to guide the surgery in the modern period(24-26). In particular, the ones who support specific interventions have proposed that the surgical approach has to be led by molecular measurement of tumor biology and advanced visualization techniques for the prediction of behaviors (26).

Only breast-conserving surgery

In patients with prognostically favorable features, only breast-conserving surgery without performing adjuvant RT is seen as an appealing approach, but there is not evidence supporting this based on prospective studies. As well as Dr. Lagios et al. are one of the researchers working out the first series of patients in breast-conserving surgery, the only excision was performed for the patients for whom bulk was not located during clinical examination and bulk of 2,5 cm or less than it was located mammographically and there was no microcalcification in postoperative mammography. While local recurrence is %12 in five years, it is %16 in ten years(27). In 2007, Silverstein said that there was no need to perform RT for all the patients for whom local excision was performed and reported that they had experienced death from breast cancer in one of more than 500 patients whom they treated by performing the only excision in the low-risk group for DCIS(28). In many studies, it is emphasized that the range of patients for whom only breast-conserving surgery will be performed has to be constituted with care. Breast-conserving surgery without RT may be performed for the patients with small or low-grade tumors or without comedo necrosis and for whom the diagnosis of the disease was not made by symptoms(29). In addition to these results, a low recurrence rate in the same breast was shown after only local excision in some retrospective non-random studies and hand-picked cases. Adding RT decreases the possibility of recurrence and invasive carcinogenesis in even the lowest risk

groups. This result is a factor that has to be taken into consideration in the time of decision by the ones preferring the only excision. The surgical limit negativity has to be over 10 mm. The surgical limit is supposed to be insufficient if it is under 1 mm.

Axillary Dissection

Axillary dissection is not suggested during the surgical treatment of ductal carcinoma in situ, because metastasis incidence of the axillary lymph node is very low such as almost %1-2 and its clinical significance is not known completely. However, axillary dissection is suggested in cases with necrosis, comedo type histology, large tumor (>3-4cm), palpable node clinically, and recurrence because microinvasion rate increases because retention rate of axillary lymph node rises to %5.1 in DCIS cases together with microinvasion(15). Thus, this kind of case is mostly treated by mastectomy because they are in a high-risk group according to USC/VNPI. For this reason, axillary dissection is suggested in the same clinic during mastectomy. In cases apart from this, namely, in cases where breast-conserving surgery is planned, axillary dissection is not suggested in the same clinic, but it is suggested as a secondary treatment in cases where an invasive component was detected during pathological examination of primary tumor material. The duty of sentinel lymph node biopsy is still a matter of debate. While it is standard for invasive breast cancer, its position in DCIS has been searched. In patients with DCIS, the positivity of SLNB varies between %1.4 and 13 in various studies(29). Nevertheless, SLNB is supposed to be commonly used either during mastectomy as a simultaneous operation or for the ones for whom invasive component was detected after breast-conserving surgery as a secondary treatment because it is less invasive than axillary dissection and it has advantages at low morbidity and complication rates and also cost-benefit rates(30). Consequently, it is not suggested to be performed as a routine examination in only DCIS because the positivity of SLNB is at low rates.

RADIOTHERAPY

In DCIS, radiotherapy is a standard after complete tumor excision, but a follow-up without radiotherapy may be possible for old patients whose tumor is low grade, under 0.5 cm especially if a tumor is removed with a limit larger than 1 cm. In cases where diffuse malign microcalcifications are located, it is multicentric or intact surgical limit cannot be obtained during excisions where breast-conserving surgery recurs, a follow-up without radiotherapy may be practiced by performing mastectomy. Radiotherapy is generally practiced to the

whole breast by conventional fractions at 46-50 Gy doses. Recently, conformal and intensity-modulated radiation therapy techniques have been used to evaluate better and taper the dose that risky tissues took. Tumor bed after complete excision is privately risky in terms of local recurrence. (This risk varies depending on the tumor's grade and size, the condition of lymphovascular invasion, surgical limit and receptor and whether he's getting a systemic treatment or not.) Due to this risk, a boost is also given to 10-16 Gy tumor bed. Local recurrence rates of RT after lumpectomy decreases from %15-20 to under %10(31). The rates of recurrence are high in presence of comedonecrosis, positivity or proximity of surgical limit, and patients under 40. As emphasized above, there is no indication of RT at the ones for whom mastectomy was performed. Radiotherapy treatment reduced the risk of recurrence, but it did not prevent deaths depending on breast cancer. It carries a risk of skin burns, cardiovascular and pulmonary toxicity in the long run. Also, the risk of post-surgical pain increases.

