Current Research in Internal Medical Sciences

Editors • Prof. Dr. Ellie Abdi
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Preface

Current Research in Internal Medical Sciences is serving an academic forum for both academics and researchers working in such fields. Internal medical sciences research is an interdisciplinary by nature. So it covers several fields Besides, have been used as a research method for the contemporary issues relevant to internal medical sciences. In this book, the academics working in different fields share their results with the scientific community. Thus more researchers will be aware of these studies and have some new ideas for their future studies. The selected articles have been reviewed and approved for publication by referees. It is hoped that the book will be of interest and of value to academics and researchers

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Chapter I

Functional Magnetic Resonance Imaging

Işıl YURDAIŞIK

(Asst.Prof M.D..) Department of Radiology, İstinye University, Medical Park Hospital, İstanbul, 34010, Turkey
isil.yurdaisik@gmail.com - İsil.yurdaisik@isu.edu.tr

Functional Magnetic imaging (fMRI) is one of the methodologies used to detect activity patterns of the brain, and although the first studies have been conducted twenty years ago, they have provided us to find revolutionary results (1).

fMRI is used in many diseases (Alzheimer, Parkinson) with electrophysiological methods and its use has increased to characterize the pathological burden, to follow up disease process, to decide new treatments (2) in diagnosis and treatment of patients with stroke (3) or searching effects of pharmacological agents at end stages (4).

The basis of fMRI is based on changes in the amount of oxygen in the area used. These changes are named BOLD (blood oxygen level depended) (5). Blood oxygen related BOLD contrast, has been widely used due to its easy application and high sensitivity. However, the BOLD signal is dependent on various anatomical, physiological and imaging parameters, so it is not easy to interpret it according to physiological parameters. To understand the physiological source of the BOLD signal, it is necessary to measure changes in brain blood flow and brain blood volume.

BOLD reflects the increase in neural activity directly and the synchronization in localization of function has been strengthened with the latest data (6).

The basis of the image is paramagnetic deoxyhemoglobin and T2 * imaging due to the short phase of the phase formation due to low signal, Oxyhemoglobin being diamagnetic, and during neural activation, both vessel dilation and increase in the amount of capillary oxyhemoglobin and this difference can be observed with

MRI. The Echo Planar Imaging (EPI) sequence is used. EPI is the filling of the k-space by rapidly switching the frequency-coding gradient on and off after the first 180° pulse sent after the RF pulse (90°).

EPI provides fast imaging that reduces imaging time by up to 20 msec for a single image. By reducing the sensitivity to movement artifacts, physiological changes can be recorded, enabling cerebral perfusion, diffusion, cardiac perfusion, rapid T1 and T2 calculations and functional activation information to be generated (7). After the RF pulse, the frequency-coding gradient is switched on and off and the k-space is filled. It is aimed to scan the entire area faster by making jumps with spiral k-space filling and to reduce the data quality while shortening the shooting time. This software is used to reduce the error rate in the space between the section slices (8,9). These techniques are also used in Slice-Time Correction. The objective is to reduce the signal to noise ratio in parallel imaging and simultaneous multi section techniques. Because the excess data increases the noise (10,11).

With these methods, TR time can be reduced up to 8 times. In this way, the effect of head movement in elderly and pediatric patients is reduced by shortening the screening time.

In the functional MRI protocol, reference MR images are generated first T2-weighted FSE or TSE (based on a number of phase coding cycles with repetitive 180 ° RF after 90 ° RF pulse) or T1 inversion recovery images, 3D T1 to allow the brain template to compare statistical data in larger groups weighted images are used (12). n some techniques, fiber-tracking or arterial spin labeling – perfusion image may be added (13,14). In addition, hypercapnic CO2 respiration or breath-holding may be used to obtain more qualified results in some studies (15).

BOLD imaging is obtained in two ways. The first is the Echo planar gradient echo (GRE) sequence (phase coding cycle is generated with RF pulses less than 90 °), the second is the echo planar spin echo (SE) sequence. EPI SE is the most sensitive way for BOLD information obtained from capillaries (16). The intravascular signal in the SE sequence at 1.5 T suppresses the fMRI signal, while the intravascular signal disappears in the SE at a magnetic field strength of 4T and above, the BOLD contrast is more localized in microvascularization. High field strengths can

increase the amount of SAR (Specific Absorption Rate), causing nausea, vomiting and other symptoms.

Since the statistical significance of the magnetic field strength over 3T also decreases, many studies are performed in 3T (17). Herein, fast SE sequences (such as HASTE, TSE) can be used to shorten the time. T2 data and BOLD signals are not missed and 1.5 T devices are insufficient in neuropsychological studies (18). After using all these data collection tools efficiently, the BOLD signal is very small; In order to interpret the results correctly, it is necessary to purify the data and make corrections (19). The characteristics of the MR device used and the equations used when reading the data are of great importance in terms of the quality and efficiency of the data. High magnetic field strength improves image clarity and improves data quality, but increases the amount of negative and positive data at the same rate, leading to more noise (18).

fMRG Techniques

Resting d-fMRG

The most important contribution of resting state fMRI is the default mode network (DMN). This network was first described by Raichi et al. in PET scans. The resting state was then monitored on fMRI scans. The brain also has certain perfusion changes and activity at rest. d-fMRG is generated following BOLD frequencies of less than 0.1. It is assumed that some domains are always in communication and connected as networks (DMN) 20.

Whether the eyes are closed or open creates differences on the basis of d-fMRI pattern and network. Therefore, the patient should not do anything during the examination (21). Almost all of the DMn could be created by resting fMRG. Recent research has shown that DMN is not only a resting and active access system, but also a rapid response system for the brain to adapt to the tasks (22).

Task Based fMRG

As its name suggests, it is a model in which the response to the stimulus is observed such as visual, sensory, auditory and behavior manipulation. Once the stimulus and response have been recorded, further analysis can be performed for hypotheses such as phenotypic, genotypic effect or age, sex to be added, level of education, and level of difficulty. This model, because we work on a system that monitors hemodynamic changes; repetitive active and passive dynamic blocks need to be designed. Thus,

oxyhemoglobin changes can be evaluated better (24). Task-based fMRI consists of three models: a: Block experiment, event-related and mixed.

1. Block Experiment: In the block experiment, the stimuli are in the same number of block forms. For example, 10 active, 10 passive dynamic images are obtained, each repeated four times. With the same amount of passive time, the activity in the region is minimized and the difference in the moment of activity is aimed to emerge clearly. It is used in tumor surgery to determine whether motor and sensory functions are affected by the tumor and to determine important functional areas and to determine the dominant hemisphere for epilepsy surgery. Tasks such as opening and closing the fingers and toes, word generation, verb derivation and eye opening and closing are given as blocks (24).

2. Event related: B Unlike the block experiment, it does not have specific gaps or stimulus times. In an experimental design, there is a random but a certain number of stimuli. The dynamics corresponding to the stimulus are marked as active and the remainder are considered passive. Face recognition, meaningful word, word grouping tasks can be defined. In the experiment, it is determined which dynamics are active (25) by which helper (button etc.) is given correct or wrong answer during the related task.

3. Mixed: Mixed Order sequences are used to analyze a cognitive / behavioral or complex task. The states measured in these sequences are not the same number and the active / passive times and numbers are different. It provides the flexibility to analyze complex responses that do not require cognitive masking, such as counting or remembering. For shortening the passive interval by extending the active process or for the localization of the areas that are activated quickly according to the stimulus, for example, 3 active 2 passives then 4 active 3 passive dynamics allow the maximum amount of data to be obtained without prolonging the acquisition time (24).

The analysis of fMRI data is performed by pre-processing the patient or patient data for preparation for analysis and then by statistical evaluation of the data. Today, patient analysis is automatically generated on many MRI devices. However, pre-processing and post-processing and analysis of fMRI data in single or multiple groups can be performed with more detailed internet

access or advanced computer programs that can be purchased. Pre-processing data has too much noise for analysis such as cardiac and respiratory artifacts, motion artifacts, false positive data. Prior to analysis, pre-processing of data should be cleared / highlighted to increase statistical power. Some of them are: Quality guarantee, Section time correction, Head motion correction (26), Distortion Correction (27), Temporary filtering (28), Spatial Smoothing: (29), Physiological noise correction (30), Functional-structural joint recording: (31) Spatial normalization (32,33).

Functional MRI has been developing rapidly and continuously since 1990. Despite criticism and reliability issues, it is one of the important analysis techniques in cognitive sciences. New research methods and statistical analysis methods can be used for the diagnosis and process evaluation of epilepsy, Alzheimer's disease, other cranial diseases and cognitive / behavioral disorders. Although many analysis processes are automated in functional MRI analyzes, the data is influenced by many factors, the variability of the data obtained and the uncertainty of the intervals (not very clear digital thresholds of positive and negative situations, changes according to the person and the mother) require the radiologist to play an active role in the decision making process. complicates case studies.

Although many artificial intelligence and learning machine techniques are used to analyze the data and increase the accuracy values, radiologist control continues to be important due to the new technologies in these processes.

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Chapter II

Incidental Findings Determined on Magnetic Resonance Imaging in Patients Applying with the Headache Symptom*

Rasime Pelin KAVAK

(MD), University of Health Sciences Dıskapi Yıldırım Beyazıt Training and Research Hospital, Radiology Department, Ankara, Turkey.

Introduction

Magnetic resonance imaging (MRI) is widely used to diagnose the cause of the headache and to exclude differential diagnoses (1). MRI use has rapidly become widespread as a result of its particular efficacy at examining soft tissue and recent advances in this field (1). Widespread use of MRI has rapidly increased the number of incidentally detected lesions (1).

Incidental findings (IF) are lesions undiagnosed before, which are detected independent of the study indication (1). The prevalence of those incidental lesions detected in neuroimaging may show variability between different populations. The clinical importance of these lesions is controversial, and there is no consensus as to whether they should be investigated further (1).

The aim of our study is to analyze incidentally diagnosed findings among patients undergoing MRI for headache.

Materials and methods

Patient population and study design

The study was carried out according to the ethical standards of the 1975 Helsinki Declaration's Human Experiment Committee, which was revised in 2000. We retrospectively reviewed the MRI

* *This study was presented as an oral presentation on June 28-30, 2019 at the 2nd International Hippocrates Congress on Medical and Health Sciences, İstanbul, Turkey.*

images of 1982 patients aged 18-85 years who underwent MRI for headache between January 2017 and January 2019. The MRI images of 2072 patients were examined via the hospital automation system. Patients with artifacts in image sections and those younger than 18 years were excluded. After excluding images meeting the exclusion criteria, 1982 patients were included in the final analysis. IF were identified in 143 (7.2%) patients. Patients who were previously diagnosed with a brain tumor, aneurysm, subdural fluid collection, arachnoid cyst, etc. and who had related complications were not regarded as having IF.

MRI protocol

The MRI was performed using two 1.5T MRI imaging scanners (Magnetom, Aera, Siemens, Erlangen, Germany) and Philips Achieva (Philips Medical Systems, Eindhoven, The Netherlands) with a standard head coil. The imaging protocol constituted five routine sequences: axial T1-weighted [repetition time (TR)/echo time (TE): 348/8.9 ms, voxel size: 0.7x0.7x0.5 mm, field of view (FOV): 23x23 cm, slice thickness: 5 mm]; axial T2-weighted (TR/TE: 4160/102 ms, voxel size: 0.6x0.6x5.0 mm, FOV: 23x23 cm, slice thickness: 5 mm); axial FLAIR (TR/TE: 8000/86 ms, voxel size: 0.7x0.7x5.0 mm, FOV: 23x23 cm, slice thickness: 5 mm); coronal T2-weighted (TR/TE: 4730/94 ms, voxel size: 0.6x0.6x5.0 mm, FOV: 22x22 cm, slice thickness: 5 mm), and sagittal FLAIR (TR/TE: 9000/87 ms, voxel size: 0.4x0.4x5.0 mm, FOV: 23x23 cm, slice thickness: 5 mm).

The patients' measurements were evaluated on MRI via Extreme Picture Archiving and Communications System (PACS) system (Ankara, Turkey). The images were examined by a radiologist with 10-years experience in neuroradiology imaging.

Statistical analysis

The data were analyzed using the SPSS package (Statistical Package for the Social Sciences for Windows, Version 22.0, SPSS Inc., Chicago, IL, U.S.A.). The distribution width of the study data was tested using the Kolmogorov Smirnov test. Quantitative data were analyzed with the Mann-Whitney U test and the qualitative data with the Pearson Chi-Square test or Fisher's Exact test. Quantitative data were expressed as mean and standard deviation (SD); qualitative data were expressed as number (n) and percentage (%). $P<0.05$ was considered statistically significant.

Results

The mean age of the study population was a 36,1±12,1 year and 58.7% of the subjects were female. Among subjects detected to have IF, 63 (44.1%) had paranasal sinus abnormalities (mucosal thickening, retention cysts, polyps, anatomical variations), 33 (22.4%) pineal cyst, 29 (20.3%) Chiari malformation 1 (CM1), 23 (16.1%) white matter abnormalities (WMA), 20 (14%) arachnoid cyst, 20 (14%) Virchow-Robin space (VRS), 15 (10.5%) aneurysm, 8 (5.6%) vestibular schwannoma (VS), 8 (5.6%) empty sella, 8(5.6%) cavum septum pellucidum (CSP), 6 (4.2%) CSP and cavum vergae, 5 (3.5%) meningioma, 4 (2.8%) gray matter heterotopia (GMH), 4 (2.8%) mega cisterna magna (MCM), 4 (2.8%) partial empty sella and 2 (1.4%) arteriovenous malformation (Table 1) (Figure 1 a, b, c).

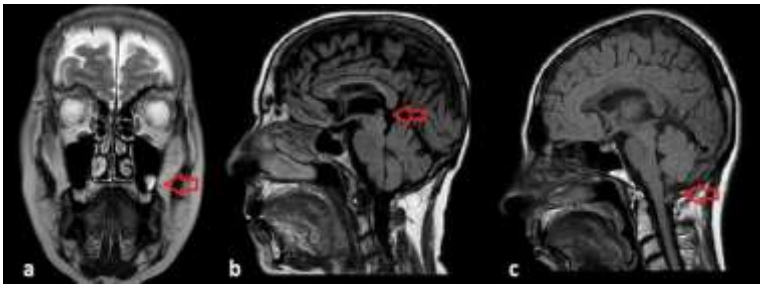

Figure 1 (a) Coronal magnetic resonance image shows left maxillary mucous retention cyst (red arrow), sagittal magnetic resonance images show (b) pineal cyst (red arrow), (c) Chiari malformation 1 (red arrow).

Pineal cyst, aneurysm, and VS were more common in the older patients ($p<0.05$); CM1, CSP and cavum vergae and arteriovenous malformation were more commonly detected in younger patients ($p<0.05$). Paranasal sinus abnormalities, WMA, arachnoid cyst, VRS, empty sella, CSP, meningioma, gray matter heterotopia, partial empty sella, and presence of MCM had no significant correlation to age ($p>0.05$) (Table 1).

Table 1. The relationship of IF with age

			IF		*p
	MRI n(%)	IFR(n:143) n(%)	Yes Mean±SS	No Mean±SS	
Paranasal sinus abnormalities	63 (3,2)	63 (44,1)	37,3±11,7	35,1±12,3	0,340
Pineal cyst	33 (1,7)	33 (22,4)	42±11,2	34,3±11,7	0,017
Chiari malformation 1	29 (1,5)	29 (20,3)	26,2±9,6	38,6 ±11,3	<0,001
White matter abnormalities	23 (1,2)	23 (16,1)	33,8±7,1	36,5±12,8	0,491
Arachnoid cyst	20 (1)	20 (14)	31,6±12	36,8±11,9	0,052
Virchow-Robin spaces	20 (1)	20 (14)	35,9±8,9	36,1±12,5	0,717
Aneurysm	15 (0,8)	15 (10,5)	47,6±6,5	34,7±11,8	<0,001
Vestibular schwannoma	8 (0,4)	8 (5,6)	47,5±9,5	35,4±11,9	0,006
Empty sellla	8 (0,4)	8 (5,6)	34,5±5	36,2 ±12,3	0,608
Cavum septum pellucidi	8 (0,4)	8 (5,6)	29±10,7	36,5 ±12	0,086
Cavum septum pellucidi and cavum vergae	6 (0,3)	6 (4,2)	23,3±8,4	36,6±11,9	0,008
Meningioma	5 (0,3)	5 (3,5)	40,8±4,6	35,8 ±12,2	0,269
Gray matter heterotopia	4 (0,2)	4 (2,8)	37±3,5	36±12,2	0,931
Mega cisterna magna	4 (0,2)	4 (2,8)	42,5±2,9	35,9±12,2	0,172
Partial empty sella	4 (0,2)	4 (2,8)	37±12,9	36±12,1	0,712
Arteriovenous malformation	2 (0,1)	2 (1,4)	18±0	36,3±11,9	0,005

Student t-test, IF: İncidental findings.

Paranasal sinus abnormalities were significantly more common in men ($p<0.05$). Gender had no significant relationship with a pineal cyst, CM1, WMA, arachnoid cyst, VRS, aneurysm, VS**,** empty sella, CSP, CSP and cavum vergae, meningioma, GMH, MCM, partial empty sella, and presence of arteriovenous malformation($p>0.05$) (Table 2).

Table 2. The relationship of IF with age

	Gender		*p*
	Male (n:59)	Female (n:84)	
Paranasal sinus abnormalities	32 (54,2)	31 (36,9)	0,040*
Pineal cyst	16 (27,1)	16 (19)	0,254*
Chiari Malformation 1	8 (13,6)	21 (25)	0,094*
White matter abnormalities	4 (6,8)	19 (22,6)	0,011*
Arachnoid cyst	6 (10,2)	14 (16,7)	0,270*
Virchow-Robin spaces	5 (8,5)	15 (17,9)	0,111*
Aneurysm	5 (8,5)	10 (11,9)	0,510*
Vestibular schwannoma	4 (6,8)	4 (4,8)	0,718**
Empty sellla	2 (3,4)	6 (7,1)	0,470**
Cavum septum pellucidum	4 (6,8)	4 (4,8)	0,605**
Cavum septum pellucidum and cavum vergae	3 (5,1)	3 (3,6)	0,691**
Meningioma	3 (5,1)	2 (2,4)	0,404**
Gray matter heterotopia	2 (3,4)	2 (2,4)	>0,999**
Mega cisterna magna	2 (3,4)	2 (2,4)	>0,999*
Partial empty sella	1 (1,7)	3 (3,6)	0,643**
Arteriovenous malformation	2 (3,4)	0 (0)	0,169**

*Pearson Chi-Square test, **Fisher's Exact test.

Discussion

Graf et al reported that IF may show variation between different age groups and societies, and they had a prevalence of

21.5% in neuroimaging performed for headache in a pediatric population. [2] A metanalysis of 16 studies involving close to 20000 subjects revealed that the mean prevalence of IF was 2.7%, which rose as high as 4.3% in MRI examinations with a good imaging quality and fell as low as 1.7% in poor-quality MRI examinations. [3] Hartwigsen et al reported an IF prevalence of 19%, 9% of which were asymptomatic and 10% were symptomatic. [4] Haberg et al identified IF in 27.1% of cases, 15.1% of which had clinical signs and symptoms. [5] Bos et al reported a corresponding rate of 9.5%. [6] In our study, we found an IF prevalence of 7.2% that was in agreement with literature reports, which may be related to the MRI device's quality and interpreting radiologist's experience. It should be remembered that many lesions detected by the present study and elsewhere cause headache and an ordered neuroimaging actually reached its ultimate goal. Furthermore, it should be remembered that as IF are not specifically sought, small lesions may have gone unnoticed and thus prevalence data may be inconsistent.

Hansen et al, among patients undergoing MRI, identified mucosal thickening of less than 1 mm, mucosal opacification, and nasal polyp in 66% and mucosal thickening exceeding 1 mm in 49%. [7] Nazri et al. detected sinus anomaly in MR at a rate of 29.5-85.2%, reporting that sinus anomaly was unrelated to gender. [8] Graf et al. reported sinus fluid, cyst, or mucocele in 7.6% of pediatric cases. [2] Hartwigsen et al reported a prevalence of 1% for multiple sinusoidal polyps among IF. [4] We most commonly detected paranasal sinus abnormalities with a prevalence of 3.2% [rate among incidental findings (IFR): 44.1%]. Although it was unrelated to age, it was significantly more prevalent in men.

Pineal cysts are benign lesions located in the pineal gland, which are usually asymptomatic. Symptomatic cases, on the other hand, may present with variable and nonspecific symptoms. [9] Studies have shown that pineal cysts have a prevalence of 6-10%, which increases later in life and reaches 40% in postmortem analyses. [9,10] Holy et al reported that, although pineal cysts are common in the pediatric population, its prevalence increases in girls and the elderly. [11] Studies on IF have revealed prevalences ranging from 1.1% to 6.3% for pineal cysts. [3,4,12] We found a pineal cyst prevalence of 1.7% (IFR 22.4%), which was the second most common incidental finding. Patients with pineal cyst had a greater mean age, and the pineal cyst had a similar prevalence in both genders. We believe that after a certain age, cystic lesions

become prevalent irrespective of age due to pathological processes and disturbed physiology.

CM 1 is a condition characterized by cerebellar tonsils or tonsils into the spinal canal, and it most commonly presents with a headache. [13,11] Studies on IF have reported that CM1 had a prevalence of 0.25-1%. [3,4,13] Graf et al reported a prevalence figure of 3.2%. [2] We detected CM1 in 1.5% (IFR 20.3%) of our patients. We noted that patients with lesions were younger, although there was no significant difference with respect to gender. This may have been a result of making the diagnosis of CM1 while investigations were performed to determine the headache origin. A higher prevalence of CM1 found in the study on children is supportive of our argument.