Endocrine Therapy

For patients with DCIS, the result of estrogen receptor have to be stated in a pathology report. If estrogen receptor is positive for the patients for whom breast-conserving surgery was performed, tamoxifen has to be given for approximately 5 years. Giving tamoxifen decreases tumor absolute risk in the same breast at the rate of %3.4 and %3.2 in the opposite breast(32). The adverse effects of tamoxifen may be named vein thrombosis, pulmonary embolism, and endometrial cancer.

RESULT

The prognosis of patients with DCIS is very good. The survival periods of nearly all the patients with breast cancer and without it is comparable because insufficient local treatments show the recurrence and frequency of the illness and its conversion to invasive breast cancer. In these cases, the individual patient follow-up has to be done. For the patient, her history and physical examination once in 6-12 months during 5 years, mammography once a year, and a follow-up once a year after 5 years are suitable.

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– Chapter-5 –

**FAMILY FUNCTIONALITY AND EMOTIONAL
REGULATION RELATION- EXAMPLE OF
TURKEY**

Gül Sultan ÖZEREN

INTRODUCTION

Family is the bridge between the individual and the society. Individuals primarily learn the emotions, thoughts and behavior patterns they have in the family system. This system is the area where basic physical needs, emotional, cognitive development, spiritual and social needs are met (Özeren et al., 2019). By sharing the same living space on a physical level, the family ensures that the world is perceived as a safe, livable place beyond meeting the need for accommodation. As Satir says, the first place that enables the socialization of the child who needs the care of an adult, is the family.

Personal development tasks are unique and different for all ages. These tasks are also the tasks that the family should perform at the expected level in order to ensure that people are in full physical, spiritual and social well-being (Bulut, 1993) Family functionality evaluates with its problem-solving skills, communication styles, sharing roles, proper emotion emergence, emotional content and general functionality dimensions (Miller et al, 2000).

Family, which is considered as the smallest unit of the society, is a system that functions with the interactions of family members and the behavior of a one family member affects other family members (Miller et al., 2000). The system model emphasizes that all family members affect each other, it is not possible to fully understand the individual without understanding the general functional structure of the family, and that the family structure affects and determines the behavior of the family members on a big aspect. According to this model, the behavior of one of the family members affects others and therefore the whole family, as well as the functionality of the family as a whole affects individuals of the family (Miller et al., 2000; Satir, 2016).

It is an important criterion in terms of whether family relations functionality is healthy or not. The way in which behaviors are controlled depending on family roles, norms and values creates family relationships. Having a sincere interest among family members, being able to react appropriately to each other's behavior, solving the problems that arise within the family and having a constructive communication to cover all of these are necessary features (Bulut, 1993).

Family functionality with its dimensions discussed in this study defines as;

(a) Problem solving (The ability of the family to solve material and moral problems at a level where it can effectively function) (b) Communication (Information exchange between family members)(c) Roles (Patterns of behavior that meet the material and spiritual needs of the family) (d) Reacting emotionally (Family members show the most proper response to all kinds of stimuli) (e) Showing the required attention (Interest that includes family members' care and

love) (f) Behavior control (The way family standards are set and disciplined in their behavior) (g) General functions (General information about other dimensions).

Emotion regulation mostly contains everything individuals do to manage the natural process of their affective responses (Thompson, 1994). The inability to regulate emotion poses a serious risk for the individual's mental health.

Emotions can be regulated at all stages of the emotional process. They can be kept voluntarily or involuntarily within certain limits by various transactions. People can make this arrangement by dealing with the situation they are exposed to, trying to review the situation and transform the reaction, or by suppressing or intensifying their reactions (Greenberg, 2011).

The evidence of correlation between the ability to effectively regulate unwanted moods and mental health has been shown for almost all mental health disorders in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; APA, 2013). Possible situations where emotional regulation deficiencies cause mental health disorders can be explained as follows; emotional regulation deficiencies result as negative moods that are exacerbated and/or maintained. Emotional regulation deficiencies trigger dysfunctional strategies in the diagnostic criteria of mental health disorders. Emotion regulation deficiencies can result as unregulated emotions that hinder self-help efforts to regulate other emotions associated with mental health disorders (Berking & Whitley, 2014).

Emotion regulation difficulties with the dimension discussed in this study defines as:

(a) Noticing emotions, (b) Understanding emotions, (c) Acceptance of emotions, (d) Controlling impulses when negative emotions are experienced, (e) To act in line with the desired goals when negative emotions are experienced, (f) the situation where lacking one or all of the skills to use the necessary emotion regulation strategies, for individual's goals and situational demands (Gratz and Roemer, 2004).

Purpose of the Study: This study was carried out to define the levels of individuals' assessment of family functions and their emotional regulation difficulties, and to examine the relationship between their family assessment levels and their emotional regulation difficulties.

Research Questions:

1. What are the levels of individuals to family assessment?
2. What are the levels of individuals' evaluation of their difficulties emotion regulation?

3. Is there a significant relationship between individuals' family evaluation levels and emotional difficulties.

MATERIAL AND METHOD

Type of the Study: This study is a descriptive-relationship seeking study.

Participants: The population of the study consists of individuals aged 18-65 (N: 65.845) living in the city of located in the north of Turkey. Individuals have been selected, by using random sampling method, are the family members who were reached by the National Education Directorate, Family, Labor and Social Services Directorate, Provincial Health Directorate and Provincial Private Administration institution employees and through home visits which carried out within the scope of "community mental health nursing", constitutes the sample (N: 580).

Inclusion Criteria: Being willing to participate in the research, being within the specified age range, not having obstructions for being able to understand what he/she read and expressing himself/herself.

Data Collection and Evaluation: In addition to the Family Assessment Device (FAD) and Difficulties in Emotion Regulation Scale (DERS), a short information form created by the researcher was used to collect data. Data were analyzed using SPSS version 23 for Windows. Descriptive statistics of the of the qualitative variables in the study are given in frequency and percentage whereas quantitative data in the study are given with average, standard deviation, median, minimum and maximum values. The suitability of quantitative data for normal distribution was examined with the Shapiro Wilk test. Mann Whitney U test was used in 2 group comparisons of variables that did not show normal distribution, and Kruskal Wallis test was used in 3 and more group comparisons. Relationships between scales were examined by Spearman correlation analysis.

Permission and Ethical Issues: The study was made up of quantitative data evaluations of the scientific research project Acquisition for Reinforced Family Structure Approval was obtained from the human research ethics committee of the relevant university for the research with the decision numbered 57452775-050.02.04-E.

Data Collection Tools

Personal Information Form: It is a short information form that provides data collection about socio-demographic variables which created by the researcher.

Family Assessment Device (FAD): It is a self-report scale that allows to evaluate the family's functions according to the perceptions of individuals in which areas they are performing or not. The Turkish adaptation of the study which was developed by Epstein et al. (1983), is made by Bulut (1990). It consists of 60 items and seven sub-dimensions. These are "Problem Solving", "Communication", "Roles", "Affective Responsiveness", "Affective Involvement", "Behavior Control" and "General Functioning". High scores from the scale indicate unhealthy family functionality. Cronbach alpha value of the scale varies between .38 and .86. In this study, Cronbach alpha value was found between 0.61 and 0.84.

Difficulties in Emotion Regulation Scale (DERS): The validity-reliability study of the scale developed by Gratz and Roemer (2004) was conducted by Rugancı and Gençöz (2010). Consisting of a total of 36 items and six sub-dimensions, DERS is a 5-point Likert scale. The high scores obtained from the scale points to the difficulty in emotion regulation. Scale sub-dimensions are; "Awareness", "Goals", "Nonacceptance", "Strategies", "Impulse" and "Clarity". The Cronbach alpha value of the scale is 0.94. In this study, Cronbach's alpha value was found to be 0.85.