WMA is a condition characterized by abnormal conduction and neuromodulator release as a result of impaired white matter integrity; it is quite common in psychiatric and neurological disorders.[14, 15] Studies on IF have shown that WMA had a prevalence ranging from 1% to 9.4%.[4,10,16,17] Vernooj et al. reported that WMA prevalence increased as people aged. [18] We found a WMA prevalence of 2.1% (IFR 16.1%). The lesions were more common in women and unrelated to age. A greater WMA frequency in women may be related to an increased prevalence of psychiatric diseases. In line with the literature, we found a greater, albeit statistically non-significant, WMA prevalence in older age, which may be related to a greater prevalence of psychiatric disorders in the elderly. A low number of patients with WMA among IF may be related to an unclear age limit of neuropsychiatric disorders.

Arachnoid cysts are benign lesions that develop as a result of arachnoid duplication or anomalous diverticula formation during fetal life. They may lead to the emergence of symptoms as they grow. They have a prevalence around 0.3%- 1.4% (19,20). As an IF, arachnoid cysts had a prevalence has been reported between 0.5% and 3.2%. [2,3,12,20-22] We detected arachnoid cyst in 1% (IFR 14%) of our subjects, and they were unrelated to age and gender. We believe that as cranium enlarges in parallel to lesion size, and these lesions do not regress with aging; lesion presence was unrelated to age and gender.

VRS is a perivascular compartment encircling small arteries and arterioles coursing into the parenchyma. There are

cerebrospinal fluid and vasoactive neuropeptides in it. Its anomalies have been linked to neurodegenerative disorders, metabolic disorders, genetic factors, alcoholism, vascular conditions, inflammation, neoplasms, and trauma. [23,24] Studies examining its prevalence in relevance to IF have reported prevalences ranging 1.1% to 1.6%. [2,24] We demonstrated VRS in 1% (IFR 14%) of the patients. VRS was common in women and unrelated to age. We believe that VRSs were diagnosed as IF as they were typically not sought for directly as a preliminary diagnosis. However, increased frequency of neurological and metabolic disorders in women may explain why VRS was common in that gender. As the pathophysiology of the disorder involves conditions of both childhood and adulthood, the presence of the disorder may not have had any correlation with age.

Aneurysms are localized dilations in the cerebral arterial walls which tend to rupture; they have a prevalence between 1% and 7% and on MRI 1%-3%. [20,25] Brain arteriovenous malformations (bAVMs) are abnormal connections between artery and vein within the intracranial space. Of bAVMs, 2-10% are detected as IF or, after they cause symptoms. [26] The prevalence of meningioma and aneurysm has been reported to be higher in women than men. [6] Studies on IF have shown that the aneurysm prevalence ranged between 0.35% and 2.3%. [3, 6, 18, 22]; bAVM prevalence has been reported between 0.05% and 1.1%. [2-4] In our study, 0.8% (IFR 10.5%) had a aneurysm; 0.1% (IFR 1.4%) had bAVM. The aneurysm was common in the elderly and bAVM in youngsters. Vascular conditions had no correlation with gender. We believe that bAVMs were detected in the early stages of life as they are congenital lesions whereas aneurysm was detected later in life as they become prominent over time.

Cavum is a CSF-filled space between the lateral ventricles, which is found in all newborns. It should be closed by the 5th month of life; inability to close or abnormal closure is termed as CSP and cavum vergae. Although its exact prevalence and clinical manifestation are unknown, it has been associated with psychiatric disorders. [27] Studies on IF have reported a CSP prevalence of 0.5% to 4.7%. [16,17] We found a prevalence of 0.4 (IFR 5.6%) for CSP and 0.3% (IFR 5.6%) for CSP and cavum vergae. CSP and cavum vergae were more common in younger patients. Although the mean age for CSP was low, it was not statistically significant. CSP and CSP/cavum vergae were unrelated to gender. We believe

that as cavum spontaneously closes in the first years of life, and later in life even if delayed, it was more common in the young. As the available data on that condition are limited and our number of cases were small, there may be no significant correlation with gender.

The prevalence of meningioma is 4-5 per 100.000, being the most common intracranial tumor. It is more prevalent in women, and it becomes more prevalent with aging. [28] VS, on the other hand, is a benign tumor of the vestibulocochlear nerve composed of neoplastic Schwann cells. Despite being typically sporadic, its association with genetic disorders has been reported. [29] IF studies have reported a prevalence of [3,6,18,22] 0.29-2.5%; while VS prevalence has been reported [18,22] 0.1-0.2%. We reported a VS prevalence of 0.4% (IFR 5.6%) and meningioma prevalence of 0.3% (IFR 3.5%). The mean age of VS patients was higher; although the mean age of those with meningioma was higher, the difference was not statistically significant. VS and meningioma were unrelated to age. The tumor prevalence may have increased with advancing age for both genders due to the impaired cellular structure by genetic and environmental factors over time. The inter-group differences may have canceled due to a small number of cases. We also believe that clinicians ordering tests for suspected tumors rendered tumors non-IF, lowering the prevalences of those lesions.

Empty sella is a condition characterized by the disappearance of hypophyseal tissue, which normally sits on Sella turcica, due to herniation. Although its exact prevalence is unknown, it has been reported between 2% and 20% and more commonly in women. It is still debated whether asymptomatic patients diagnosed with empty sella as IF need to be investigated with respect to hormonal status. [30,31] As an IF, empty sella has been reported at prevalences ranging between 0.35% and 1.3%. [17,22] In our study 0.4% of cases (IFR 5.6%) had empty sella, and 0.2% (IFR 2.8%) had partial empty sella. Empty sella prevalence did not differ by age or gender. We believe that groups were indifferent with regard to age and gender as congenital and other risk factors are similar for both genders, and as those risk factors may be aggravated at any period of life. Furthermore, a low number of patients with that condition may have affected statistical results.

GMH is a congenital developmental anomaly of the nervous system with an unknown prevalence. In GMH there is restricted

movement of neurons toward the cortex. It has been suggested that the disorder is more common in men and that it may manifest neurological signs in any period of life. [4, 32] IF studies have reported GMH prevalence ranging from 0.2% to 0.7%. [4,5,16] We demonstrated a figure of 0.2% (IFR 2.8%), with the prevalence being unrelated to age and gender.

MCM is a CSF-filled space in the posteroinferior of the brain, which forms as a result of infection, chromosomal anomaly, or any other cause. No prevalence study has been performed yet. It has been reported to cause a variety of neurological symptoms from speech disturbances to catatonia. [33] IF studies have shown a prevalence of 0.2-1%. [3-5,16,22] We demonstrated a prevalence of 0.2% (IFR 2.8%) and there was no correlation with age or gender. We believe that societies' level of development, as well as perinatal follow-ups, can alter MCM prevalences, with viral infections may variably affect pregnancies at regions where no follow-up is made. A low number of cases may have canceled statistical significance with regard to age and gender.

The biggest limitation of our study was its retrospective nature and data limitation about the patient. In the past, data about imaging and diagnoses performed outside our hospital are limited.

Conclusion

IF are common in the brain, MRI examinations and some of them are pathological findings while some are anatomical variations.

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Chapter III

Dolichocolon Findings in MR Enterography

Recep Yilmaz BAYRAKTARLI
(MD), Istanbul Okmeydani Research and Training Hospital Radiology Department

Introduction

In recent years, with the progress of technology, many new methods to screen small intestines have been developed such as fluoroscopy enteroclysis, magnetic resonance (MR enteroclysis), magnetic resonance enterography (MRE), computed tomography enterography (CTE), capsule endoscopy and nuclear transit scintigraphy (Figure 1).

Since colons are seen within imaging area of MR Enterography, large pathologies in these regions can be incidentally evaluated.

In this section, findings of dolichocolon which are seen in MR Enterography evaluations are discussed.

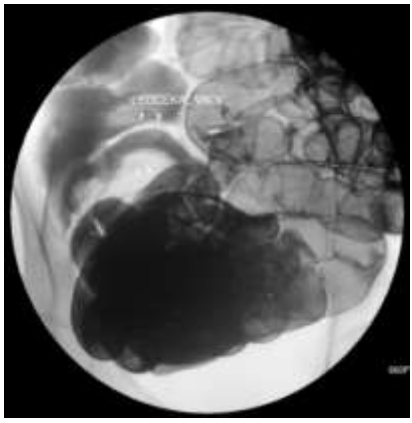

Figure 1a: Enteroclysis
The small intestine is evaluated with a mixture of oral contrast media given through the catheter placed in the third part of the duodenum.

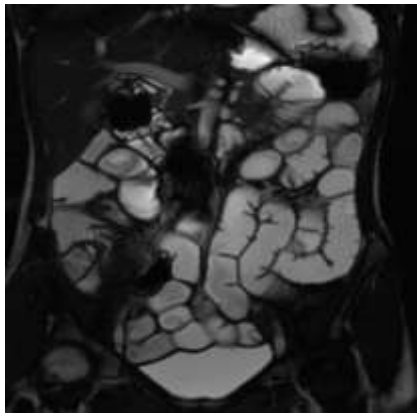

Figure 1b: MR Enteroclysis
Patients whose small intestines were distended in fluoroscopic examination are evaluated by MR Enteroclysis.

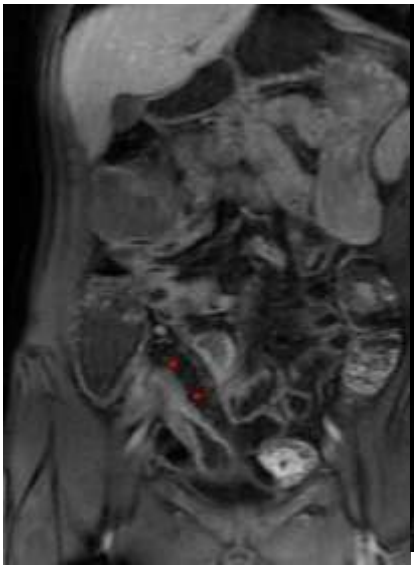

Figure 1c) MR Enterography with contrast
T1 – weighted with contrast, 40 y.o, male, known Crohn's disease, Wall thickening at terminal ileum (straight arrows)

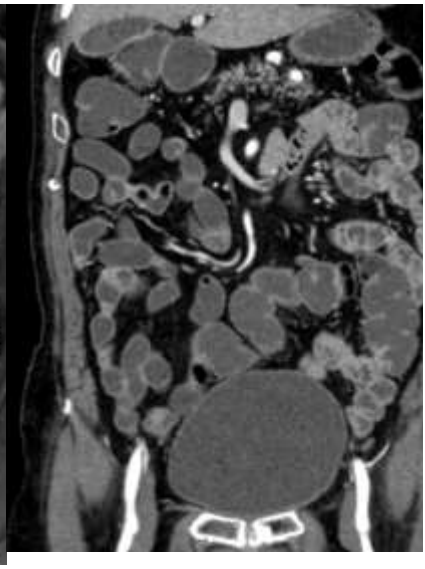

Figure 1d) BT Enterography
Intestines are distended by having the patient drink water which contains 2% mannitol.

MR Enterography

MR Enterography is screening intestines which are distended with oral contrast by rapid MR sequences. It is an examination method that is developed to screen intestines and caecum. This method is mainly used to diagnose inflammatory bowel diseases such as crohn's disease and to evaluate the degree of them. It is also used to investigate inflammatory bowel diseases such as celiac and behcet disease, brid, and causes of anemia (Figue 2). In addition, colons are seen within these screened regions and pathologies, if there is any, are evaluated.

- MR Enterography is mainly used to find;
  - Type of inflammatory bowel disease
  - Single segment or multisegment involvement
  - Active or nonactive
  - Complications (abscess, fistule, brid)
  - Accompanying colonic findings
- Other reasons to request MR Enterography;
  - Constipation

- Abdominal pain
- Distension
- Known crohn's disease control
- Pericular abscess
- Small intestine masses
- IBD such as celiac, behcet disease, tuberculosis
- Brid
- Anemia
- Endometriosis in the small intestine

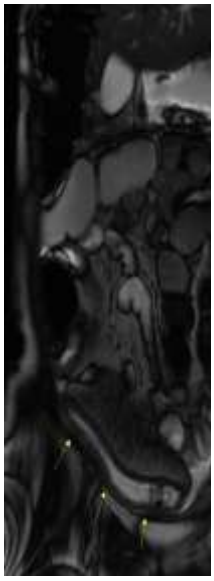

Figure 2a) Coronal T2 – weighted fiesta sequence

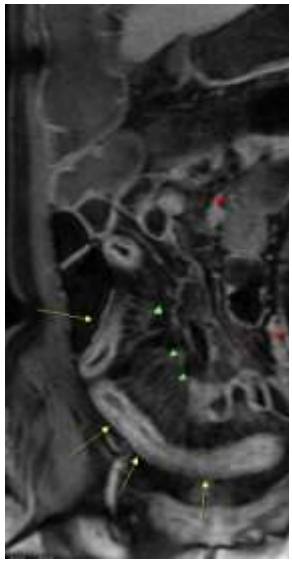

Figure 2b) Coronal T1 – weighted with contrast sequence

55 y/o, female, weight loss, 6-7 times defecation per a day, Crohn's disease. Wall thickening at terminal ileum – with contrast and without contrast (straight arrows), long sigmoid colon (red striped arrows)

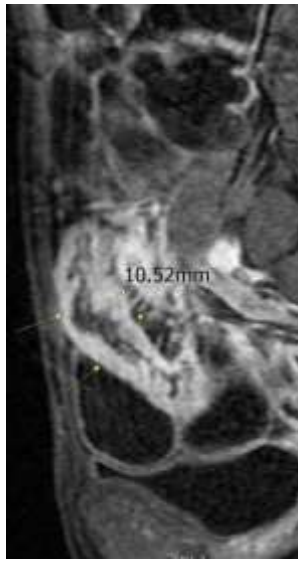

Figure 2c) T1 – weighted with contrast, oblique sagittal,

14 y/o, female, diarrhea and vomitting, active crohn's disease

Findings

368 MR enterography and enteroclysis examinations that were done between 2014-2019 in our clinic showed many incidental redundant sigmoid, long transverse colon, extra loop or wide colon findings. The youngest patient was 8, while the oldest one was 86 years old, and the mean age was found as 40.

MR enterography examinations were asked for these patients suspecting small intestine disease. However, along with small instentine diseases, incidental colon findings were also seen in these examinations. The findings are presented in this paper. In fluoroscopic enteroclysis (herlinger method), the colon segments were excluded from the evaluation since the examination was ended before they enter the image area. All the examinations which segments of colon were seen were evaluated and noted for dolichocolon.

			number	rate
Number of all examinations			368	
Could not evaluated			25	
Evaluated colons			343	
	Normal colon		230	67,05%
	Short colon		1	0,41%
	Dolichocolon	Total	112	32,65%
		High sigmoid	104	30,32%
		Long transverse colon	6	1,74%
		Ekstra loop	2	0,58%

Table 1: Rate of dolichocolon cases found in MR enterography and MR enteroclysis

Colons

Colons are the organ of digestive system that surrounds the small intestines. They have six sections (Figure 3).

1. Caecum; Its average length is 6 cm and width is 7.5 cm.

2. Ascending colon extends from the caecum to the lower face of the liver and is approximately 15-20 cm

3. Transverse colon; The average length is 30 – 60 cm.

4. Descending colon; Its average length is 25 cm and it extends until left iliac fossa.

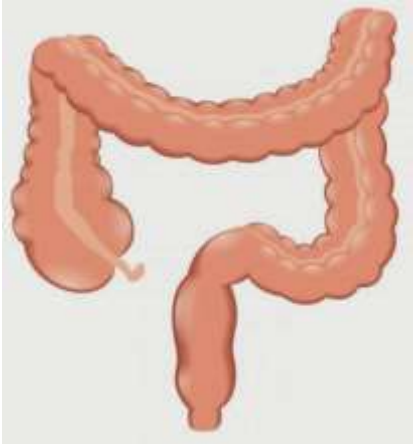

Figure 3: Diagram of colonic segments

5. Sigmoid colon; It is 40 cm on average from minor pelvis to rectum.

6. Rectum; The average length is 12 cm.[1]

Dolichocolon

It is the name given to the colons being variably long (dolicho-, Greek: long). It is mostly congenital, but it may also be acquired. The colons may grow up to 20 cm in older ages.

Symptomps of Dolichocolon

General symptoms of dolichocolon are constipation, cramp-like abdominal pain and, distension. However, other than these symptoms, nonspecific symptoms such as general weakness, headache, mild fever (due to faecal stasis) may also be seen.

Diagnostic criterias of imaging dolichocolon;

- The sigmoid colon goes above the line drawn between the iliac crest (Figure 4),
- The transverse column falls below this line (Figure 4),
- There is an extra loop in the flexures.[2]

Various researches, though not too many, were done to determine types of dolichocolon. Monterossi drew long colon types and published them. Caffey also showed types of dolichocolon by drawings in 1960s (Figure 5). It is seen in the MR Enterographies which were performed in our clinic based on these information that the majority of dolicocolon types are long and redundant sigmoid colon.[2,3,4]

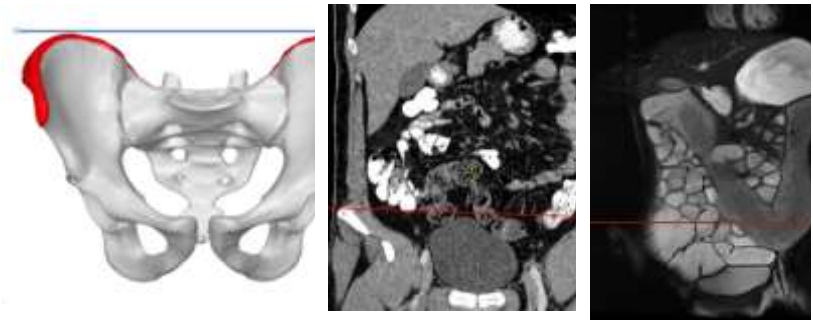

Figure 4: The sigmoid colon goes above the line drawn between the iliac crest.

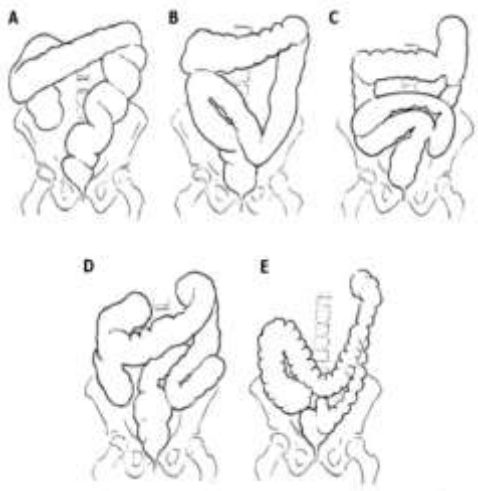

Figure 5: Different types of dolichocolon.

A-C:Redundant Sigmoid colon D: Generalized redundancies E:Low transverse colon [2,4]

Incidence of Dolichocolon

Dolichocolon is anatomical variant however, it is not uncommon either.

There are publications which shows that incedence of dolichocolon is between 1.9% - 28.5%. Raahave showed some of the found rates as below;

- Kantor, 16%, with roentgenogram 258 cases out of 1614
- Müller, 2,4%, 18 cases out of 477
- Larimore, 28,5%, 116 newborns in total of 562 patients
- Bryant, 14%, in 242 cadavers
- Brumer, 30,2%, 32 out of 106 patients with chronic constipation
- Raahave, high rate of dolichocolon in 236 patients with constipation, reported in 2009 [2]

The rate is found as 32,8% in our study. However, our findings shows the rate of dolichocolon in patients with specific symptoms who came for small intestine diseases (Figure 6 and 7).