RESULTS

In the statistical data analysis of the study findings, data of 580 people, 360 women and 220 men, were included. Age ranges of the participants; 18-24 = 12 (2%), 25-34 = 160 (28%), 35-44 = 240 (42%), 45-54 = 120 (21%), 55-64 = 40 (7%). Distribution of education levels; primary and secondary education = 124 (21.4%), high school = 124 (21.3%), undergraduate = 316 (54.5%), postgraduate = 16 (2.8%).

Findings regarding the family evaluation levels of the individuals participating in the study

Table 1. Family evaluation sub-dimension average scores of the individuals participating in the study

FAD	Average ± Std. Deviation	Median	Min	Max
Problem Solving	1,90 ± 0,65	1,83	1,00	3,83
Communication	1,79 ± 0,52	1,78	1,00	3,22
Roles	1,98 ± 0,37	1,91	1,27	3,09
Affective Responsiveness	2,01 ± 0,46	1,83	1,50	3,33
Affective Involvement	2,27 ± 0,40	2,29	1,57	3,71
Behaviour Control	2,13 ± 0,37	2,11	1,33	3,44
General Functioning	1,63 ± 0,50	1,50	1,00	3,27

It was determined that the individuals who participated in the study got the lowest score from the “general functioning” sub-dimension and the highest score from the “Affective Involvement” dimension. High scores from the required dimension of interest for family members to participate in each other’s activities and what interests them indicate higher dysfunction in this area.

Findings related to emotion regulation difficulties of individuals participating in the study

Table 2. Emotion regulation sub-dimension average scores of the individuals participating in the study

DERS	Average ± Std. Deviation	Median	Min	Max
Awareness	2,62 ± 0,46	2,57	1,57	3,71
Clarity	2,08 ± 0,73	2,00	1,00	4,00
Nonacceptance	2,12 ± 0,90	2,00	1,00	5,00
Strategies	2,21 ± 0,81	2,13	1,00	4,63
Impulse	2,21 ± 0,77	2,33	1,00	4,67
Goals	2,62 ± 0,76	2,60	1,00	4,60

Within the scope of the Difficulties in Emotional Regulation Scale, it was determined that the individuals who participated in the study got the highest score from two dimensions as “goals” and “awareness”. This situation indicates significant difficulties in family relations in terms of lack of awareness about emotional reactions and not understanding emotional responses.

Distribution of the sub-dimension average scores of the FAD and DERS from individuals participating in the study based on gender

Table 3. The distribution of the scale sub-scale average scores of the individuals participating in the study

FAD	Women	Men	p
Problem Solving	1,79 ± 0,63 1,75 (1,00-3,33)	1,96 ± 0,64 1,83 (1,00-3,83)	0,002
Communication	1,88 ± 0,55 1,89 (1,00-3,22)	1,74 ± 0,49 1,67 (1,00-2,89)	0,008
Roles	2,02 ± 0,40 2,00 (1,27-3,09)	1,96 ± 0,34 1,91 (1,27-3,09)	0,086
Affective Responsiveness	2,05 ± 0,42 2,00 (1,50-3,00)	1,98 ± 0,49 1,83 (1,50-3,33)	0,006
Affective Involvement	2,38 ± 0,38 2,43 ((1,46-3,49)	2,21 ± 0,39 2,14 (1,57-3,71)	<0,001
Behaviour Control	2,16 ± 0,40 2,11 (1,33-3,11)	2,11 ± 0,34 2,11 (1,44-3,44)	0,189
General Functioning	1,67 ± 0,49 1,67 (1,00-3,00)	1,60 ± 0,51 1,50 (1,00-3,17)	0,079
DERS	Women	Men	p
Awareness	2,60 ± 0,46 2,57 (1,57-3,71)	2,65 ± 0,46 2,71 (1,57-3,57)	0,046
Clarity	2,00 ± 0,68 2,00 (1,00-4,00)	2,20 ± 0,81 2,20 (1,00-4,00)	0,006
Nonacceptance	1,97 ± 0,83 1,75 (1,00-4,83)	2,37 ± 0,96 2,33 (1,00-5,00)	<0,001
Strategies	2,42 ± 0,86 2,38 (1,00-4,50)	2,07 ± 0,74 2,00 (1,00-4,63)	<0,001
Impulse	2,10 ± 0,70 2,08 (1,00-4,00)	2,40 ± 0,84 2,33 (1,00-4,67)	<0,001
Goals	2,77 ± 0,70 2,60 (1,40-4,40)	2,53 ± 0,77 2,60 (1,00-4,60)	0,016