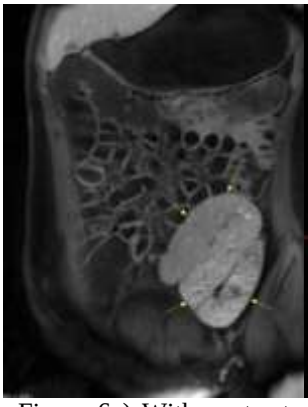

Figure 6a) With contrast T1 – weighted sequence 11 y/o, female, chronic abdominal pain, IBD redundant sigmoid colon (straight arrows)

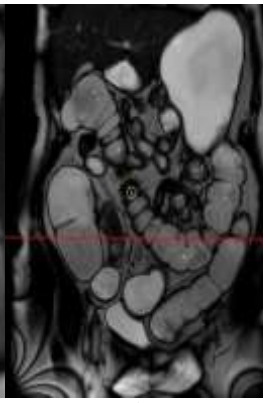

Figure 6c) Long transverse colon; Transverse colon descending below the line drawn from the upper level of the iliac crest

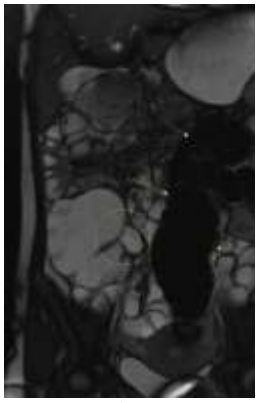

Figure 6c) 19 y/o, female, Continuous diarrhea for 3 years, bilateral pain in the abdomen, Crohn's disease
Coronal T2 – weighted fiesta sequence, Redundant sigmoid (straight arrows), Ileocecal valve (circle)

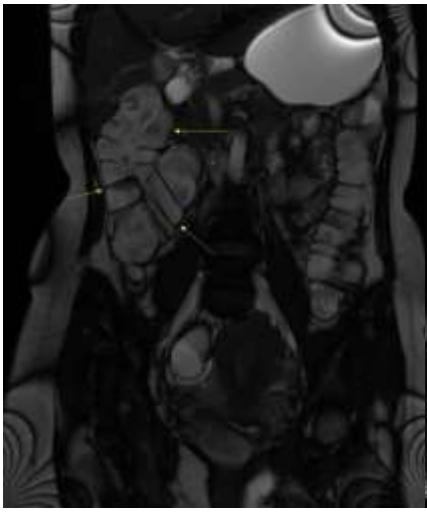

Figure 7a) Coronal T2 – weighted fiesta sequence, Redundant sigmoid (straight arrows) Long caecum, compresses to bladder (striped arrows)

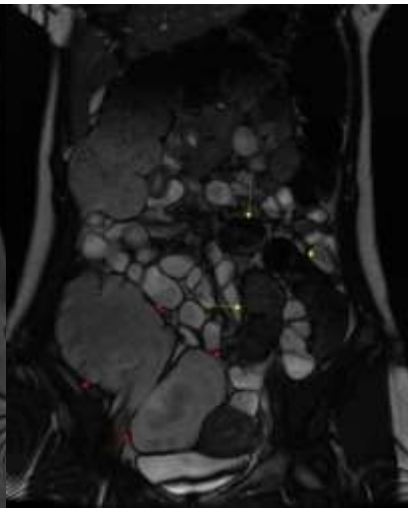

Figure 7b) Coronal T2 – weighted fiesta sequence, long hepatic flexura (straight arrows)

32 y/o, female, pain in inguinal, occasional diarrhea, operated perianal fistula and abscess patient, colonoscopy is normal

SUMMARY

Dolichocolon is an anatomical variant with colonic segments being longer than normal. It is one of the reasons for constipation and also volvulus in children. It should be considered in the persistence of patients' complaints such as constipation and distension. The rate of dolichocolon is more than predictions, and is found as 32.6% in our examination. It is sometimes not noticed during colonoscapy, and it is one of the causes why colonoscopy cannot be completed. Dolichocolon is easy to recognize by MR enterography, and if it is suspected before screening, it can be shown more effective by delayed sequences. Studies should be conducted on the rate of dolichocolon which does not cause any complaints in normal population.

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Chapter IV

Principles of Non-Vitamin K Antagonist Oral Anticoagulant Use in Patients with Non-Valvular Atrial Fibrillation After Percutaneous Coronary Intervention

Eser AÇIKGÖZ

(MD), Ankara Abdurrahman Yurtaslan Oncology Education and Research Hospital, Department of Cardiology

Atrial fibrillation (AF) is the most prevalent cardiac rhythm disturbance which accounts almost 30 percent of hospitalizations due to cardiac arrhythmia. Estimated AF prevalence is 2.7 to 6.1 million in the United States and 8.8 million in Europe. AF prevalence increases with age and is projected to reach 12.1 million in 2030 in the United States. Association of AF and thromboembolic complications such as stroke and systemic embolic events are well known and oral anticoagulant (OAC) use should be considered for all AF patients according to thromboembolic risk profile. While Vitamin K antagonist oral anticoagulants (VKA) have been the drug of choice for anticoagulation in patients with AF, recent invention of non-vitamin K antagonist oral anticoagulants (NOAC) such as dabigatran, rivaroxaban, apixaban and edoxaban provide more efficacious and safer alternatives for non-valvular AF patients.

Coronary artery disease and need for coronary revascularization which necessitate further anti-thrombotic therapy are common among AF patients. Approximately 5 to 10 percent of patients referred to coronary angiography use OAC for AF or other indications. Theoretically, AF patients undergoing percutaneous coronary intervention (PCI) requires both OAC and dual antiplatelet therapy (DAPT) including aspirin and a P2Y12 inhibitor such as clopidogrel, ticagrelor and prasugrel for

thrombotic events due to AF and coronary stents. However, such a triple antithrombotic therapy (TAT) approach increases the risk of major bleeding events. As a result of this and invention of NOACs as safer drugs, randomized controlled trials about alternative two-drug antithrombotic regimens including an OAC and single antiplatelet therapy (SAPT) were performed.

DAPT vs. SAPT after percutaneous coronary intervention

Dual antiplatelet therapy with aspirin and a P2Y12 inhibitor is the standard of care after percutaneous coronary intervention. Improvements in the stent design and invention of more potent P2Y12 inhibitors give rise to clinical trials in order to define whether SAPT is as protective as DAPT with fewer bleeding events after stent implantation. The GLOBAL-LEADERS (A Clinical Study Comparing Two Forms of Antiplatelet Therapy After Stent Implantation) trial demonstrated that DAPT with aspirin and ticagrelor for one month, followed by SAPT with ticagrelor for 23 months gives similar results with DAPT for 12 months followed by aspirin for 12 months. Recent STOPDAPT-2 (ShorT and OPtimal Duration of Dual AntiPlatelet Therapy-2 Study) and SMART-CHOICE (Comparison Between P2Y12 Antagonist Monotherapy and Dual Antiplatelet Therapy After DES) trials revealed that SAPT after short-term DAPT may be superior to long term DAPT in patients implanted newer generation DES.

Oral anticoagulant therapy for non-valvular atrial fibrillation

Results of the ACTIVE W(Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events) and ACTIVE A (Effect of Clopidogrel Added to Aspirin in Patients with Atrial Fibrillation) trials demonstrated that dual antiplatelet therapy with aspirin and clopidogrel is superior to aspirin but inferior to warfarin for the prevention of embolic events with similar bleeding rates in patients with atrial fibrillation. Thus, role of the antiplatelet therapy for stroke prevention in AF is limited.

Both 2019 ACC/AHA/HRS and 2016 ESC guidelines for AF recommend risk stratification with CHA2DS2-VASc (Congestive Heart failure, hypertension, Age > 75 years [2 points], Diabetes, Stroke [doubled], Vascular disease, Age 65 to 74 years, and Sex

[female]) score in patients with AF. OAC, preferably NOAC is indicated in patients with a CHA2DS2-VASc score > 2 in men or > 3 in women. Indication of OAC for patients with a CHA2DS2-VASc score > 1 in men or > 2 in women is less clear and should be individualized. It should be kept in mind that NOACs are not indicated in case of moderate to severe mitral stenosis and mechanical valves.

Antithrombotic therapy after PCI in AF patients: Double vs. Triple

Doubts about efficacy of double antithrombotic therapy (DAT) and safety of TAT are main concerns in this scenario. In an attempt to elucidate the safety of different antithrombotic regimens, a recent nationwide Danish cohort study strikingly showed that in comparison with VKA monotherapy, adjusted hazard ratios of major bleeding were 1.13 (95% CI, 1.06–1.19) for dual antiplatelet therapy, 1.82 (95% CI, 1.76–1.89) for therapy with a VKA and an antiplatelet drug, 1.28 (95% CI, 1.13–1.44) for therapy of a NOAC with an antiplatelet drug, 3.73 (95% CI, 3.23–4.31) for VKA triple therapy, and 2.28 (95% CI, 1.67–3.12) for NOAC triple therapy. In VKA era, WOEST (Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention) trial showed that DAT with clopidogrel and VKA is associated with a significant reduction in bleeding complications compared to patients receiving TAT with clopidogrel, aspirin and VKA. ISAR-TRIPLE (Duration of triple therapy in patients requiring oral anticoagulation after drug-eluting stent implantation) is another VKA trial and revealed that 6 weeks of clopidogrel therapy in addition to aspirin and VKA gives similar net clinical outcomes compared to 6 months of clopidogrel therapy after DES implantation. Although these two trials were encouraging for DAT with VKA and clopidogrel, neither had enough power to detect significant differences in ischaemic endpoints. Thereafter, NOACs were tested in similar scenarios in trials named PIONEER AF-PCI(Prevention of bleeding in patients with AF undergoing PCI) , RE-DUAL PCI (Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation) and AUGUSTUS(Antithrombotic therapy after acute coronary syndrome or PCI in atrial fibrillation). In PIONEER AF-PCI trial, 2,214 patients with non-valvular AF and recent stent implantation were randomized to three groups. Group 1 was given Rivaroxaban 10-15 mg and a P2Y12 inhibitor for 12

months, group 2 was given Rivaroxaban 2.5mg BID and DAPT for 1, 6 or 12 months and group 3 was given warfarin and DAPT for 1, 6 or 12 months. Clinically significant bleeding was lower in group 1 and 2 than group 3 (16.8% vs. 18.0% vs. 26.7%). However, the study was not powered to detect ischaemic endpoints. In addition, rivaroxaban doses used in this study were not FDA approved. RE-DUAL PCI randomized 2,725 AF patients underwent PCI to 3 groups as triple therapy with aspirin, clopidogrel/ticagrelor and warfarin; dabigatran 150 mg BID and clopidogrel/ticagrelor and dabigatran 110 mg BID and clopidogrel/ticagrelor. Compared to TAT, DAT with dabigatran causes an 11.5% absolute reduction in major and clinically significant minor bleeding. Compared to dabigatran 150 mg group, dabigatran 110 mg group has statistically non-significant 11% more thromboembolic events. RE-DUAL PCI trial stopped before it reached the initial target sample size of 8,520 and thus underpowered to assess thrombotic events. Since only 12% of patients received ticagrelor, generalizability of the study findings to this drug is not possible. Furthermore, due to the study design it is not clear whether the reduction in bleeding was a result of use of Dabigatran instead of warfarin, avoidance of aspirin or both. In AUGUSTUS, 4,614 AF patients with recent acute coronary syndrome(ACS) or PCI were randomized to apixaban 5 mg BID versus VKA and to aspirin versus placebo in a 2 x 2 factorial design. The study revealed that apixaban use is associated with a 4.2% absolute reduction in major or clinically significant minor bleeding compared to warfarin at 6 months. Death or hospitalization was also reduced by 3.9% in apixaban group. Triple therapy with VKA, aspirin and P2Y12 inhibitor was associated with 7.1% increase in bleeding. In contrast to PIONEER AF-PCI and RE-DUAL PCI, AUGUSTUS has enough statistical power to assess thrombotic events, which were found similar between groups. 90% of patients received clopidogrel and extrapolation of study results to ticagrelor and prasugrel is not possible. Unlike PIONEER AF-PCI and RE-DUAL PCI, 2 x 2 factorial design of AUGUSTUS render it possible to evaluate individual contribution of apixaban and aspirin to clinical outcomes. Moreover, AUGUSTUS included medically managed ACS patients for the first time. Results of the ENTRUST-AF PCI study was recently made public in ESC 2019 congress. The study showed that in patients with atrial fibrillation who underwent successful PCI, edoxaban plus clopidogrel is non-inferior but not superior to triple therapy regarding both ischemic and bleeding outcomes. A recent

meta-analysis including WOEST, ISAR-TRIPLE, PIONEER AF-PCI, and RE-DUAL PCI trials showed that while major and minor bleeding events were reduced by 47% in DAT, all-cause and cardiac death, myocardial infarction, stent thrombosis, or stroke rates were similar between TAT and DAT groups.

Risk scores for thrombotic events and bleeding

Individual risk factors for thrombosis and bleeding or risk scores such as SYNTAX and GRACE for thrombosis or HAS-BLED, ATRIA or HEMORR(2)HAGES for bleeding can be used to aid selection of P2Y12 inhibitor or duration of TAT. Performance of risk scores in predicting bleeding events is generally weak. Although ESC guidelines recommend HAS-BLED score for estimation of bleeding risk, RE-DUAL PCI trial showed that benefit of DAT with dabigatran was irrespective of baseline HAS-BLED score.

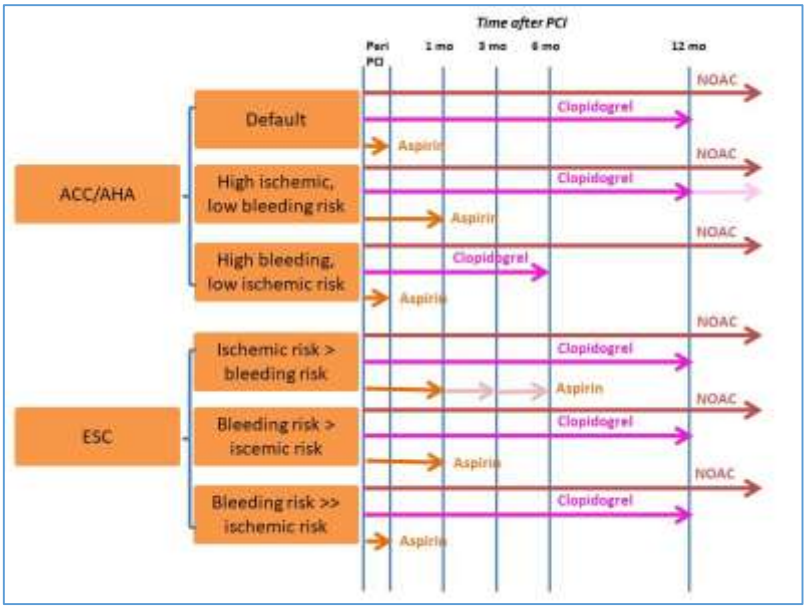

Figure 1. Recommendations of American and European guidelines about thrombotic therapy after PCI in patients with AF.

Periprocedural recommendations

Avoidance of unnecessary PCI procedures with prudent patient selection is especially important in patients already on

OAC. NOAKs should be chosen over VKAs and radial access should be preferred to reduce bleeding rates. Interruption of OAC before the procedure is recommended for elective procedures. Additional heparin should be administered anyway and bivalirudine use may be considered particularly in high bleeding risk. Glycoprotein IIb-IIIa inhibitors should be reserved for bail-out situations.

OAC dosage after PCI

If TAT is planned, INR should be kept between 2.0-2.5 and dabigatran 110 mg BID, rivaroxaban 15 mg OD or apixaban 5 mg BID should be used. Established stroke prevention doses can be used in DAT.

Duration of TAT

ACC/AHA recommends peri-PCI only TAT whenever possible. 1 month TAT is recommended for patients at high thrombus and low bleeding risk. On the other hand, ESC recommends 1 to 6 months for elective procedures and 3 to 6 months TAT for ACS. Low dose aspirin and clopidogrel as P2Y12 inhibitor should be given in TAT. For DAT, clopidogrel rather than aspirin should be given. After 12 months, SAPT should also be stopped in most patients. Recommendations of American and European guidelines are summarized in figure 1.

Conclusions

Recent studies demonstrated that a dual anti-thrombotic therapy strategy clearly reduces bleeding complications after PCI in AF patients who are on OAC therapy. It was also shown that NOAKs are superior to VKA regarding bleeding events. However, duration of TAT is still under debate as seen in the recommendations of American and European guidelines. Integration of the results of AUGUSTUS and ENTRUST-AF may eliminate the disagreement between guidelines. Until then, duration of the TAT should be decided case-by-case.

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Chapter V

The Reverse Radial Forearm Flap for Soft Tissue Reconstruction of the Hand

Hasan Murat ERGANI

(MD), Çankırı Stated Hospital, Çankırı, Turkey,
dr.hasanmrt_06@hotmail.com

Introduction

The radial forearm flap, developed in China as a free flap, was originally used after release of burn scar contractures of the neck and for intraoral reconstruction after resection of head and neck cancer (1). While the flap was thin and pliable, it was used to reconstruct the contralateral hand injuries at the beginning, and it was seen that the flap could be harvested retrograd flow-through from the palmar arches to the ulnar artery after ligation of the proximal radial artery and it was used as a radial forearm flap on the distal base (2).Lin et al. (3) examined the venous drainage of the radial forearm flap with reverse-flow, and the comminication between the cephalic vein and the assocaiated vena concomitantes.As a result it was thought that free flaps could be used in the reconstruction of existing defects in this region.

The reverse radial forearm (RRF) flap can be used to cover moderate-sized defects of the dorsal or volar hand extending to the metacarpophalangeal joints as well as for treatment of median nerve neuromas (4).The flap can be used in many ways and the radial artery perforator alone without sacrificing of a major artery to the hand.İt can be used with or without skin and fascia.

Radial forearm flap is used in the reconstruction of soft tissue defects of the hand and wrist area.There are approximately 10 small perforators (0.3-0.5 mm in diameter)

arising from the radial artery around the radial styloid.These perforators can be used to harvest the flap without sacrificing the radial artery. Weinzweing et al. (5), Chang et al. (6) described the connections between septofasciocutaneous perforators and the transverse carpal vascular plexus around radial styloid in their anatomical and clinical studies. . This plexus provides a robust blood supply to the forearm fascia, subcutaneous tissue, and skin.

Hand and finger injuries can cause soft tissue damage and may also result in expose bones,tendons,nerves and vessels. The protection of the vital structures and function of the hand is provided by the appropriate skin covering (7). Optimal hand reconstrukction allows the patient to use his/her hand in a functional way. The reverse radial forearm flap is ideally suited to many hand defects because it consists of the same thin, mobile skin, as the dorsum of the hand . For those defects that are limited to palmar or dorsal aspects of the hand and wrist,a pedicled, reverse radial forearm flap may be performed without the need for an additional contralateral donor site and without needing to attach the hand to the groin or chest.

Reverse radial forearm flap is used in the reconstruction of defects, including the fingers, extending to the volar or dorsal metacarpopahalangeal joints. A preoperative Allen test confirming good collateral low through the ulnar artery and palmar arches is absolutely mandatory. There are certain defects for which the reverse radial forearm flap is especially well suited, including defects of the dorsal and palmar aspects of the hand and wrist due to trauma or after tumor resection,after release of thumb-index finger web space contractures,and for coverage of thumb amputations in preparation for subsequent toe-to-thumb transfer.

The reverse radial forearm flap can also be used as adipofacial flap without any additional comorbidity and without bulky tissue.Adipofacial flap can be used: persistent carpal tunnel syndrome and de-quervain syndrome resistant to surgery and medical treatment.

Technique

The brachial artery is divided into two parts as the radial and ulnar artery, approximately 2 cm distal to the antecubital fossa.The line drawn from the antecubital fossa hill to the radial styloid distance determines the radial artery line (Figure 1).The proximal

forearm is located just beneath the ulnar border of the brachioradialis muscle at the surface of the pronator teres muscle. More distally,the radial artery lies radial to the flexor carpi radialis tendon, superficial to the flexor pollicis longus muscle, accompanied by 2 venae comitantes. The radial artery pursues a relatively superficial course down the forearm from its origin at the bifurcation of the brachial artery to just distal to the radial styloid,where it passes deep to the abductor pollicis longus and extensor pollicis brevis tendons through the anatomic snuffbox. This region is divided into 2 branches as superficial and deep distal.

Throughout its course, the artery gives off branches to a plexus of vessels in the overlying deep fascia that supply the skin of the anterior and radiodorsal surfaces of the forearm. Similarly, deep fascial branches supply the periosteum of the distal half of the radius between the pronator teres and brachioradialis, providing the basis for a reverse osteocutaneous radial forearm flap that can potentially be used for thumb reconstruction (8).

Radial artery line is determined and the flap is measured after debridement according to the size of the defect. After exsanguination, the tourniquet is inflated and the margins of the flap are incised, as well as a lazy s incision extending proximally from the distal proximal margin overlying the course and find and ligated of the radial artery. The deep fascia should be incised all around the flap, thereby gaining the plane of dissection. Extreme care should be taken to preserve the superficial branch of the radial nerve and the lateral antebrachial cutaneous nerve.we prefer to suture with 4-0 vicryl the deep fascia to the skin at several points around the flap to prevent shearing during elevation.The flap is harvested from ulnar to the radial. After the flap has been elevated from the ulnar margin across to the flexor carpi radialis tendon, traction on this tendon in an ulnar direction will reveal the radial artery and venae comitantes.The septum is harvested from the proximal to the distal and the branches of the radial artery is ligated to the muscles and the bone. In this way, the vascular pedicle can be visualized directly to avoid any kinking, twisting,or compression. The tourniquet is then deflated. After hemostasis of both the defect and the donor sitenThe flap is then inset directly into the defect.

Case 1

A 36-year-old female patient was injured by electric burn. She was sustained a severe injury to the sekond,third and fourth web space,thenar eminence and proximal thumb.There was a 8x6 cm skin defect , including first web space and interphalangeal joint. the tendons of the fingers ,flexor tendons,lumbrical tendons and interosseos tendons. All fingers were hypoesthesia and puncture of fingers with capiller bleeding.No flexion movement on all fingers except thumb.Firstly radial forearm flap was planned for hand defects and reconstructed.Donor area had split thickness graft on the anterolateral thigh.After 6 months were created web space and tendon prothesis was applied for movement. Reconstruction of the tendon in the first stage when the pulleys were intact in the case of damaged pulleys the tendon was reconstructed with tendon graft after three months following prothesis . Tensor fascia lata was harvested and reconstructed flexion movement of finger.(Figure 2)

Case 2

A 34-year-old male injured in a gun-shot injury,The injury resulted in a 3x3 cm defect, including interphalangeal joint,both digital arteries and dorsal and volar soft tissues.Extensor tendons were intact (Figure 3).Bone defect was reconstructed by a bone graft harvested from ipsilateral iliac crest.İnterphalangeal joint artrodesis at 30 degree flexion was performed.A distally pedicled radial forearm flap was harvested in standart fashion,transferred into the defect.The distal radial lateral digital artery was prepared for anastomosis.A vein graft was harvested from the dorsum of the hand to compensate for the diameter difference in between vessels.The reverse radial artery was anastomosed to the vein graft.A fish mouth incision was applied to the distal of vein graft to faciliatate the anastamosis.The flap healed uneventfully and the thumb was well vascularized.(Figure 4).

Case 3

A 45 year old male injured unkonown insect.The injury resulted in a 6x5 cm defect including dorsal metacarpal area.(Figure 5).Extensor tendons were nonviabl and debrided.The patient was consulted infection disease and was given antibioteraphy for about 2 weeks.Radial forearm flap was planned

and tendon reconstruction was perfomed simultaneously. Tensor fascia lata was harvested anterolateral thigh. (Figure 6). Radial forearm donor areas was reconstructed split thickness skin graft.

Discussion

Soft tissue defects in hand must be reconstructed with thin, pliable and hairless skin. A single-step reconstruction procedure decreases immobilization and risk of contracture (9). Although the success and results of free flaps are excellent in the defects that occur in the hand, the localized planned flaps(pia flap,radial forearm flap,metakarpal flap…) provide easier one-stage reconstruction with similar tissue in a shorter time. Distant flaps, including the groin and inferior hypogastric flaps, have some drawbacks, such as requiring multistage operations necessitating prolonged immobilization, which may increase morbidity and lengthen hospital stay (10). Liu et al(11) reported their experience of reconstructing hand defects with the use of reverse forearm flap that does not contain the radial or ulnar artery.

As shown in the functional outcomes of this study, radial forearm flaps were returned to their daily activities in a short time, while at the same time they were single stage and reconstructed with similar tissue.

In order to allow early mobilization and to reduce the cost and duration of treatment, it was accepted that soft skin cover should be made in the early period (12). If local flaps are not suitable, free flaps are the preferred treatment modalities due to functional and aesthetic results. It is a suitable option in the treatment of anterior thigh,,parascaphular flap, serratus and temporal facial flaps (13).

There are two majör disadvantages of this flap ,one of which is majör artery sacrifing and another one is donor site morbidity. All efforts should be made to improve donor site appearance. We therefore prefer to harvest the flap as a fascial flap as described by Jin (14), especially in staged coverage. This variation offers a superior esthetic outcome of the donor site as well as the recipient site (15).

Compared to the posterior interosseous island flap (pia) defined in 1985 by Zancolli (16), the ulnar and radial artery are protected, but also have advantages due to similar tissue color

and primary closure of the donor site (defect <5 cm). Since the existing anatomy of the flap is mixed and the existing pedicle is thin from its proximity to the posterior interosseous nerve that provides finger exten- sions and the more frequent venous congestion in the flap has restricted the preference of the flap. In the studies performed with pia flap, 23% complication was reported (17). Compared to this flap, reverse radial forearm flap is harvested more quickly, hospitalization time is less, complication rates can be used in volar defects

Another alternative fasciocutaneous flap is based on a consistent dorsal branch of the ulnar artery as described by Becker and Gilbert (18). The main disadvantage is the considerably shorter vascular pedicle and the limited arc of rotation,which only allows coverage of the proximal palm and ulnar dorsal, but not the radial border of the hand. The RRF pedicle is long and it can cover the defect to the extent that the palmar arc is intact.

Conclusion

As a result, the reverse radial forearm flap for the reconstruction of the defect in the hand region may be preferred due to its rapid removal, similar texture, thin and pliable

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Figure 1

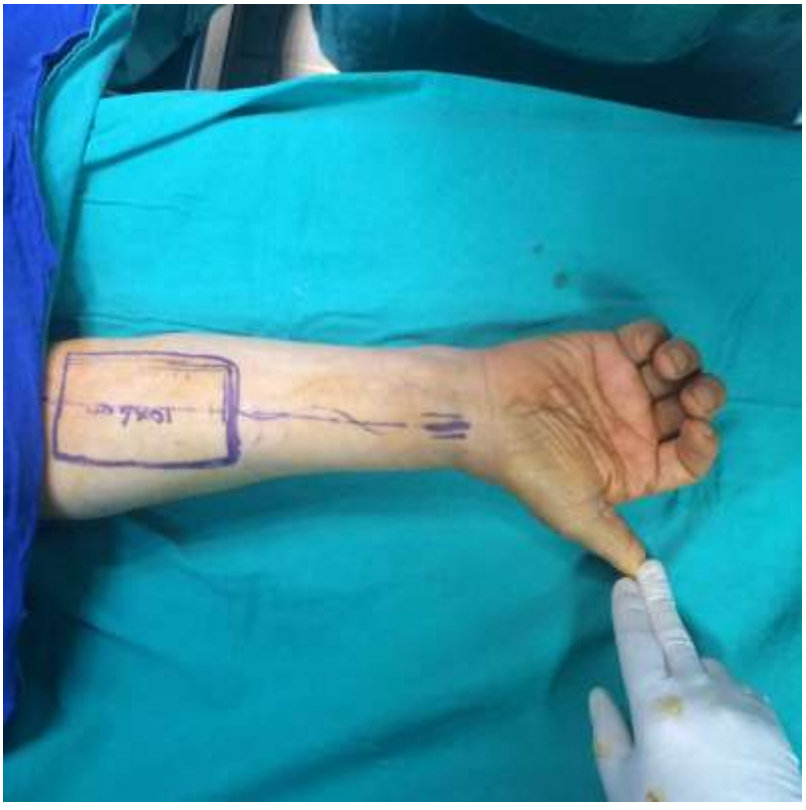

Figure 2

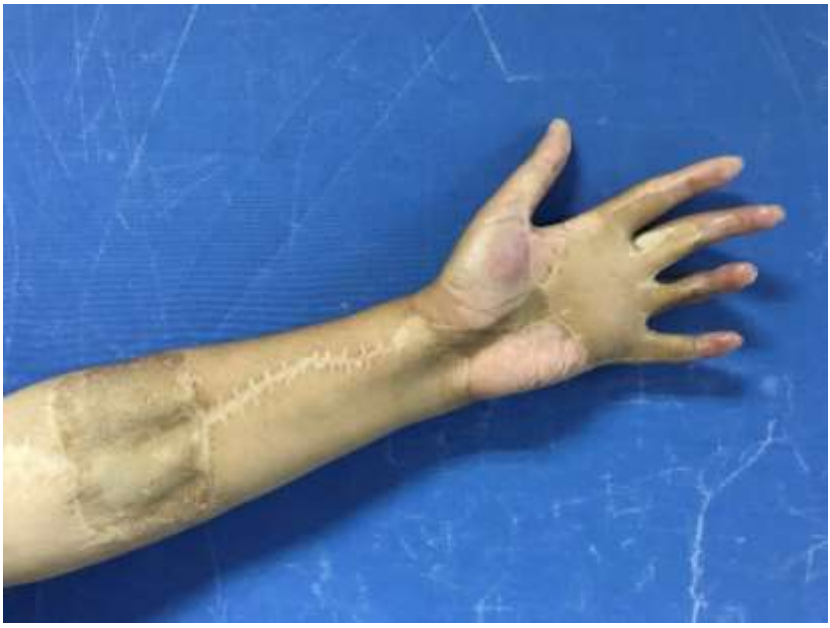

Figure 3

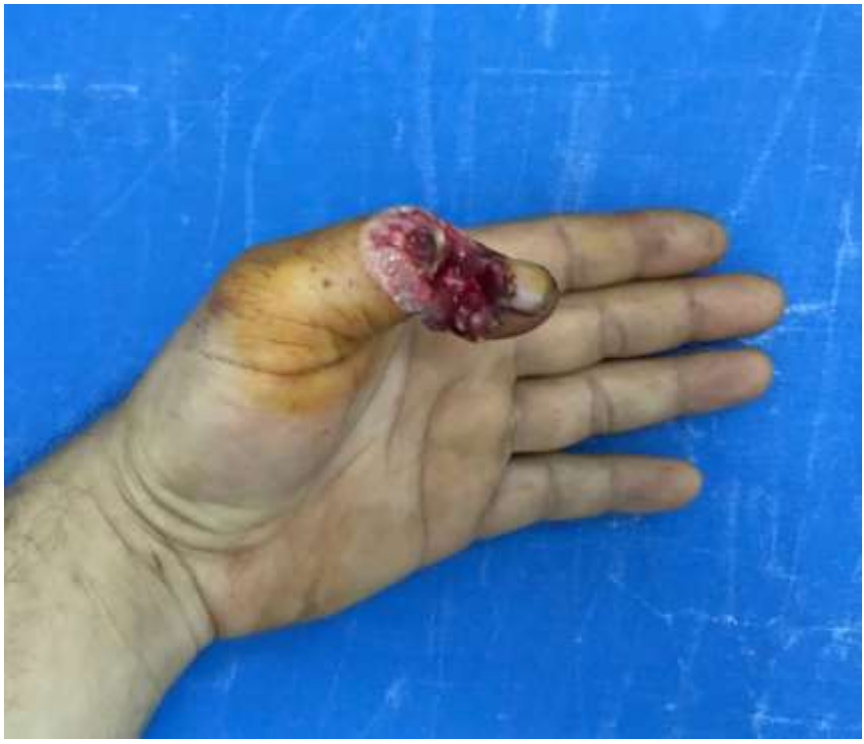

Figure 4

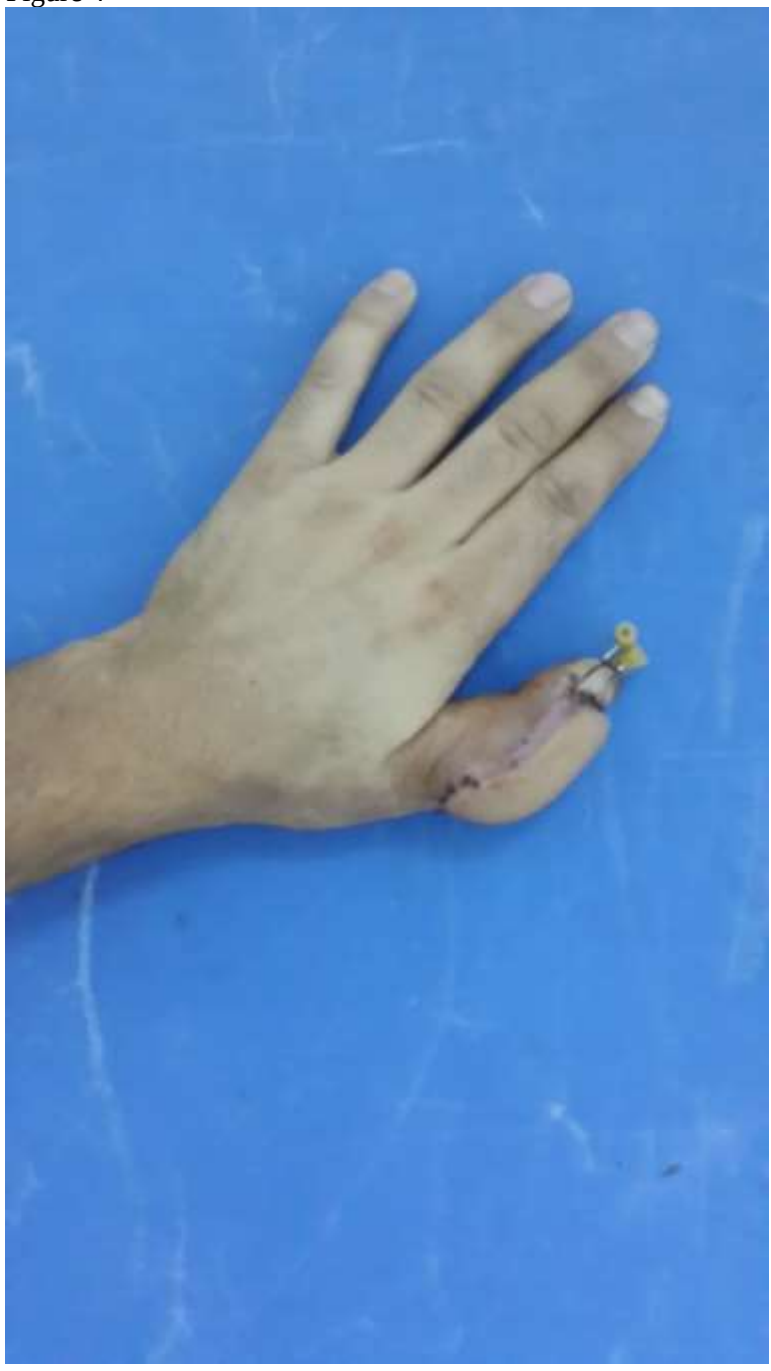

Figure 5

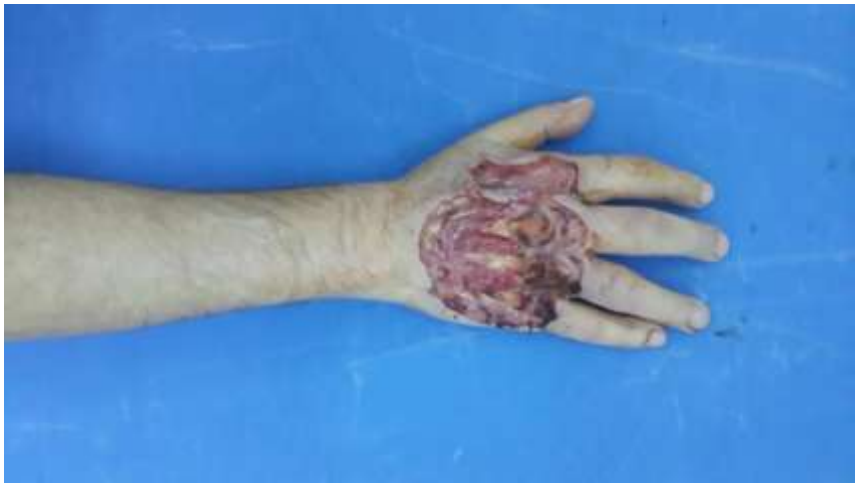

Figure 6

Chapter VI

Effect of Urinary Incontinence, Overactive Bladder and Bladder Pain Syndrome on Female Sexual Dysfunction

Mehmet Yılmaz SALMAN

Sancaktepe Sehit Prof. Dr. Ilhan Varank Training and Research Hospital, Urology, Istanbul, Turkey, mdyilmaz@gmail.com

Sexual Function and Dysfunction in Women

Sexuality is an integral part of human life and a healthy sexual life is one of the most important parameters of health and quality of life.

Studies performed by Kinsey in 1950s and Master & Johnson im 1960s are the first studies that have been conducted on the definition of sexual response in men and women. In 1966, Master & Johnson described the reactions developing against arousal and reported that sexual response is a linear model consisting of four phases as excitement, plateau, orgasm, and satisfaction. In the Basson model developed based on female sexual experiences, female sexual response was defined as a circular rather than linear mode. According to the Basson's model, emotional and relational intimacy has been accepted as the most important power that motivates physical and sexual behaviour[1].

Another important factor is the status of the sexual partner. In a study by Patel et al., the most important factor for arousal, orgasm and sexual pleasure has been reported as status of the sexual partner[2]. Recently, Tiefer described the presence of a nongenital component in female sexual happiness. According to Tiefer, respect, mutual understanding, emotional dependency and sincerity play an important role in the occurrence of sexual activity and intercourse[3].

Female sexual dysfunction (FSD) is age-related and progressive and very common in patients with lower urinary tract symptoms[4-14]. These data are of utmost importance for physicians dealing with women's health, especially because urinary incontinence, overactive bladder syndrome (OAB), voiding-phase LUTS, and bladder pain syndrome (BPS) are exceedingly common and increasing in incidence worldwide[15,16]. Sexual dysfunction has been reported between 24% and 64% in women with lower urinary symptoms[5-7,17].

Sexual dysfunction has been found in 64% of sexually active women who presented to urogynecology clinics[11]. Although FSD is a very common problem, A recent study by the American Urogynecologic Society with 471 gynecologists revealed that only a very small proportion of patients is examined for sexual dysfunction[18]. In a community-based study from England, it was found that 54% of women had experienced at least one sexual problem which lasts for at least 1 month within the last 1 year, and this sexual problem was at a level enough to prevent sexual intercourse in 62% of them. However, only 21% of these women had received help[19]. A study from the United States with 3807 women who had FSD problem revealed that the most important factors preventing women to seek help were embarrassment, and thinking that healthcare personnel cannot help. In this study, only 42% of the women received help from their gynecologists[20].

The worldwide incidence of urinary incontinence (UI) is estimated between 5,2% and 70,8%[21]. The incidence of UI varies between 25,8% and 68,8%[22,23]. Whereas the incidence of overactive bladder syndrome (OAB) is 17% on average in women[24]. In a comprehensive study on bladder pain syndrome (BPS), a total of 32,474 women were interviewed via phone, and the incidence was found as approximately 2,7%[25].

Evaluation of The Patients and Query Forms

Query forms are of paramount importance in the evaluation of a person’s quality of life and sexual competence and treatment planning[26]. The most commonly used query forms are as follows (Table 1).

- Psychosocial Adjustment to Illness Scale (PAIS),
- Brief Index of sexual Functioning-Women (BISF-W),
- McCoy Female Sexuality Questionnaire (MFSQ),

- Female Sexual Function Index (FSFI),
- The Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ),
- Golombok-Rust Inventory of Sexual Satisfaction (GRISS)

Table 1: Common used query forms in the evaluating of female secual functioning

QUERY FORM	CONTENT
Female Sexual Function Index (FSFI)	Desire, Lubrication, Arousal, Orgasm, Pain, Satisfaction
Pelvic Organ Prolapse/ Incontinence Sexual Questionnaire (PISQ)	Emotional, Physical, Partner Related
McCoy Female Sexuality Questionnaire (MFSQ)	Sexual Interest, Satisfaction/Frequency of Intercourse, Lubrication, Orgasm, Partner
Golombok-Rust Inventory of Sexual Satisfaction (GRISS)	Anorgasmia, Sexual Anorexia, avoidance of intercourse, Vaginismus, Dissatisfaction
Brief Index of Sexual Functioning-Women (BISF-W)	Sexual Desire, Arousal, Frequency of Intercourse, Starting the Intercourse, Satisfaction, Partner Compatibility, Orgasm, Sexual Problems
Psychosocial Adjustment to Illness Scale (PAIS)	Quality, Sexual Interest, Frequency of Intercourse, Satisfaction, Incompatibility, Dysfunction

Attempts have been made for the classification of female sexual dysfunctions utilizing these forms (sexual interest/decreased desire, arousal disorders, orgam disorders, pain, vaginismus and sexual anxiety disorder). On the other hand, onset time of sexual function, and the settings where sexual functioning occur should be taken into account independently of sexual functioning disorders. If the problem has been experienced from the first sexual experience of the person, the presence of primary sexual dysfunction can be mentioned. Whereas in the secondary sexual functioning disorders, there is a satisfactory period in which the

person has not experienced any sexual function dysfunction in sexual life, and the problem manifests later[27,28].

Urınary Incontinence and Sexual Dysfunction

UI has been defined by the International Continence Society as involuntary leakage of urine, which is a social and hygienical problem occurring due to various reasons, and can be objectively identified[29]. The prevalence of UI is estimated as 5,2% to 70,8% worldwide[21]. The prevalence of UI varies between 25,8% and 68,8% in Turkey[22,23]. In a recent study conducted in our country with women in menopausal period, this rate was reported as 56%, and in another study UI was found in 50% of patients, but only 18% of these patients have presented to a physician for treatment[30,31].

In a study on 216 women with the complaint of UI, decreased sexual desire in 34%, sexual arousal disorder in 23%, and orgasm failure in 11% of the participants[5]. In Turkey, patients with UI experience decreased frequency of coitus and sexual desire by 83,6%, decreased sexual satisfaction by 78,1%, difficulty in orgasm by 77,7%, pain during intercourse by 45,3%[32]. Of women suffering UI 11-77% experience urinary incontinence during coitus[33,34-38]. The forms of leakage of urine may differ depending on the type of urinary incontinence (leakage of urine during orgasm/penetration). Whereas leakage during penetration is most common in urinary stress incontinence, this is more commonly seen during orgasm in detrusor overactivity and urge incontinence[33]. Urinary incontinence during intercours may negatively affect self-confidence and self-respect, leading to decreased sexual desire, shortened duration of intercourse, and problems during coitus and subsequently in satisfaction[33]. Urinary incontinence during intercourse has been reported to result from the displacement of the bladder neck, stretching of the anterior vaginal wall and bladder neck, urethral sphincter failure and detrusor contractions due to stimulation of the bladder and trigone during itercourse[39]. Beji et al. investigating sexual behaviours of women with urinary incontinence during intercourse (2003) found that 50% of these women keep their incontinence and do not inform their spouses, 28% avoid intercourse with their partners, 25% convince themself that this is not a problem, 19% urinate before intercourse, 19% break the intercourse short, and 6% have anal sex[40].

In a study by Aydınoğlu et al. investigating effect of lower urinary system symptoms on female sexual health, FSD was found in 31 of 39 patients and 5 of healthy women[41].

Aslan et al. applied a query form including questions about sexual desire, arousal, lubrication, orgasm, sexual satisfaction and pain, in 21 premenopausal women with incontinence. There was a significant difference in all situations except for pain. In addition, sexual dysfunction was investigated in UI subtypes, and but no significant difference was found among the subtypes[42].

In a study by Çoksuer et al., associations between UI subtypes and FSD were studied. In that study, 118 patients were asked to fill PISQ-12 query form. Total and physical scores were found to be significantly higher in women with detrusor overactivity compared to women with stress and mixed type incontinence. Similarly, total and physical scores were significantly higher in women with stress incontişnence compared to women with mixed type incontinence. Whereas no significant difference was observed between UI subtypes in emotional and partner-related scores[43].