#Mann Whitney U Test

When the family evaluation subscale scores of the individuals participating in the study were examined, the “problem solving” subscale score of men was higher than women (**p=0.002**). The “communication” subscale score of women

is higher than men ($p=0.008$). The “affective responsiveness” subscale score of women is higher than men ($p=0.006$). The “affective involvement” sub-dimension score of women is higher than men ($p=0.008$). There is no statistically significant difference between women and men in terms of “behavior control” and “general functionin” sub-dimension scores.

There is a gender difference in all dimensions of emotion regulation difficulties of individuals participating in the study. The “awareness” sub-dimension score of men is higher than women ($p=0.046$). The “clarity” subscale score of men is higher than women ($p=0.006$). The “nonacceptance” sub-dimension scores of men are higher than the men ($p<0.001$). The “impulse” subscale score of men is higher than women ($p <0.001$). The “goals” sub-dimension score of women is higher than men ($p = 0.016$). The “strategies” sub-dimension score of women is higher than men ($p <0.001$).

Relationship between family assessment subscales and emotion regulation subscales of individuals participating in the study

Table 4. Relationship between family assessment subscales and emotion regulation subscales

		Family Assessment Device						
		Problem Solving	Communication	Roles	Affective Responsiveness	Affective Involvement	Behaviour Control	General Functioning
Difficulties in Emotion Regulation	Awareness	r=-0,043 p= 0,360	r=0,063 p=0,176	r=0,213 p<0,001	r=0,049 p=0,298	r=0,081 p=0,085	r=0,053 p=0,275	r= -0,010 p=0,828
	Clarity	r=0,300 p<0,001	r=0,435 p<0,001	r=0,351 p<0,001	r=0,382 p<0,001	r=0,288 p<0,001	r=0,374 p<0,001	r=0,485 p<0,001
	Nonacceptance	r=0,234 p<0,001	r=0,484 p<0,001	r=0,406 p<0,001	r=0,351 p<0,001	r=0,238 p<0,001	r=0,243 p<0,001	r=0,472 p<0,001
	Strategies	r=0,251 p<0,001	r=0,441 p<0,001	r=0,411 p<0,001	r=0,291 p<0,001	r=0,201 p<0,001	r=0,219 p<0,001	r=0,431 p<0,001
	Impulse	r=0,237 p<0,001	r=0,408 p<0,001	r=0,426 p<0,001	r=0,269 p<0,001	r=0,261 p<0,001	r=0,268 p<0,001	r=0,404 p<0,001
	Goals	r=0,109 p=0,019	r=0,248 p<0,001	r=0,272 p<0,001	r=0,146 p=0,002	r=0,061 p=0,188	r=0,037 p=0,438	r=0,289 p<0,001

There is mostly a moderately linear significant relationship between “Awareness”, “Problem Solving”, “Communication”, “Roles”, “Affective Responsiveness”, “Affective Involvement”, “Behavior Control” and “General Functions” which are the sub-dimensions of Family Evaluation Scale and Emotion Regulation Strong Scale; “Aims”, “Not Accepting”, “Strategies”, “Impulse” and “Openness.” In other words, as the difficulties in emotion regulation increase in general, the inadequacies in family functionality increase. In addition, as long as the family functionality is insufficient, emotion regulation skills are also insufficient.