In a study by Salonia et al. FSFI query form was used. In that study conducted on 216 women with the complaint of UI, FSD was found in 99 patients (46%), and decreased sexual desire was found in 34%, sexual arousal disorder in 23%, orgasm failure in 15%, and pain in 44% of these patients. In addition, when the patients were compared with control subjects, a significant difference was observed in desire, lubrication, satisfaction and pain scores (Table 2)[5].

Table 2: Significant results from the study by Salonia et al.

	Patient	**Control**	***p***
Desire	2	3,2	<0,01
Lubrication	3,2	4,4	<0,01
Satisfaction	2,7	4	<0,01
Pain	1,8	4	<0,001

In a study by Sako et al., 576 female hospital workers were given FSFI forms and 146 from 276 persons who filled the form were evaluated. While nos significant differences were found in the scores of the groups with and without lower urinary system

symptoms (LUSS), while a significant difference was found in desire, arousal, lubrication and total scores between the groups with and without stress incontinence (Table 3)[44].

Table 3: Significant results from the study by Sako et al.

	LUSS (+)	**LUSS (-)**	***p***	**Stress Incontinence (+)**	**Stress Incontinence (-)**	***p***
esire	3,0	3,0	0,597	2,7	3,1	0,034*
Lubrication	3,1	3,5	0,072	2,5	3,6	0,001*
Satisfaction	4,1	4,5	0,110	3,4	4,6	0,001*
in	21,6	23,2	0,057	19,4	23,3	0,004*

In a study by Kime et al., 3372 women were asked a total of 23 questions consisting of 6 groups via the internet, overactive bladder syndrome was found in 12.7%, and UI in 21% of the participants. FSD was found by 16.1% in the groups with OAB and 2.6% in the group without OAB ($p<0.01$). Similarly, FSD was found by 12.4% in the group with UI, and 3.3% in the groups without UI ($p<0.01$). In conclusion, sexual problems or difficulty were significantly higher in the groups with UI compared to the other groups[45].

Overactive Bladder and Sexual Dysfunction

Another important problem is overactive bladder (OAB), which can be defined feeling of urgency and frequent urination with or without urinary incontinence. People with OAB have social and psychological problems that disrupt quality of life as well as sexual functions. The prevalence of OAN is 17% on average in women over 18 years old[24]. According to Salonia, the rate of FSD is 46% in women with urinary incontinence or OAB[5].

Yaşar et al. investigated the effect of urinary disorder on sexual function in women with overactive bladder, and found that overactive bladder may cause sexual dysfunction in women, and in addition incontinence is one of the factors impairing orgasm satisfaction in women with overactive bladder[46].

Studies with wide series have shown that decreased desire, arousal, and lubrication, orgasm disorders, decreased satisfaction and complaints such as pain were higher in women with OAB and UI compared to women without urinary complaints[5,42]. However, some studies have argued that urinary complaints are not associated with FSD[2].

In a study with 1988 women who have lower urinary system complaints, 70% of patients with stress incontinence and 4% of patients with OAB suffered from urinary incontinence during coitus, while 42% of patients with stress incontinence and 3% of patients with OAB have incontinence during coitus[47].

In a study with 112 sexually active women who were urodynamically diagnosed withOAB and 165 healthy women without urinary symptoms, FSFI query forms were used, and sexual dysfunction was found by 22% in the control groups (FSFI score <26.5), and 47% in the OAB group. The scores were lower in all the 6 groups in FSFI forms in the OAB group[48].

Bladder Pain Syndrome and Sexual Dysfunction

Interstitial cystitis / bladder pain syndrome is a chronic inflammatory disease of the bladder with unknown etiology. This disease which is mostly seen in women and is characterized by dysuria, nocturia, pollakiuria and severe suprapubic pain may lead to morbidity of various degrees. The disease begin in about 40 years of life, however 25% of patients are under 30 years old. Sometimes, symptoms of the disease may be severe, negatively affecting patients' quality of life[49]. Studies have found that quality of life was lower in patients with interstitial cystitis even than the patients with chronic renal failure[50].

The incidence of FSD has been reported as 13% to 87% in patients with bladder pain syndrome[51,52,53]. Sacco et al. applied PISQ-12 query form in 188 women with lower urinary system symptoms. Sexual dysfunction was significantly higher in women with lower urinary system symptoms. While the group with bladder pain syndrome received the highest score, the score was

higher especially in mixed and urge incontinence groups among the incontinence subgroups. In addition, the rate of sexual dysfunction was significantly higher in women with mixed and urge incontinence compared to stress incontinence and women with a dry-overactive bladder. Whereas no significant difference was found between the women with urination dysfunction alone and the control subjects in terms of sexual dysfunction[54].

In a study with 97 women with 75 having bladder pain syndrome and 22 being healthy, pelvic pain and urge/frequency questionnaire score was found as 18 vs 3 ($p<0.0001$), total FSFI score as 20.2±9.6 vs 29.0±6.8 ($p<0.001$), and when cutoff value was taken as 26.55, abnormal FSFI scores were found in 3 women (14%) in the control group and 51 (68%) of the patients with bladder pain syndrome ($p<0.001$). All scores of the FSFI subgroups were significantly lower in the bladder pain group compared to the control group ($p<0.01$)[13].

In a study conducted by Bolong et al. in 2014, the authors stated that FSD is an important component of the clinical phenotype of bladder pain syndrome, and recommended to include sexual dysfunction in the UPOINT classification system in order to help the diagnosis and understand the etiology in bladder pain syndrome[55].

Sexual Dysfunction After Treatment

Especially two studies performed in 2013 about the surgical treatment and posttreatment sexual functioning in UI, have revealed that the complaints of UI were significantly improved after the surgery, but the improvement in sexual dysfunction was not so much[56,57]. In another publication by Şimşek et al. in 2014, pre-op ICIQ-SF score was found as 2±2.9, and post-op ICIQ-SF score as 17.3±1.8, while pre-op FSFI score was found as 16.2±7.9 and post-op FSFI score as 21.3±7.9, and the differences were significant[58] (Table 5).

Table 5: Treatment related results in FSD

Study	Number	Treatment	Incontinence	Sexual function
Numann et al. 2013	150	TVT/sling	84– 88% improvement (Cough stress test)	% 53.3 improvement % 6.7 worsening % 38 no change (FSFI),
Dursun et al. 2013	96	TOT	86% improvement (ICIQ-SF)	Despite 95% improvement in coital incontinence, no change in overall FSFI (some improvement in sexual satisfaction and pain)
Simsek et al. 2014	81	TOT	Pre-op ICIQ-SF score 2±2.9 Post-op ICIQ-SF score 17.3±1.8	Pre-op FSFI score 16.2±7.9 Post-op FSFI score 21.3±7.9

In a small-scale study using the Arizona Sexual Experience Scale (30 women), female sexual dysfunction was observed by 70% pre-treatment, The study was repeated after tolterodine therapy for three months, and sexual dysfunction was reported by 13% in 28 women who continued the treatment. The improvements were especially observed in the titles of desire, arousal, lubrication, orgasm, and satisfaction with more significant improvement in the women with more complaints at the beginning[59].

In a multicenter, double-blind, parallel group clinical trial patients were treated with 300 mg/day pentosan polysulfate sodium

for 32 weeks. A retrospective analysis was performed in 128 patients with bladder pain syndrome. The patients were evaluated with Interstitial Cystitis Symptom Index (ICSI), Interstitial Cystitis Problem Index (ICPI), Quality of Life Short Form-12 and Medical Outcomes Study Sexual Functioning Scale at the beginning and in the 8th, 16th, 24th, and 32th weeks. A decrease was observed in the symptom index in more than 30% of the patients who gave response to the treatment[60].

In a multicenter prospective study, 103 women whom sexual dysfunction was evaluated with PISQ-9 form, were additionally filled ICSI, ICPI, and Visual Analogue Scale (VAS). Significant improvements were observed in the ICSI, ICPI and VAS scores in the post-treatment 1st and 6th months ($p<0.001$). Significant improvement was found in the scores in the post-treatment 1st and 6th months in 87 (84.5%) women evaluated with PISQ-9 forms. Significant improvement occurred especially in "pain" and "negative reaction" during coipus" and "intensity during orgasm" areas [61].

Conclusion

When women experiencing urogynecological problems are examined; low body image, high feelings of embarrassment, not feeling themselves physically and sexually feminene, feeling anxious because of fear, continuous use of diapers/pads, fear of urinary incontinence, urinary incontinence during coipus, negative reactions of spouse/partner, thinking that their attraction has been decreased and related depression negatively affect female sexual life, causing different types of female sexual dysfunction[57,58]. Therefore, women experiencing urogynecological problems and presenting to a clinic should definitely be evaluated for sexual functioning.

In conclusion; sexual desire disorder, severe need for urination during sexual intercourse, and subsequent leakage, arousal disorder, anorgasmia and dyspareunia may be commonly seen in women experiencing urogynecological problems. In addition, there are publications supporting that treatments administered in women with urogynecological problems significantly improve sexual dysfunction.

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Chapter VII

Prediabetes Mellitus At A Glance

Mujgan GURLER

(Asst. Prof. MD), Abant Izzet Baysal University, Faculty of Medicine, Department of Internal Medicine, Bolu, Turkey, drmgurler@gmail.com

Prediabetes Mellitus (PDM) diagnosis concept

It is called prediabetes when the plasma glucose level is higher than normal but does not reach the diagnostic limits of diabetes. Prediabetes has been shown to be associated with increased cardiovascular risk and mortality (1,2). The rate of diabetes development in prediabetic patients is reported to be 70% in some publications. Therefore, prevention of the development of diabetes and clinical complications due to diabetes increases the clinical importance of the disease (3).

For the first time in the British Medical Journal in 1952, Jackson used the term prediabetes to emphasize the increased risk of postpartum pregnancy in women with gestational diabetes, and the same researcher defined what we used today in 1959. In the 60's, individuals at risk for prediabetes were described. For the first time in 1979, the National Diabetes Data Group (NDDG) described impaired glucose tolerance. In 1997, the American Diabetes Association (ADA) described impaired fasting glucose (IFG) and impaired glucose tolerance (IGT). ADA; since 2005, it has been using the term prediabetes for IFG and IGT (4).

Table-1. Categories of prediabetes according to diabetes guidelines and changes in historical identification process

	ADA 1997	ADA 2003	WHO 2006	ADA 2014	TEMD 2015	TDV 2015
IFG Impaired Fasting Glucose (mg/dl)	110-125	100-125	110-125	100-125	100-125	100-125
IGT Impaired Glucose Tolerance 75g. OGTT 2. Hour (mg/dl)	140-199	140-199	140-199	140-199	140-199	140-199
A1c %*	-	-	-	5.7-6.4	5.7-6.4	5.7-6.4

* It must be certified by national glucohemoglobin standardization program and calibrated according to **HPLC** (high pressure liquid chromatography) method used in **DCCT** (diabetes control and complications trial). **OGTT**: oral glucose tolerance test, **ADA**: American Diabetes Association, **WHO**: World Health Organization, **TEMD**: Turkish Society of Endocrinology and Metabolism, **TDV**: Turkish Diabetes Foundation.

The remarkable difference in these definitions; while the World Health Organization still considers the fasting plasma glucose limit to 110 mg/dl for IFG, it is reduced to 100 mg/dl in ADA, TDV and TEMD guidelines. According to the World Health Organization, A1c measurement is still not among the diagnostic criteria, while ADA, TDV and TEMD accept A1c levels within defined limits for high risk group identification.

The World Health Organization uses moderate hyperglycemia and the International Expert Committee uses high risk status for diabetes development as the prediabetes equivalent (5,6).

Epidemiology of Prediabetes

In the 2015 prediabetes atlas of the World Diabetes Federation (IDF), the prevalence of impaired glucose tolerance worldwide is 6.7%, an estimated 318 million people are assumed to be prediabetic, and this number is projected to reach 481 million people by 2040.

The frequency of prediabetes increases with age (7). According to the National Diabetes Statistics Report published by the Diabetes Collaboration Community in 2014, 37% of the population is prediabetic (8). According to the 2005-2006 data of the North American Cohort (NHANES), 34.62% of the population is prediabetic, 19.4% is impaired fasting glucose, 5.4% is impaired glucose tolerance and 9.8% is the combination of these two conditions (9).

In Turkey, epidemiology most comprehensive conducted on this subject, one of the research and Turkish Diabetes Epidemiology Study, published in 2002 (TURDEP) while prediabetes prevalence in Turkey 6.7%, according to data ten years after repeated TURDEP-2 increased to 30.4% of respondents in survey it was determined (10,11).

The increase in the frequency of prediabetes in the world and in Turkey has been associated with increased fat consumption and increased habit of feeding with food which has high glycemic load as a result of rapid urbanization, decreased movement and increased obesity related to these conditions. It is also possible that sources of stress increase and ethnic group effects may also play a role (12).

The main differences between IFG and IGT; IGT is mostly associated with peripheral (skeletal muscle) insulin resistance, whereas IFG is associated with increased gluconeogenesis.

In the combined state there is hepatic and extrahepatic insulin resistance and increased gluconeogenesis. While isolated first-phase insulin secretion defect (early phase) is present in IFG, IGT is associated with both first and second (late phase) release defects (13). IGT is more closely related to future diabetes progression. The combination of IFG and IGT doubles the risk. IGT is more associated with increased cardiovascular risk. IGT is more closely related to microvascular complications such as retinopathy and neuropathy (14). The most commonly used glycemic targets in the

diagnosis of prediabetes are fasting plasma glucose (FPG), postprandial plasma glucose (PPG) and A1c values. At least one of the diagnostic criteria is within the defined limits is sufficient for diagnosis (Table-2).

Table-2. Prediabetes Diagnostic Criteria (TDV Diabetes Diagnosis and Treatment Manual 2015)

Prediabetes Diagnostic Criteria	
Fasting Plasma Glucose	100-125 mg/dl
75 g. OGTT 2. hour plasma glucose	140-199 mg/dl
A1c	% 5.7-6.4

Which test is more valuable in diagnosis?

It has been shown that there is a linear relationship between fasting plasma glucose levels and the risk of developing diabetes, even if within normal limits (15). A meta-analysis of 102 clinical trials published in 2010 demonstrated a clear association between fasting plasma glucose levels and cardiovascular events (16). In addition, the relationship between impaired fasting glucose levels and increased mortality in coronary heart disease has been shown (17). Apart from the risk of future diabetes and increased cardiovascular risk, impaired fasting glucose is also linked to microvascular events. In a study conducted in three different races, it was found that impaired fasting glucose at similar levels is closely related to the risk of retinopathy (18). In 2003, ADA reduced fasting plasma glucose levels in the definition of impaired fasting glucose and fasting plasma glucose levels from 110 mg / dl limit to 100 mg / dl limit, since the studies showed that the risk of developing diabetes according to the ROC curves was close to the impaired glucose tolerance. However, it was not accepted by the WHO on the grounds that there was a significant increase in the incidence of risky populations to be screened and did not reflect cardiovascular risk at low A1c and normal postprandial glucose levels (19). Although A1c levels were subsequently acceded to prediabetes diagnostic criteria, the individual variability was minimal (<2%), meaning different results at different times in the same person, and A1c was increased in diagnosis due to higher differences in fasting plasma glucose and OGTT assessments, such as 12-17% (20). However, the disadvantages of this test are that

many clinical conditions can affect A1c levels and have lower sensitivity to starvation plasma glucose and OGTT in determining prediabetes. When the 1988-2006 NHANES studies were adapted to A1c criteria, it was found that 1/3 of those diagnosed with prediabetes were omitted (21).

A1c has been reported to have sensitivity in prediabetes diagnosis between 16.7% and 59% compared to OGTT, which has been accepted as the gold standard in various clinical trials, whereas it has specificity up to 92%. Studies have shown that the false positivity rate increases similarly when the A1c threshold is lowered to increase sensitivity (22). Another evidence of low sensitivity is that the prevalence of prediabetes decreased to 26.4% when A1c was 30.4% when PFG and OGTT were taken together in TURDEP 2 study in Turkey (11).

Disadvantages of A1c test in prediabetes diagnosis are standardised method requirement, high cost, not being able to be done in every center, medical interactions, low because of some cases (hemoglobinopathies, shortened erythrocyte life, acute blood loss or transfusion and pregnancy), in some cases because of high measurement (iron deficiency anemia, uremia, hypertriglyceridemia, alcohol addiction, etc.), can vary according to ethnicity and it has lower sensitivity than fasting plasma glucose and OGTT in diagnosis.

Studies have shown that postprandial glucose levels can better predict cardiovascular events and cardiovascular mortality than fasting plasma glucose and A1c levels (23,24). Prediabetes diagnostic value of plasma glucose measurements after OGTT was lower than those measured with fasting plasma glucose. While the prevalence of prediabetes was 7.2% in the screening performed on the basis of the second hour plasma glucose level in the TURDEP study published in Turkey in 2002, in another regional screening study conducted in Turkey in the same period, when OGTT and fasting plasma glucose combined were used, this rate increased to 11.6% (10,11).

Table-3. Comparison of advantages and disadvantages of tests used in the diagnosis of Prediabetes

Fasting plasma glucose	Lower costs Increases diagnostics when other tests are added	Low diagnostic and risk prediction alone
OGTT 2.hour plasma glucose	High risk prediction	Burdensome Low sensitivity in diagnosis
A1c	Does not require hunger Low individual variability High specificity	Expensive High test susceptibility Not standardized Low diagnostic sensitivity

The advantages and disadvantages of fasting plasma glucose, second hour venous plasma glucose levels and A1c levels after 75 g oral glucose loading are summarized in Table-3. Today, as the diagnostic test is based on venous plasma glucose levels at the 2nd hour after 75 g.oral glucose challenge, recent studies show that 1st hour plasma glucose levels may be more effective in determining future diabetes levels than fasting plasma glucose and OGTT 2nd hour plasma glucose (14). In a study published in 2009, it was reported that those with plasma glucose levels of 155 mg / dl or more after 75 g. OGTT developed diabetes more than the standard prediabetes diagnostic criteria at 8-year follow-up, especially if there was accompanying metabolic syndrome (25). However, there is still no data available for routine screening of 1 hour plasma glucose after OGTT and it should be remembered that it will increase the cost. Based on the studies, it can be said that there may be different parameters that can predict future risk of diabetes in prediabetic individuals. For instance, in a review published by Stephan N et al., they determined that insulin secretion insufficiency, insulin resistance, visceral obesity and the presence of nonalcoholic fatty liver disease (NAFLD) were effective factors in the process of going to diabetes in prediabetic period (26). Another investigator reported that these factors should include a

history of gestational diabetes, polycystic ovary syndrome (PCOS), and ethnicity (27).

From these studies, it was suggested that there are risky prediabetic phenotypes for diabetes and that phenotype differences determine the chances of success of diabetes prevention approaches. It has been observed that the risk of developing diabetes is lower in individuals with the mentioned phenotypes despite lifestyle changes and similar weight loss with the control group of prediabetes. As a result, the exact diagnostic compliance of the diagnostic methods used today to determine prediabetes was determined to be around 50% (28). In order to increase the diagnostic value of the tests used in one study, the combined tests were listed from the lowest to the highest diagnostic combinations, respectively, OGTT-PFG, OGTT-A1c, PFG-A1c and PFG-OGTT-A1c combinations (29). It is obvious that cost and time loss will increase as the number of tests used increases. In order to prevent this situation, suitable individuals to be screened should be determined according to the risk status. In a guideline published by the American Association of Clinical Endocrinologists and the College of American Endocrinology in 2015, it was emphasized that A1c assessment can only be used for prediabetes screening, and OGTT and PFG measurements should be performed for diagnosis of prediabetic borderline cases (30). Also, TEMD indicated that fasting plasma glucose and OGTT should be examined together for the diagnosis of isolated impaired fasting glucose, isolated impaired glucose tolerance or combined condition, and used the 2.hour plasma glucose levels to identify prediabetic borderline A1c levels to identify high risk patients (31).

Again, Turkish Diabetes Foundation, according to the diabetes diagnosis and treatment guidelines established by the National Diabetes Consensus Group created by the diabetes diagnosis and treatment guidelines which was published in 2015, fasting plasma glucose is between 100-125 mg/dl, impaired fasting glucose, venous plasma glucose in the 2 hours after 75 g. OGTT was between 140-199 mg/dl, impaired glucose tolerance and risky group definitions with A1c level between 5.7-6.4% in the diagnosis of prediabetes (32). Fasting plasma glucose measurement is expected to be performed with a sample taken from venous blood following an 8-12 hour fasting. Measurement of capillary glucose with glucose test strips has no place in screening and diagnosis (as different values will be obtained from venous plasma). Again,

OGTT should be done 8-12 hours after fasting with a solution of 75 grams of glucose prepared in 200 ml of water, during the test as long as possible to remain immobile and do not drink or eat something, no smoking and glucose should be completed by venous plasma sample at the 2nd hour after taking the solution. According to the Prediabetes Workshop Consensus, in order to use A1c level, firstly, it should be done with standardized method. For this, it must be certified by the National Glucohemoglobin Standardization Program and calibrated according to the High Pressure Liquid Chromatography Method used in DCCT, which is considered the gold standard. According to the Consensus of the Prediabetes Workshop, in order to use the A1c value, the standardized method should be sought first. For this, the National Glucohemoglobin Standardization Program was certified and DCCT was used and calibrated according to the High Pressure Liquid Chromatography Method, which is considered the gold standard. In our national guidelines, it is recommended to look for confirmation if there are high values in the low risk group or normal values in the high risk group. It has been reported that values between 5.7-6.4% of A1c represent high risk for diabetes (31,32).

How to Prediabetes Screening?

On 29 to 30 October 2016 in Turkish Diabetes Foundation made prediabetes workshop led to be applied for the diagnosis prediabetes testing and diagnostic criteria were determined, diagnostic and cost criteria of these tests has been shown to who the basis should be applied in which cases.

It is stated that the terms synonyms of prediabetes are moderate hyperglycemia, high risk condition for diabetes development, preclinical diabetes and early diabetes. In the workshop, prediabetes screening was based on catching the most patients with the lowest screening cost and the best risk prediction.

Accordingly, it was emphasized in the workshop report that prediabetes screening should first be determined that the subjects do not fall into the high risk group according to the principles specified in the table, and that a separate approach will be appropriate for prediabetes screening in high risk individuals and non-high risk individuals (Table-4). According to high risk groups (Figure-1) and low risk groups (Figure-2), the following algorithms are used for screening and diagnosis.

Table-4. Prediabetes risk groups

- **From the age of 45**

- Obese/overweight (BMI ≥ 25 kg/m^2), especially central obese individuals
  waist circumference female ≥ 80 cm, male ≥94 cm.

- **Individuals from one of the following risk groups, regardless of age**

- Individuals with only one first-degree relative diabetes mellitus or individuals with two or more than two consecutive relatives of diabetes
- High birth weight baby delivery history (> 4000 g) or women with a diagnosis of Gestational DM
- Hypertension (BP >140/90 mmHg)
- Dyslipidemia (HDL-cholesterol <35 mg/dl or Triglycerides >150 mg/dl)
- Polycystic ovary syndrome
- Clinical disease or signs of insulin resistance (acanthosis nigricans or skin tags)
- History of coronary, peripheral or cerebrovasculary disease
- History of birth with low birth weight (≤ 2500 g)
- Sedentary life and low physical activity
- Patients with schizophrenia and atypical antipsychotic drug use
- Patients with major depression
- Solid organ transplant patients
- Non alcholic steatohepatitis
- Hyperuricemia
- Sleep apnea syndrome
- Taking medication at risk of developing diabetes (corticosteroids, beta blockers, antipsychotics, thiazide diuretics, immunosuppressives)

Risk factors that play a role in the development of prediabetes

Risk factors that play a role in the development of prediabetes are the same as type 2 diabetes (33). The factors that play a role in the pathogenesis of the disease are similar. These include genetics, environmental factors, defects in insulin secretion and insulin

resistance (34). Although insulin resistance is sometimes incorrectly used to express prediabetes, prediabetes is a different condition. In addition, it should be noted that insulin resistance is not always pathological. Although insulin resistance is common in type 2 diabetes and obesity, it has been found in 25% of healthy individuals with essential OGTT and non-obese subjects (35). Although insulin resistance is common in type 2 diabetes and obesity, it was found in 25% of healthy individuals with non-obese and normal OGTT and patients with essential hypertension (35). Insulin resistance can be seen in many physiological conditions (puberty, pregnancy, old age, physical activity) and drug intake (corticosteroids, oral contraceptives, diuretics) (36).

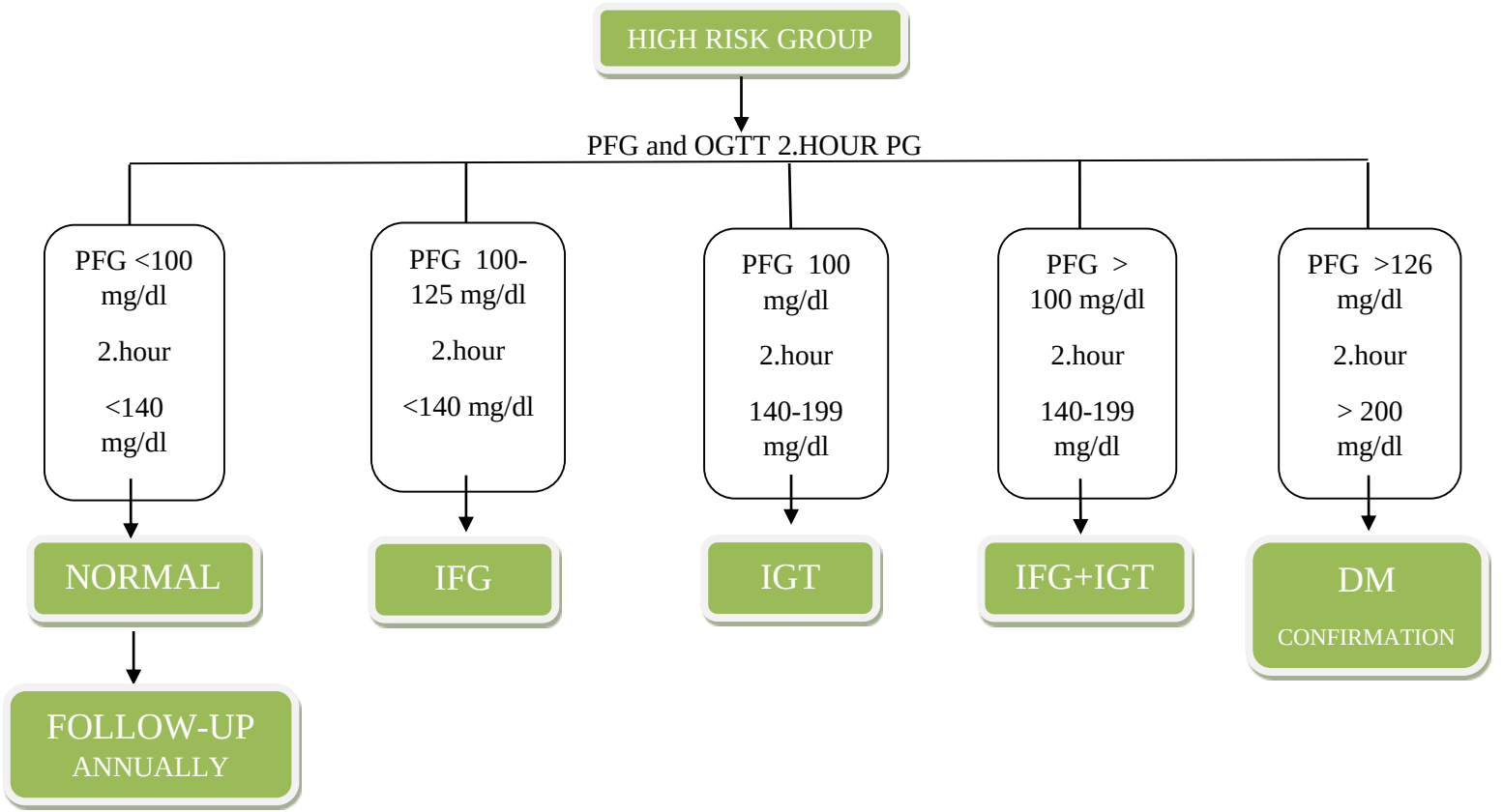

Figure-1. Use of prediabetes diagnostic criteria in high-risk group

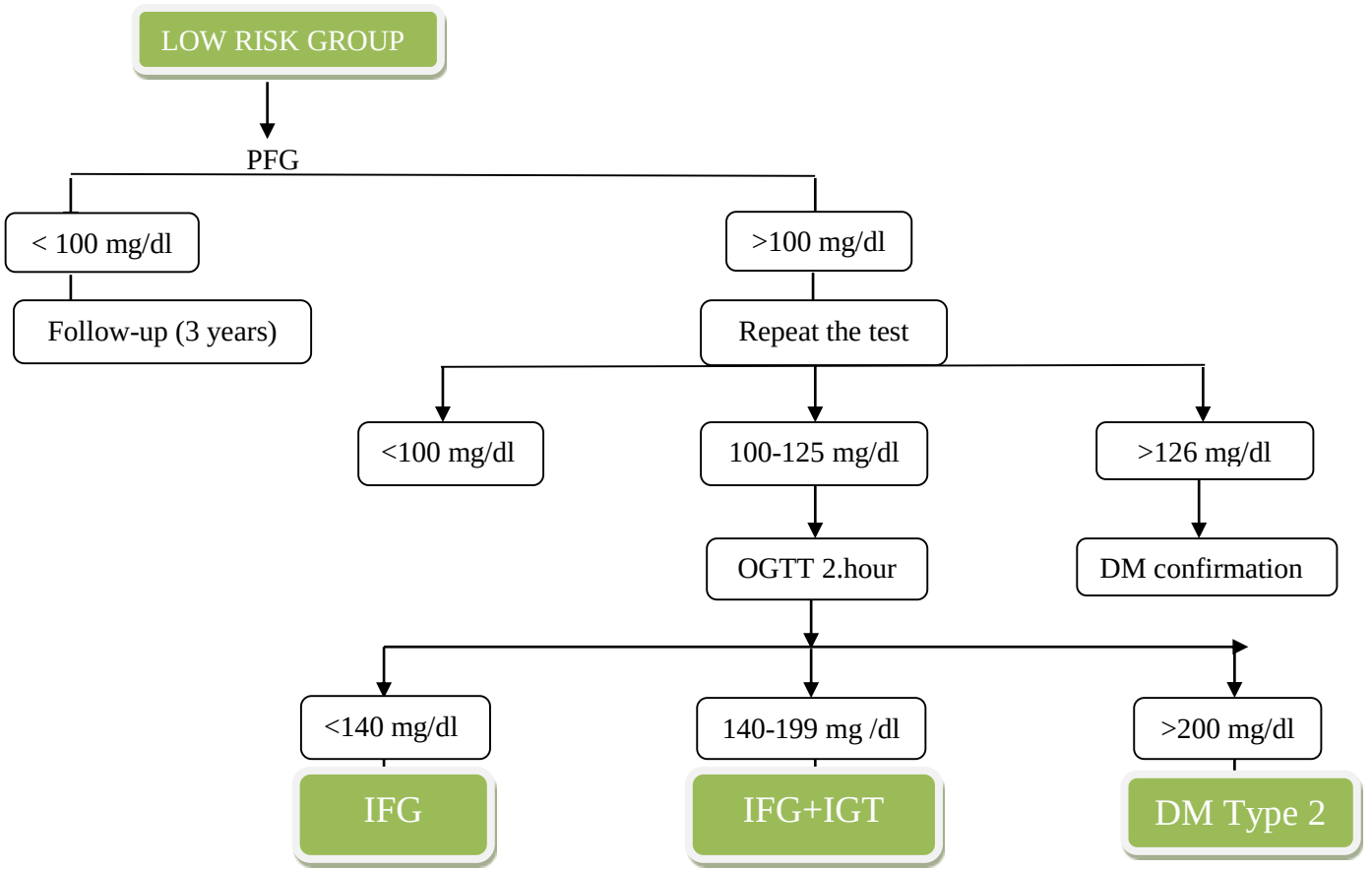

Figure-2. Approach to prediabetes screening and diagnosis in low-risk group

Health risks caused by prediabetes

At the time of diagnosis of type 2 diabetes, 10-40% of patients have complications. This should make us think that prediabetes is not a silent stage and that it involves the health risks posed by prediabetes. This period leads to a number of problems, both for the development of microvascular and macrovascular diseases, as well as other health risks, which are further described below.

Prediabetes and Type 2 Diabetes Risk

The main purpose of prediabetes is to prevent the development of diabetes. To achieve this result, beta cell function should be maintained, microvascular complications should be prevented or delayed, and additionally cardiovascular complications should be prevented or delayed. In addition to maintaining beta cell function, applications that alter insulin sensitivity also determine the risk of developing type 2 diabetes. The most important clinical data determining the risk of developing type 2 diabetes in prediabetic patients vary according to the parameters used in the diagnosis of prediabetes. Overall, the rate of progression of IFG and IGT to diabetes in 3-5 years is 25% (37). In 50% of these patients, glucose tolerance remains the same, with 25% returning to normal. Patients with additional risk of diabetes (obesity, family history) are at greater risk of developing diabetes. In general, the risk of impaired glucose tolerance to return to annual diabetes varies from 3-11%, while the lifetime risk of type 2 diabetes is 50% (38-40). The rate of return of prediabetes to diabetes with different genetic characteristics is 114.4 vs. 2.3/1000 per person (40).

1) Risk of type 2 diabetes in impaired fasting glucose: Isolated impaired fasting glucose (PFG; 100-126 mg/dl), (OGTT 2.hour glucose <140 mg/dl). The rate of initial evaluations is 12-28% in 3-5 years (41). If no intervention is performed, the risk of developing type 2 diabetes is 51.3 versus 12.3 / 1000 per person in isolated IFG (HR 3.61) (41).

2) Risk of type 2 diabetes in impaired glucose tolerance (IGT): (PFG <100 mg/dl, OGTT 2.hour glucose <200 mg/dl). The risk of developing diabetes over 4 years is 23% in overweight IGT patients (17-29%) (11). The rate of diabetes development in IGT in 3-5 years is 31% in weight-independent assessment (9). In the study conducted in Korea, the risk of developing type 2 diabetes is

53.1 versus 12.3 / 1000 people per year if no intervention is performed (HR 4.06) (40).

3) Risk of type 2 diabetes in impaired fasting glucose (IFG) and impaired glucose tolerance (IGT): (PFG 100-125 mg/dl and OGTT 2.hour glucose 140-199 mg/dl). There are rates up to 33-36% in people followed for three to five years (41). If no intervention is performed, the risk of developing type 2 diabetes is 114.4 versus 12.3 per 1000 people (HR 8.21) (42).

4) Risk of type 2 diabetes in patients with A1c between 5.7-6.4%:

If no intervention is performed, there is no data on the risk of developing type 2 diabetes. Since groupings are generally performed according to IFG, IGT and combination, there is no follow-up data in untreated patients.

TREATMENT OF PREDIABETES

Non-Pharmacological Treatment in Prediabetes

Non-pharmacological treatment in prediabetes includes medical nutrition therapy, exercise and other lifestyle changes (LC) in general. The main objectives of the treatment are to slow down the progression from prediabetes to diabetes and / or to stop it if possible completely, to prevent or delay possible micro and macrovascular complications and to ensure the continuity of the benefits to be achieved in an effective cost framework. The results of classical studies on the efficacy of non-pharmacological treatment such as the Finnish Diabetes Prevention Study, the Da Qing Study and the Diabetes Prevention Program (DPP) are very promising (44-46). In these studies, the prevalence of prediabetes to diabetes was reported to be 58-69% in the non-pharmacological group. In the DPP study, a 58% risk reduction was detected in the group receiving non-pharmacological treatment, while the risk reduction in the group receiving metformin remained at 31% (46). Other studies using drugs such as metformin, acarbose, rosiglitazone and pioglitazone, such as DPP, DREAM, STOP-NIDDM and ACT NOW, have also yielded significant positive results for diabetes prevention (43,46-51). However, in almost all of these studies, the benefits obtained with the discontinuation of the pharmacological agent are lost or diminished. Continuity of non-pharmacological treatment is more common than pharmacological treatment (47-49). Initiation of pharmacological

treatment at the stage of prediabetes yet; non-pharmacological treatment is more prominent in prediabetes stage due to cost effectiveness problem, lack of continuity of effectiveness and how long time treatment will be given. However, well-planned training programs and follow-up that provide awareness and motivation are essential for the success and continuity of non-pharmacological treatment. There are studies suggesting that even a one-hour training program that describes the risks of prediabetes can provide significant benefits in the long term. Non-pharmacological treatment should be adopted as a lifestyle and maintained for life.

Recommendations for non-pharmacological treatment are as follows:

1-Medical Nutrition Therapy

2- Exercise

3- Others

1. Medical Nutrition Therapy

The goal is to achieve and / or maintain an ideal weight. If weight loss is aimed, daily caloric intake should be limited to 500 kcal / day.

Carbonhydrate (CH) Consumption

50-60% of the daily energy needs should be met by unprocessed complex CHs (whole wheat, whole grains, legumes, brown rice, bulgur and buckwheat).

Fruit should be consumed slowly and not to exceed 100 grams / portion at a time when it is desired to be eaten. Fruit consumption should be no more than 200 grams per day. In addition, juicy, fast-mixing fruits should not be preferred. Consumption of any kind of fruit juices is not recommended.

Vegetable soups should be preferred as soups, floury, creamy and oily soups should be avoided.

Oil Consumption

Fat consumption should include up to 30-35% of daily calories. Preferably consumption of olive oil is recommended. It should be remembered that 100 grams of oil gives 880 kcal energy in oil consumption. Saturated fat intake should be limited (less than 7% of total fat intake).

Protein Consumption

15-20% of daily calorie requirement should be protein-based. Protein should be taken from 30-40% of animal and 60-70% of plant origin.

Fiber Consumption

It is recommended to take 30 grams or 15 grams of fiber per 1000 kcal per day. It is recommended that salads should be consumed as the first choice of main meals.

Fluid Consumption

Fluid should be taken to the extent required. 1-1.5 liters of daily liquid should be directly from the water source.

Salt Consumption

Salt consumption should be less than 6 grams / day.

Sweetener Use

They are recommended not to be used if possible. There is no consensus on the damages they may ocur. Should not be used more than 8-10 pieces per day. Not recommended for pregnant women. Sweeteners are reported to be calorie-free, but have been shown to increase insulin secretion and insulin resistance. Food and beverages containing sweeteners should be avoided.

Alcohol Consumption

Alcohol consumption is not recommended in prediabetic individuals. However, in cases where it should be consumed, 1 unit per day should be consumed in women and 2 units per day in men.

2. Exercise

Detailed physical examination before exercise planning. (especially respiratory and cardiovascular system, conditions that may prevent exercise). Exercise should be regular and sustainable every day, if possible. No specific recommendations for exercise type (aerobic or resistance exercises). Ideally, it should be done 1 hour after the main meals. In general practice, 8000-10000 steps of activity are recommended within 24 hours. If weight loss is desired, the number of steps can be increased further.

3. Others

- Sleep: It is suggested to sleep up to 6-8 hours. There are studies suggesting that sleep of less than or longer than this may adversely affect healthy life. In addition, possible sleep apnea cases should be questioned.

- Micronutrient additions are not recommended.

- Processed foods should be avoided.

- Consumption of foods offered as diabetic and / or dietary products should be avoided.

- Conditions that increase food motivation should be determined and avoided.

- Snack meals: Milk and dairy products and / or cereals recommended. Snack meals containing carbohydrates between long meals without changing total calories are recommended.

- Smoking not recommended.

Pharmacological treatment in Prediabetes

Pharmacological treatment may be initiated in prediabetic patients who can not undergo lifestyle changes (LC) or who have no results in 3-6 months with LC. Treatment failure is defined as the continuation or progression of parameters that make the diagnosis of prediabetes (eg. A1c elevation despite LC). As a general principle, only LC is recommended initially in patients with prediabetes but pharmacological treatment with LC can be considered from the beginning in patients at high risk of developing diabetes (eg. IFG + IGT together, history of gestational diabetes mellitus (GDM) , BMI ≥35 kg/m^2, A1c ≥%6).

Metformin, thiazolidinediones, acarbose, orlistat and GLP-1 receptor agonists have been shown to reduce the risk of developing diabetes or the prevalence of prediabetes in prediabetic patient groups (43,48,50-54). Metformin should be preferred as a first-line treatment in patients with prediabetes because it is cheap, effective, long-term safe and it has strong evidence. Although metformin was found to be less effective in the prevention of diabetes compared to LC in patients with prediabetes, DPP and DPPOS were reported to be cost-effective over a 10-year follow-up period (55). In the DPP study, metformin was found to be as effective as LC in prediabetic patients with BMI ≥35 kg / m^2 and age <60 (43). In DPP, there was

an equivalent reduction in the risk of diabetes in women with a history of GDM with metformin and LC, and also the effect was persistent over a 10-year follow-up (56,57). In the Indian DPP study (IDPP), no difference was found between LC alone, metformin monotherapy, and LC + metformin treatment in terms of risk of developing diabetes (58). Metformin should be preferred as the first-line treatment in patients <60 years of age and BMI is ≥35 kg / m^2, because it is cheap, effective and safe in the long term. Metformin was not found to be effective in patients older than 60 years (43). In prediabetes, metformin daily dose is 1000-1700 mg and effective dose is 1700 mg/day. It is recommended that metformin treatment be started at 2x500 mg daily and increased to 2x850 mg depending on tolerance. Many studies have shown that thiazolidinediones are highly effective in preventing diabetes. In the development of diabetes, troglitazone reduced risk by 50% in TRIPOD study (51), 60% in rosiglitazone DREAM study (52) and 72% in pioglitazone ACT-NOW study (50). In another study, the risk of developing diabetes decreased by 52% in patients with non-diabetic, insulin-resistant ischemic stroke or transient ischemic attack with pioglitazone (IRIS) (59). In contrast, no significant difference was found between pioglitazone and LC in the IDPP-2 study (60). In the ADA 2016 guideline, only the thiazolidinediones are mentioned as the primary physiological effect of the agent that increases insulin sensitivity (61). However, metformin should be preferred in primary care because of its side effect profile and cost. On the other hand, pioglitazone may be preferred in the initial treatment of diabetic risk factors such as NASH or combined prediabetes (IFG + IGT) and a strong family history of type 2 DM, dyslipidemia (high TG, low HDL), hypertension, and insulin-related clinical status such as PCOS and acanthosis nigricans. Thiazolidinediones may be recommended if there is no barrier in prediabetic cases where metformin treatment is not effective initially. (Note: Only pioglitazone is available in Turkey). Pioglitazone may be used at a low dose of 15-30 mg / day, preferably. Another approach is low-dose metformin + pioglitazone combination therapy (eg. 500 mg metformin + 15 mg pioglitazone) in cases where metformin treatment fails. In the CANOE study, the incidence of diabetes was reduced by 66% with low-dose metformin + rosiglitazone combination (62). GLP-1 agonists or orlistat which is a lipoprotein lipase inhibitor may be considered in patients with prediabetes BMI ≥35 kg / m^2 who do not benefit from metformin therapy. In a 20-week study of patients

with prediabetes, the prevalence of prediabetes decreased by 84-96% with liraglutide doses of 1.8, 2.4 and 3.0 mg (54). In the same study, there was no decrease in the prevalence of prediabetes with orlistat. In contrast, orlistat reduced the risk of diabetes by 37% in the XENDOS study (53). Acarbose, an alpha-glucosidase inhibitor, has been shown to have a positive effect on the prevention of diabetes and cardiovascular outcomes in patients with prediabetes. Acarbose reduced the risk of diabetes by 25% in the STOP-NIDDM study. In this study, when sub-analyzes were performed, acarbose was found to be more effective, especially in patients older than 55 years and with a BMI <30 kg / m^2 (5). Considering that metformin is especially useful in patients with BMI ≥35 kg / m^2 and under 60 years of age in DPP study; acarbose may be preferred in the first step if pharmacological treatment is to be started in patients with low BMI or advanced age. The preventive efficacy of drugs in pharmacological treatment is limited to the duration of use. Possible side effects should be considered during the use of pharmacological therapy, patients should be closely monitored, especially in terms of the development of hypoglycemia.