DISCUSSION AND CONCLUSION

According to the findings obtained from the study, dysfunction was found at least in the “general functions” dimension and the most “Affective Involvement” dimension in the family relations. The interest shown by the family members to each-other includes care and love. Optimum care is within the scope of healthy family functions. Too little or too much attention is considered unhealthy (Bulut, 1993). In a recent thesis study conducted in our country, it was found that the lowest score was in the “general functions” dimension, and the highest score was in the “showing the required attention” dimension (Ayaz Lale, 2019). The researcher Bulut, who used the family assessment scale for the first time in our country, stated that when he compared the unhealthy rates among the FAD sub-dimensions, the dimension with the highest level of unhealthiness was the “Affective Involvement” dimension (Bulut, 1993). It has been determined that individuals’ healthy lifestyle behaviors will increase with the decrease of the problems in family functionalities (Sahin, 2012).

According to the findings obtained from the research, it was found that most difficulties were found in “regulation” and “awareness” dimensions within the scope of emotion regulation. Studies that deal with the relationship between family functionality and emotion regulation are quite limited. On the other hand, when evaluated in terms of functionality or health, some relevant results can be mentioned. Clarity and awareness among the sub-dimensions of emotion regulation difficulties were found to be related to family functionality (Ayaz Lale, 2019).

Cheng et al (2017) state that there is a relationship between family functions and mental health, and that a better family function causes a better mental health (Cheng et al 2017). The difficulties in emotion regulation prevent the decrease of traumatic effects over time and this leads to the persistence of traumatic effects (Bardeen et al., 2013). Knafl et al. (2015) found that the prevalence of depressive symptoms and depression in parents caused poor family functioning and a worse mental health and quality of life in children diagnosed with arthritis (Knafl et al

2015). In a study of Lam et al. (2012) investigating family health in the Chinese people, they found that effective communication is effective in family harmony, and common time with the family affects both family health and happiness (Lam et al 2012). Kivela et al. (2018) found that those who experienced or used domestic violence had more unhealthy family functions than those who did not (Kivela et al 2018). In a study carried out by Mennin, Haloway, Fresco and Moore (2007), it was found that individuals who have difficulties in regulating emotional responses in daily life are exposed to long-term distress, which causes predisposition for depression and anxiety. In the study of Mitrofan and Ciuluvica (2012), it was determined that impulse, nonacceptance, clarity and goals can be used as the most important indicators in increasing life satisfaction and maximizing personal development. Research findings are in line with these data in the literature.

Findings from the study showed that there was a statistically significant difference between men and women regarding difficulties in evaluating family functionality and regulating emotions. Gutiérrez-Matta et al (2017) also found that women perceived more family dysfunction than men (Gutiérrez-Mata et al 2017). Shahmahmoudi and Mazandarani (2015) found that women's functions of problem solving, communication, roles, behavioral control and emotional response are unhealthy (Shahmahmoudi and Mazandarani 2015). In a study by Sancho et al. (2019), it was found that there was a difference between genders in terms of not accepting emotions, and men experienced more difficulty.

In a study conducted with adolescents in Spain, while there was no gender difference for awareness, impulse, nonacceptance and goals sub-dimensions, it was determined that women experienced higher levels of emotional difficulty in terms of openness and strategies (Gómez-Simón et al., 2014). In a study by Neumann et al. (2010), it was found that it is more difficult for women to use effective strategies compatible with the situation than men, and they encounter more difficulties in understanding the emotional responses or clarity of emotions compared to men. In this context, in this study, the difference between women and men in terms of evaluating family functionality and emotion regulation difficulties is related to the literature.

In conclusion, according to the findings obtained from this study, as the difficulties in emotion regulation increase, the inadequacies in family functionality increase. In other words, as long as the family functionality is insufficient, emotion regulation skills are also insufficient. The fact that the first close relationships are healthy enables individuals with healthy emotion regulation systems to be raised, and it is possible to raise similar children in families formed by the choices of similar individuals. (Siegel, 2012).

As a result, this research; It provides data supporting the knowledge that there is a circular relationship between functional families and healthy emotion regulation.

In light of the findings obtained from the research; It is thought that family relations, pre-marriage, and parenting education will create effects that increase family functionality when prepared within the scope of emotion regulation skills and emotion-oriented approach.

Etic issue

The study was approved by the ethics committee of the Sinop University. (No: 57452775-050.02.04-E.)

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