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Chapter VIII

Management of Crush Syndrome Related Problems and Nursing Care

Neslisah YASAR

(Lec.) Beykent University Vocational School, Istanbul-Turkey, neslisahyasar@beykent.edu.tr

Semiha AKIN

(Prof. Ph.D.), University of Health Sciences Faculty of Nursing, Istanbul-Turkey, semiha.akin@sbu.edu.tr

Crush Syndrome in the World and in Turkey about the Earthquakes

The changing and developing world is exposed to sudden and unexpected natural and artificial disasters such as earthquake, hurricane, tsunami, train crashes, fires and building collapses (Rajagopalan, 2010). The mortality and morbidity rates differ according to the factors such as the type, impact area and timing of the disaster (He et al., 2011). Deaths due to disasters increase because of the pressure duration in the thoracic and abdominal area and septicemia (Erek, 2010). This rate also differs according to the earthquake intensity, building durability, pressure dissemination due to the trauma and the status of intervening in the first 2-12 hours (Tanaka et al., 2014).

It was reported that Seigo Minami was the first person who recorded the Crush syndrome pathogenesis in German literature after the Second World War and after the Sicily earthquake (1908 Messina, Italy). The development of acute renal failure (ACF) tables about the rhabdomyolysis, myoglobinuria and Crush syndrome in the injured people who were trapped in the wreckage after the bombardment of London in 1940, during The Battle of Britain, were first published in British Medical Journal by EGL Bywaters and D. Beall in 1941 (Santo et al., 2016). When the

effects of disasters that take place in the world and in our country are examined (1976 China-Tangshan; 1988 Armenia; 1995 Japan Hanshin-Away; 1999 Marmara Earthquake; 2005 America's Hurricane-Katrina Disaster; 2011 Van Earthquake) it was observed that the Crush syndrome is the leading mortality reason for people who were rescued from the wreckage after the earthquake (Erek, 2010; Aygin et al., 2008).

91% of Turkey's lands consist of the earthquake-prone regions (Health services in earthquakes, 2017). The data indicate that Turkey is "the country of earthquakes" (Istanbul earthquake report, 2017). It was reported that the Crush syndrome case was observed the most in the 1999 Marmara Earthquake with a rate of 1.4%. The death toll was calculated as 17,480 and the number of injured was 43,953 after Marmara Earthquake. A total of 639 victims was diagnosed with Crush syndrome and 477 of them reported that they are receiving dialysis treatment. In the report that was published after the 1999 Marmara Earthquake by The Ministry Of Interior Disaster And Emergency Management Presidency (AFAD), mortality/morbidity rate was determined as 1/3 (Gölcük Earthquake, 1999). It was reported that in the earthquakes that took place in Van province on October 23, 2011 and November 9, 2011 the death toll was 604 and approximately 6000 people were injured due to the earthquake (Van Earthquake, 2011). Soft tissue trauma was determined in 95% of the victims after the Van Earthquake and multiple extremity fractures and compartment syndrome followed this table (Turgut et al., 2012). It was reported that victims received hemodialysis treatment in Van city center and in Erciş after the earthquake with 49 hemodialysis machines and 35 dialysis patients were treated in the hospitals of Diyarbakır province (Van earthquake, 2011).

Crush Syndrome, Rhabdomyolysis and Compartment Syndrome

The word crush stands for "smash, compress or suppress" (Yıldırım et al., 2018). Crush syndrome is the renal damage tables that emerge as a result of accidents, earthquake, hurricane, tsunami, war or traffic accidents, carbon-monoxide intoxication and drug toxicity (Sever et al., 2015). *Crush syndrome* is defined as the acute renal failure of which the most important reason is earthquakes and which occurs due to long-term traumatic compression on the muscular tissue (Lovallo et al., 2012). Traumatic compression injury on the muscular tissue requires

immediate surgical and medical treatment (Sever, 2002). In crush syndrome, critical systemic problems may emerge in muscles which are exposed to trauma such as local findings, compartment syndrome, systemic or crush syndrome findings, liquid-electrolyte imbalances, infection and hypovolemic shock (Akdam et al., 2015).

Rhabdomyolysis is clinical *compartment syndrome* which means "the breakdown of striated muscles" (Sever, 2002). Striated muscles are surrounded by fascias that are rigid and have low compliance (He et al., 2011). As a result of cellular membrane damage after trauma, extremity losses are observed as well as the intravascular liquid losses (Lovallo et al., 2012). As a result of the damage of trauma to the striated muscles, abnormal clinical and laboratory findings emerge as a result of getting into the systemic circulation by the intracellular matters, edema formation in the extremity muscles and the increase of pressure to the extremities (Akdam et al., 2015). In the blood biochemistry analyses of traumatic rhabdomyolysis, an increase is determined in the creatinine kinase (CK), creatinine phosphokinase (CPK) and aldolase enzyme levels (Tanaka et al., 2014; Erek, 2010). In the measurement that was performed with central venous pressure (CVP) manometer on edematous extremity (lower extremity in particular), it was determined that intracompartmental pressure increased up to 30 mm Hg (normal value 0-15 mm Hg). Some of the rhabdomyolysis phenomena may develop due to alcohol and drug use. These phenomena are named non-traumatic rhabdomyolysis and do not cause acute renal failure (Yıldırım et al., 2018; Sever et al., 2015).

Etiopathogenesis of Acute Renal Failure Associated with Crush Syndrome

Crush syndrome can be evaluated in two groups as "associated with traumatic and nontraumatic causes" or "associated with non-physical and physical causes". Traumatic rhabdomyolysis is the catabolism that occurs in the musculoskeletal cells related to the pressure that will impair blood circulation. Nontraumatic rhabdomyolysis occurs as a result of hypotension and intravascular volume loss. In the cases of rhabdomyolysis, renal failure develops due to hypovolemia and hyperkalemia (Vale, 2016; Lovallo et al., 2012). Electrolyte disturbances, alcohol, drugs, toxins and infections can be given as examples of non-traumatic causes that can lead to Crush syndrome. Earthquakes and natural disasters,

hypoperfusion or ischemia of muscles, overstimulation of muscles (heavy exercise, epilepsy, tetanus, delirium), electric shocks and hyperthermia (heavy exercise, malignant condition, sepsis), and muscular compression can be given as examples of the traumatic causes of Crush syndrome (Erek 2010; Sever 2002).

Muscle fibers are stretched as a result of the muscle sarcolemma being exposed to pressure for longer than 30 minutes of blood circulation disruption (baromyopathy). Permeability in ischemia and baromyopathy sarcolemma increases. Calcium ion enters the intracellular area. The increase in the cytosolic Ca+2 ion causes failure in the Na-K-ATPaz and Ca-ATPaz pumps and an imbalance between the energy consumption and production of the muscle as a result (Vale, 2016; Sever et al., 2015). Potassium, myoglobin and creatinine, which are 98% in the cell, enter the extracellular area while electrolytes such as sodium and calcium enter the intracellular area with water (Janice et al., 2013). An increase in the levels of potassium, phosphate, myoglobin and creatine kinase, lactate dehydrogenase, AST (Aspartate Aminotransferase), ALT (Alanine Aminotransaminase) and uric acid in the serum are observed in blood analyses (Yıldırım et al., 2018, Gibney et al., 2013). Compartment syndrome status emerges as a result of myocyte edema and cytologic lysis (Janice et al., 2013). Ischemia emerges as a result of an additional 30 minutes of pressure in the muscles (Yıldırım et al., 2018; Vale, 2016). In the patients, capillary perfusion decreases commonly in forearms and legs, feet, arms, shoulders and sacrum, and distal pulse loss, ischemia, edematous extremity paresthesia or anesthesia and discomfort is developed (Lovallo et al., 2012).

Clinical and Laboratory Findings on Crush Syndrome

Rapid diagnosis of post-trauma crush syndrome, initiation of the appropriate treatment and taking detailed medical history carry great importance in decreasing morbidity and mortality (Janice et al., 2013). The *clinical findings* of crush syndrome can be classified into two groups as local and systemic (Sever, 2002).

- Local findings are generally myalgia, swelling of extremities or other important dark soft tissue injuries (contusion), muscle laceration and compartment syndromes that are caused by fractures (Lovallo et al., 2012). Shock and hypotension may develop with pain and infection especially in the lower extremity (Erek, 2010). Compartment syndrome is characterized with certain

clinical findings that are abbreviated as "6P" depending on the long duration pressure. The abbreviation "6P" comprises of the initial letters of six findings in English as pain, paresthesia, paresis, pallor, pressure and pulselessness (Akdam et al., 2015; Durna et al., 2009).

- The systemic effects of compartment syndrome differ in accordance with the organ that is affected by the trauma. Hypotension, hyperthermia, cardiac arrhythmia, hypovolemic shock, acidosis, hyperkalemia, hematuria and oliguria or anuria, in other words, acute renal failure findings develop (Lovallo et al., 2012; Rajagopalan, 2010). In victims who were rescued in late-term, nausea, vomiting, agitation and delirium may develop related to uremia due to acute renal failure (Rajagopalan, 2010).

Following the increase of myoglobin levels that are released in the muscles in post-trauma, the increase of certain matters in the blood plasma causes the development of acute renal failure. Myoglobin which is a protein that contains iron in skeletal muscle which stores oxygen for aerobic mitochondrial metabolism, plays an important role in the process of rhabdomyolysis (Janice et al., 2013). Having a serum creatinine phosphokinase (CK) level that is five times higher than the normal value is distinctive for the diagnosis of Crush syndrome. The serum CK usually increases after the crash in 2-12 hours, peaks in 1-3 days and decreases in 3-5 days. As a result of the rapid increase of serum creatinine level, BUN/creatinine ratio decreases. Early stage hyperkalemia development plays an important role in the diagnosis of acute renal failure and is the reason of indication for hemodialysis treatment (Akdam et al., 2015; Erek, 2010; Rajagopalan, 2010). At this stage, blood type and venous blood gas analysis should be carried out, appropriate fluid replacement should be started rapidly, serum sodium and bicarbonate levels should be examined (Kazancıoğlu, 2012).

Renal Replacement Treatment in Acute Renal Failure

Complications such as hyperkalemia and acidosis are more serious in Crush syndrome with the effect of diseases that accompany with pre-trauma diabetes, hypertension and vascular diseases. In disaster conditions, it is necessary to administer two intravenous when the extremity of the injured is seen. The victim should be inserted potassium-poor hypotonic NaCl (5% Dextrose + 0.9% NaCl) and intravenous infusion should be sustained until the victim is pulled from the wreckage (Yıldırım et al., 2018). If the

patient lost <400 ml urine, hypotonic NaCl infusion should be started with a rate of 15-20 ml/hour for children and 1000 ml/hour for adults according to the blood pressure value and the intake-output fluid. The infusion should be sustained with 500 ml/hour two hours after the victim is rescued and should be monitored for hypervolemia (Genthon et al., 2014).

Na, K, Ca, Ph, HCO_3 and myoglobin values are monitored with blood tests. Furthermore, with complete urine examination (CUE) pH, urea and creatinine values of urine are monitored (Wilkinson, 2017; Davies, 2013). 40 mEq sodium bicarbonate ($NaHCO_3$) should be added to 500 ml 0.9% isotonic in order to increase the pH of urine to 6.5 and to prevent the myoglobin to precipitate in proximal tubules. The mannitol-alkaline application increases renal bloodstream and glomerular filtration in patients who don't have oliguria or anuria (Peltonen et al., 2007). The mannitol-alkaline solution is applied for the first three days after the trauma (until myoglobinuria disappears). Mannitol-alkaline or hypotonic NaCl (5% Dextrose + 0.9% NaCl) infusions are given 3-6 L/day if the urination is <50 ml per hour and can be given <6 L/day more by monitoring the vital signs and intake-output fluid (Wilkinson, 2017; Akdam et al., 2015).

With hydration support, it is aimed to prevent the acidosis, acute renal failure and target organ damage. Sufficient hydration protects proximal tubules, reduces the risk of hyperkalemia and regulates metabolic acidosis. The hydration treatment is sustained until the serum CK level drops under the level of 1000 U/L. After the sufficient fluid replacement, fluid is drawn to the interstitial area with diuretic treatment, glomerular filtration increases and additional myoglobin is filtered. Diuretics in furosemide group that are used to provide diuresis cause renal vasodilation and urination is provided (Vale, 2016; Akdam et al., 2015; Davies, 2013). In hyperkalemia or hypocalcemia treatment, Ca gluconate and chloride are given. Intravenous calcium treatment would be effective in the treatment of cardiac conduction disorder (Wilkinson, 2017).

The first priority in the scene of the accident is to save lives and to obtain data on the factors that affect prognosis. Pre-trauma diseases, sustaining nutrition in disaster conditions and experiencing difficulties in providing the continuity of drug treatment may have negative effects on renal (Erek, 2010). As a result of fluid-electrolyte and acid-base imbalances parallel to the

prolongation of staying under the pressure of muscle in post-trauma, serious uremic toxicities emerge (Kazancıoğlu, 2012). In this case, renal replacement treatments can be applied such as hemodialysis, constant and slow treatments (arteriovenous or venenous hemodiafiltration) and peritoneal dialysis (Sever et al., 2015; Peltonen et al., 2007). Logistic support should be provided for the referral of patients to the dialysis units who require renal replacement treatment (Peltonen et al., 2007).

Hemodialysis treatment is the process of removing electrolyte and urea from the body by benefiting from the concentration difference between blood and dialysate (Janice et al., 2013; Rajagopalan, 2010). The first option for renal replacement treatment is hemodialysis that is applied 3-4 times a week. Hemodialysis has significant importance in crush syndrome cases since it rapidly decreases hyperkalemia and is the most efficient treatment method that removes it from the body (Janice et al., 2013). Products such as myoglobulin, urea, creatinine and electrolyte which emerge as a result of compression longer than 30 minutes on the muscle tissue in crush syndrome cases can be removed from the body with hemodialysis (Wilkinson, 2017).

Arteriovenous or venenous hemodiafiltration filters more fluid under high hydrostatic pressure (Janice et al., 2013). Hemofiltration is used in extremity edema and hypervolemia management and high volume ultrafiltration in crush syndrome cases (Sever et al., 2015; Erek, 2012). Non-anticoagulant hemodialysis or hemofiltration treatment should be applied in patients who have bleeding tendencies (Kazancıoğlu, 2012; Li et al., 2011). In disaster conditions, pure or ultrapure water and infrastructure conditions such as electricity and communication should be provided. Difficulties are experienced in providing dialysis units, single-use sterile materials, logistics, sufficient dialysis nurses or dialysis technicians and efficient working environment (Sezen et al., 2015; Gibney et al., 2013).

Peritoneal dialysis treatment is not the first option in hyperkalemia treatment which emerges in Crush syndrome cases due to its low clearance (Sever et al., 2015). This treatment is applied in patients who do not have abdominal trauma in disaster conditions. Peritoneal dialysis is applied by using a catheter and solution that are placed in the abdominal region. Hemodialysis is easier to apply than hemofiltration in patients who have bleeding tendencies and require fasciotomy or amputation (Wilkinson,

2017). Its advantages are; it does not require special equipment, electricity, machine and vascular access. It is advantageous in terms of contributing to nutrition since it balances fluid solute clearance and has glucose dialysate (Sezen et al., 2015; Li et al., 2011). The requirement of a sterile surgical environment, equipment and crew for placing the peritoneal catheter makes it difficult to start the peritoneal dialysis process (Sever et al., 2015; Erek 2012).

Final stage renal failure may develop in Crush syndrome cases due to an underlying renal problem. It is necessary to analyze the benefits and risks of *renal transplantation* in disaster conditions (Dunsmore, 2016). Renal transplantation from a living donor or a cadaver is carried out more frequently than other visceral organ transplantations (Erek, 2010). Donor and recipient matching is performed in order to define renal transplant contraindications and for the organ to survive (Dunsmore, 2016). ABO (blood type), HLA (human leucocyte antigen) compatibility, seeking of cytotoxic antibodies and cross-match test should be conducted between the donor and recipient for the transplantation process (Erek, 2010). Problems on not providing sufficient immunity, infection risk and drug use may increase the risk of graft rejection in disaster conditions (Sever et al., 2015).

Nursing Care In Acute Renal Failure Related To Crush Syndrome

Disaster Management and Nursing Care

Florence Nightingale who is one of the important theoretician of nursing carried out her most difficult duty in the Crimean War between 1854-1856. Nightingale decreased the death rate from 42% to 2% with her reforms during the war. Nurses took an active part in disasters and calamities throughout history. The priority of nursing is care and then treatment and coordination (Taşkıran et al., 2017; Kaptan et al., 2012).

Disaster management is a multidisciplinary approach which includes firefighting, police and ambulance services (Aslan, 2014). Institutions such as Hospital, Disaster and Emergency Plans (HAP), AFAD (The Ministry Of Interior Disaster And Emergency Management Presidency), National Medical Rescue Team (UMKE) and Red Crescent should be prepared for disaster management (Taşkıran et al., 2017). Nurses perform risk identification of society and patients under their care in disaster

conditions. They aim to improve and protect the health of victims by determining their physical and emotional health needs (Kaptan et al., 2012).

It is required to record the patient before the hospital, to evaluate and to determine the life-threatening problems. A systematic approach to the patient should be planned by creating a safe environment in the scene of a disaster. It is compulsory to triage since there would be many consultations in disaster conditions such as earthquake, hurricane, tsunami, train wrecks, fires and collapses (Sever et al, 2012). Triage planning would provide convenience to the patient in the consultation to the emergency unit. Immediate treatment area should be separated into five main areas according to the seriousness of the injury as "red area" (life-threatening phenomena), "yellow area" (fracture, open wounds), "green area" (patients who can walk, require no emergency), "gray area" (patients who have no chance to survive) and "black area" (people who arrive dead) (Aksoy, 2010).

Complaints on extremity pain, weak ecchymotic or erythematous extremities, swollen and tense legs and skin wounds are asked to patients who are conscious (Genthon et al., 2014). In the initial diagnosis of trauma patient ABCDEFG (A: Airway, B: Breathing, C: Circulation, D: Disability, E: Exposure and Environmental Control, F: Foley and G: Gastric) method is accepted (Aslan et al., 2014; Sever, 2002).

In disaster conditions, the condition of the patient is evaluated with vital signs such as pulse, breathing and blood pressure (Aslan et al., 2014). If a stable patient is not evaluated with Crush syndrome suspicion, a rapid impairment may be observed in the clinical course (Hayashi et al., 2017; Genthon et al., 2014; Kaptan et al., 2012). Tissue perfusion deteriorates as a result of being trapped under the wreckage. Reperfusion occurs in the tissues of the rescued victim as a result of the remaining pressure on the extremity. Metabolic acidosis and hyperkalemia take place parallel to the accession of tissue destruction products to the circulation (Hayashi et al., 2017). The condition of a patient who looks fine under the wreckage and when rescued may get worse as a result of reperfusion. This situation is called “rescue death” (Erek, 2010).

Even though the victim is under the wreckage, establishing vascular access to one of the extremities that are free and starting hydration treatment would reduce the risk of death (Akdam et al.,

2015). Not monitoring the hypovolemia immediately triggers acute renal failure. Intravenous access is checked for rubescence and swelling. In order to control the hyperkalemia effects, potassium-free hypotonic NaCl (5% Dextrose + 0.9% isotonic NaCl) infusion should be started with a rate of 15-20 ml/kg/hour for children and 1000 ml/hour for adults. If the rescue process does not take more than two hours, the process should be continued with a rate of hypotonic NaCl 500 ml/hour. When the patient reaches the aseptic environment, renewing the peripheral vascular access would reduce the septicemia and bacteremia possibilities (Karakovan, 2016). The fluid that patient took-lost monitoring should be conducted by urethral catheterization, the catheterization area should be monitored for infection risk. Hypervolemia and heart failure symptoms can be seen in patients whose input-output fluid is not monitored. Central venous pressure (CVP) monitoring is suggested in a hospital environment (Aksoy, 2010; Erek, 2010). In nursing care, respiration, circulation and neurological signs of the victim are monitored. Their identifying information is recorded (Duran, 2018; Karakovan 2016; Sever, 2002).

In physical examination, pupillary reflex, edema cervical, the existence of serious wounds in the thoracic-lumbar area, pale skin and confusion are evaluated. ABCDEFG should be checked in the initial diagnosis of the trauma patient (Aslan et al., 2014). Airway circulation should be provided and the cervical and thoracic area should be fastened. Oxygen source may be limited due to safety (Wilkinson, 2017). If the patient has metabolic acidosis, Kussmaul respiration should be monitored in terms of bleeding that would cause arrhythmia and hypovolemia (Genthon et al., 2014; Durna et al., 2009). The victim should be clothed if the victim has hypothermia after the monitoring of vital signs. Intracranial bleeding or serious head traumas that affect the mental state, orientation, cooperation of the patient, answers to verbal and painful stimulus should be evaluated (Sever et al., 2015).

Blood biochemistry should be monitored 3-4 times a day if possible. If the hyperkalemia is not monitored, it may cause electrocardiography changes, ventricular fibrillation or asystole. If lactic acidosis or hypocalcemia develops, rhythm problems may grow worse (Genthon et al., 2014; Rajagopalan 2010). In hyperkalemia treatment, calcium gluconate can be given since it decreases the membrane excitability of myocardium (Sever, 2002). The transition of potassium from the extracellular area to the

intracellular area can be provided with insulin or dextrose. Diuretic treatment supports the removal of extra potassium in the circulation with urine (Thomas, 2016; Janice et al., 2013; Sever, 2002). In cases of which hyperkalemia is not taken under control, the excision of the necrotic area is considered (Genthon et al., 2014). The necrotic area should be evaluated with the existence of infection symptoms-signs such as rubor, calor and dolor and wound care should be provided. Intake-output and vital signs should be monitored. The patient is monitored and EKG changes are monitored (Thomas, 2016; Adem et al., 2015).

Logistic planning, patient transfer and the activation of trauma crew are vital due to the gradual increase in the disasters and collective calamities (Sever et al., 2015). It is required to provide continuity in patient treatments, management of health personnel and medical equipment and to determine the reference hospitals that are not damaged by the disaster. In dialysis treatment, the availability status of dialysis units of hospitals and health personnel such as doctors, nurses and dialysis technicians are important (Korkmaz, 2014; Sever, 2002). Transportation problems may emerge due to the disaster. In this process, the collaboration of military and civil institutions would provide a contribution.

Hospital Nursing Care for Patients with Crush Syndrome

Nurses participate not only in the emergency phase of disaster management but also in disaster preparedness by cooperating with team members in the coordination phase with their supporting role. Their participation also includes admission of victims to the hospital after disasters, conduction of physical examinations and evaluations, gathering information about the patient, establishing the continuity of care and improving its quality, communicating effectively with health care personnel, and giving long-term training to patients and their relatives (Taşkıran et al., 2017; Güngör, 2015).

Vomiting respiration should be monitored in terms of renal failure findings such as mental changes, dysrhythmia, hypertension, edema, ecchymosis, nausea, vomiting, metabolic acidosis, hyperkalemia, oliguria development or anuria (Davies, 2016). The patient's vital signs are monitored, cardiac monitorization and oxygen support are provided and monitored in terms of orthostatic hypotension. Two central venous pathways are opened and fluid replacement and diuretic treatment are continued.

If the urinary system catheter is present, it should be monitored in terms of infection signs such as catheter area colonization, redness, temperature, defluxion, swelling, burning and hyperthermia (Sever et al., 2015; Temiz, 2015). In blood biochemistry, serum electrolytes, BUN, creatinine and myoglobin levels, full blood test and blood gas should be monitored in accordance with the doctor's request (Aygin et al., 2008). Fluid intake-output balance, weight tracking, turgor and tonus, peripheral edema, CVP and jugular venous pressure, diarrhea, vomiting, the amount of fluid output by drainage if there is any, and the amount and type of drainage, if there is any wound drainage, should be recorded, and gastrointestinal system bleeding should be monitored (Wilkinson, 2017; Erek, 2012; Durna et al., 2009).

Preparations are made for renal replacement treatments. Development of conditions such as metabolic acidosis, pulmonary edema and shock, fluid-electrolyte balance and glomerular filtration rate are closely monitored. The patient is evaluated in terms of changes in thought process due to BUN increase, sensory and perceptual changes such as agitation and confusion, fluid volume increase, dietary habit and deterioration of skin integrity, electrolyte imbalances, vital signs and EKG follow-up, risk of arrhythmia and risk of infection (Wilkinson, 2017; Taşkın Yılmaz et al., 2014).

In disasters, the treatment of the myoglobin and hyperkalemia that emerge after the disruption of extremity blood circulation may require necrosis and removal of the infected extremity from the body. Fluid treatment, transfusion treatment and replacement treatment are the main therapeutical approaches in individuals with Crush syndrome. Fasciotomy, extremity debridement or amputation can be performed as surgical treatment methods (Genthon et al., 2014; Erek 2010).

Surgical incision of the muscle fascia in order to reduce intracompartment pressure is called *fasciotomy* (He et al., 2011). Intramuscular pressure, which is normally 0-15 mmHg, increases between 30 and 50mmHg or exceeds 50mmHg (Akdam et al., 2015; Erek, 2012). The pressure that disrupts blood circulation for more than six hours may cause ischemia and necrosis in the distal of the extremity due to vasoconstriction (Sever et al., 2015). Muscle masses that are exposed to severe necrosis trigger renal failure. Regulation of renal blood flow prevents acute tubular necrosis, increases glomerular filtration, enables blood flow to

tubules, and may reduce the severity of renal failure (Akdam et al., 2015). Intracompartment pressure exceeding 50 mmHg leads to irreversible neurological damage and even amputation requirement. Application of fasciotomy is more advantageous in terms of protecting the distal extremity (Sever et al., 2015). The nurse should inform the patient that will undergo fasciotomy or amputation about the procedure along with the doctor, and cooperate with a psychologist before and after the operation (Yıldırım et al., 2018). The victim should be allowed to express their feelings and thoughts openly, to ask questions if they have any, and assistive tools such as crutches should be provided (Durna et al., 2009).

In the application of fasciotomy, the area covered in skin gets opened and this is an important risk factor for septicemia. It should not be performed unless there is an exact indication (Akdam et al., 2015). Extremity amputation may be necessary due to local infections. The duration the patient was left under debris, the inflammatory response of the extremity and the development of compartment syndrome suggest the options of fasciotomy and amputation (Sever et al., 2015; He et al., 2011). Bandage should not be applied to the extremity to which fasciotomy is applied in order not to disrupt blood circulation, and the localization, width, length and depth of the wound should be recorded. If there is an exudate in the incision area, it should be monitored, the humidity of the surrounding area should be sustained, the surrounding tissue should be preserved, and the extremity should be monitored in terms of hypothermia (Uysal et al., 2017; Wilkinson, 2017; Durna et al., 2009).

Amputation is among the oldest surgical procedures (Maralcan, 2017). Developed for the first time in 1990 and still used today, the "traumatized extremity severity score" (MESS [Mangled Extremity Severity Score]) is the most commonly used score in making an amputation decision. In this scoring system, the patient is evaluated with four parameters as "muscle and skeletal tissue injury, extremity ischemia, shock and age". Scores of 7 or greater at the end of the patient evaluation strengthen the possibility of amputation (Erdem et al., 2017). Disruption of blood circulation for extended periods of time, victims who were saved late, traumatized tissue and muscle group that cause myoglobin, advanced myonecrosis and infected extremities are workloads on organs and systems. The application of amputation may be opted

for in order to save the patient (Sever et al., 2015). Signs of infection such as state of consciousness, vital signs, tissue perfusion, follow-up of drainage and bleeding if there is any, fever, shivering, and redness at wound site are monitored in the nursing care of the amputated patient. The amputated extremity is elevated and edema is monitored (Uysal et al., 2017; Wilkinson, 2017).

Another treatment that is applied to patients with compartment syndrome is *hyperbaric oxygen treatment (HBO_2)*. It is the process of exposing the entire body of the patient to 100% oxygen and pressure in order to break the cycle of hypoxia and edema in extremity damage (Sever et al., 2015; Dougherty, 2013). It is a treatment method performed by inhaling 100% oxygen in a closed high-pressure room under three times more atmospheric pressure than at sea level (Turgut et al., 2012; Rajagopalan, 2010). Hyperbaric oxygen therapy has positive effects on blood vessel and collagen formation and reperfusion damage as the infection is taken under control as a result of the reduction of colonization of anaerobic microorganisms on the tissue, the reduction of extremity edema due to vasoconstriction, and the increase of capillary blood circulation (hyperoxygenation) (Dougherty, 2013; Rajagopalan, 2010). Hyperbaric oxygen treatment should be applied once a day for 60-90 minutes in later times with 12-hour intervals after 6-8 hours for the first one or two days, 60-90 minutes once a day with 12-hour intervals (Turgut et al., 2012). Tissue perfusion follow-up, edema follow-up, pulse control especially in distal extremities, oxygen saturation monitoring, blood gas follow-up, and fluid intake-output follow-up are performed (Uysal et al., 2017; Wilkinson, 2017; Durna et al., 2009).

Another long-term complication that is observed in patients with crush syndrome is *infection*. Septicemia and multiorgan failure after disasters increase morbidity rates. For this reason, the appropriate prophylactic antibiotic treatment affects prognosis positively (Akdam et al., 2015). Application of prophylactic antibiotic treatment 24 hours before procedures such as fasciotomy, amputation, fracture reduction and laparotomy is of importance (Sever et al., 2015). Dirty and open wounds should be cleaned, the wound area should be monitored in terms of redness, temperature increase, swelling and defluxion and surgical debridement should be performed if necessary (Eti Aslan et al., 2014). Appropriate antibiotics should be planned out in accordance with the doctor's request as a result of the blood, urine and culture

samples taken from the defluxion area if there is any, treatment related to anaerobic bacteria, staphylococci and secondary gram-negative bacteria should be referred to if culture positivity is not in question. Dose planning should be made while taking the nephrotoxicity of pharmacological treatment into consideration. Tetanus toxoid vaccine should be administered to patients with open wounds who have no history of vaccination in the last five years or whose history of vaccination could not be determined in disaster conditions (Akdam et al., 2015; Sever et al., 2015).

Hospital nursing care for patients with crush syndrome is evaluated in terms of bleeding, infection risk, discomfort, wound care, changes in mental state, fluid electrolyte imbalance, deterioration in tissue perfusion, oliguria, anuria and hematuria. Casts and dressings that disrupt blood circulation should not be applied to extremities (Davies, 2016). Follow-up of vital signs and antibiotic treatment in accordance with the doctor's request should be initiated, renal failure findings should be monitored due to the nephrotoxic effect of the drugs (Eti Aslan et al., 2014). In blood biochemistry, the amount of fluid intake-output should be followed as well as BUN, creatinine and hyperkalemia, and mental state should be monitored and recorded. The intravenous catheter and urinary catheter probe opened in the emergency area should be renewed in the hospital environment. In hospital care, the removal of catheters such as unused drains, nasogastric/orogastric probes, urinary catheters and intravenous pathways will reduce the risk of infection (Davies, 2016).

Conclusion

Crush syndrome is a condition that occurs as a result of disasters, war, and accidents and requires immediate treatment. The management of the problems associated with Crush syndrome is done by training nurses, doctors, and first aid teams on the subject. The individual should be approached with the suspicion of crush syndrome from the moment they are recovered from trauma and potassium-free hypotonic NaCl (5% Dextrose + 0.9% isotonic NaCl) fluid replacement should be initiated. In nursing care, evaluations should be made in terms of the establishment of tissue perfusion, hydration support and diuresis, follow-up of intake-output, the establishment of fluid-electrolyte balance, hyperkalemia, hypovolemic shock and infection risk.

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Chapter IX

Homocystein Mechanism and Relation to Alzheimer

Ayhan VURMAZ

(Ph.D.), Afyonkarahisar Health Sciences University Medical Faculty Medical Biochemistry. Afyonkarahisar-Turkey, ayhan.vurmaz@gmail.com

Mine DOSAY-AKBULUT

(Assoc. Prof. Ph.D.) Mine Dosay Akbulut Afyon Kocatepe Uni. Veterinary Faculty, Medical Biology and Genetics Dep., Afyonkarahisar-Turkey, E-posta: minedosay@aku.edu.tr

Introduction

Alzheimer's disease (AD) is a progressive and irreversible neurodegenerative disorder that results in massive hippocampal and neocortical neuronal loss leading to dementia and eventual death. Alzheimer's disease (AD) is the most seen form of neurodegenerative disease. The Alzheimer's disease' specific pathological findings have been identified more than 100 years are as follows; senile plaques (CPs), synaptic loss, neurofibrillary tangles (NFTs) and neurodegeneration. Senile plaques are composed of amyloid-β (Aβ) and are surrounded by microglia, the primary immune effector cell in the central nervous system. Neurofibrillary tangles have been reported to occur by neurons accumulation of hyperphosphorylated tau protein. The cognitive deficiency in AD is associated with progressive synaptic and neuronal losses (1,2).

Molecular genetic and epidemiological hypotheses have been reported to cause amyloid beta and tau protein accumulation. The main problem in explaining the pathophysiology of Alzheimer's disease; is that the real mechanism causing to disease is still unexplained.

The vast majority of AD included a sporadic, clear cause and a combination of environmental and genetic factors. Sporadic AD (sAD) is determined as follows; It has been reported that combined metabolic systemic factors such as atherosclerosis and cardiovascular disease, increased serum homocysteine levels and hypercholesterolemia and family dementia in the middle ages have been reported.

Homocysteine is a naturally occurring amino acid produced as part of the body's methylation process. The level of homocysteine in the plasma is increasingly being recognised as a risk factor for disease and seen as a predictor of potential health problems such as cardiovascular disease and Alzheimer's (1,3,4).

The hypothesis that homocysteine (Hcy) is a risk factor for AD occurred at the beginning by observing that patients with histologically confirmed AD were more likely to have plasma levels of Hcy, also referred to as hyperhomocysteinemia (HHcy), than those controlled by age. Most of the evidence collected so far implies HHcy as a risk factor for the onset of AD, but there are also contradictory results. Assessments of hyperhomocysteinemia leading to vascular damage, cognitive impairment, neurological complications, congenital defects and pregnancy complications are common to all these cases.

According to different studies, elevated plasma homocysteine levels have been linked to poor cognition, Alzheimer's, dementia, poor concentration, diminished memory, reduced judgment and mood. Also these studies results indicate that; increased plasma homocysteine level was found to be a strongly independent risk factor for the progress of dementia and Alzheimer's disease.

Epidemiological studies have revealed a relationship between hyperhomocysteinemia with both histologically supported AD and disease progression, and it has been demonstrated that dementia in AD is associated with evidence of brain infarcts in the autopsy. For this reason, hyperhomocysteinemia and AD may be associated with stroke or microvascular diseases.

Hyperhomocysteinemia (HHcy), the abnormal elevation of blood levels of homocysteine (Hcy), has been proposed to be a modifiable risk factor for AD. Hcy is a sulfur-containing, non-protein amino acid produced in the methionine cycle. Its metabolism is at the overlap of two main pathways: trans-sulfuration and remethylation. While methionine levels are high,

Hcy follow the trans-sulfation path with cystathionine including serine and then to form cysteine with a irrevocable reaction. Therefore, the high level of Hcy, can be reduced via the diet of folic acid and vitamin Bs.

When the methionine level is low, Hcy is remethylated into methionine; a process which needs vitamin B12 and folic acid as cofactors (2,3).

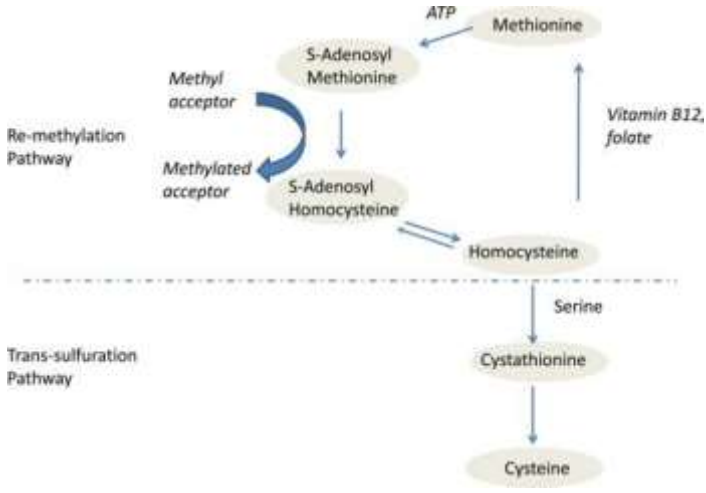

Fig. 1: Homocysteine mechanism(5).

Since the first article reporting the rise of Hcy in AD patients, a number of studies have been conducted to investigate the relationship between HHcy and AD risk. Results from human and animal studies suggest that moderate Hcy elevation in the elderly population is a potential risk factor for AD. When the Hcy level is higher than 14 μM, the risk of AD almost reach to twice in people over 60 years of age. However, there is also contradictory evidence, and it is still controversial whether HHcy is a risk factor for AD or just a bio producer.

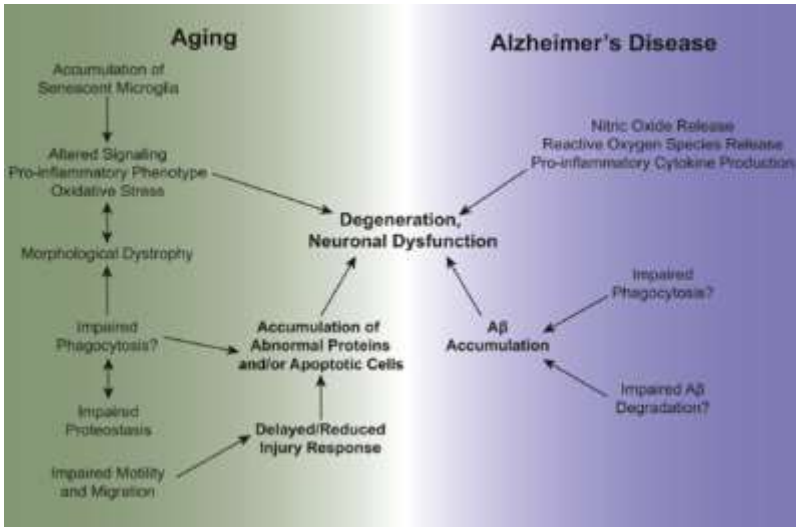

Fig. 2: Aging and Alzheimer Disease (6).

Sporadic AD (sAD) is determined by:

(a) Apolipoprotein allele ε4 (ApoE4), α2-macroglobulin, low weight lipoprotein receptor 1 (both on chromosome 12), very low weight lipoprotein R (chromosome 9), interleukin 1a (chromosome 2), clusterin (chromosome 8), single or combined low-impact genetic factors, such as the phosphatidylinositol binding clathrin binding protein (PICALM, chromosome 11) and the complement component (3b / 4b) receptor 1 (CR1 chromosome 1) and others; (7-9).

(b) Environmental factors such as recurrent brain trauma (eg pugilistic dementia).

(c) It has been reported that atherosclerosis and cardiovascular disease, increased serum homocysteine levels in middle age and combined metabolic systemic factors such as hypercholesterolemia and family history of dementia (10-12) .

Betain converts itself into dimethylglycine (DMG) by giving Hcy a methyl group, while Hcy becomes methionine. It has been shown that choline indirectly supports Hcy methylation (13-16).

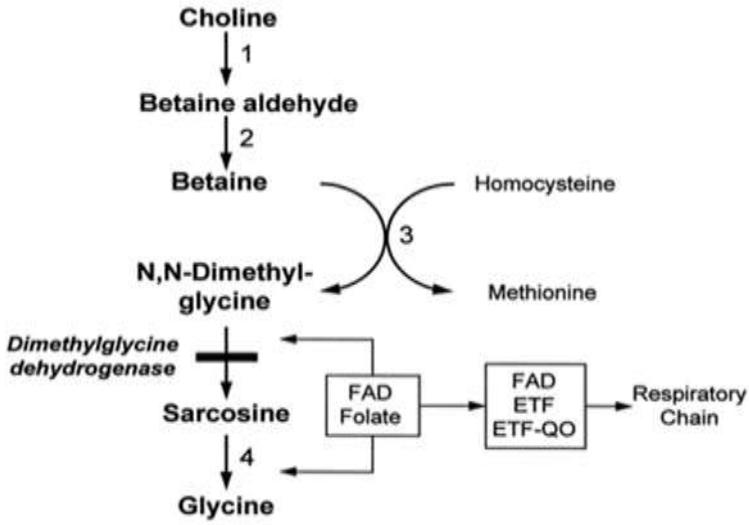

Fig. 3: Glycine occuring mechanism (17).

The complex metabolism of homocysteine within the body is highly dependent on vitamin derived cofactors, and deficiencies in vitamin B12, folic acid and vitamin B6 are associated with raised homocysteine levels. Other factors thought to raise levels are poor diet, poor lifestyle - especially smoking and high coffee and alcohol intake, some prescription drugs (such as proton pump inhibitors), diabetes, rheumatoid arthritis and poor thyroid function(18).

Raised levels of homocysteine are also linked to Alzheimer's, dementia, declining memory, poor concentration and judgment and lowered mood. Women with high homocysteine levels possibly come a cross with repeated early miscarriage. High homocysteine has also been linked to migraines, and those with conditions such as diabetes and osteoporosis are at increased risk of raised homocysteine levels. Homocysteine has therefore been shown to play a crucial role as a key marker for disease development

Why is Homocysteine Harmful?

Homocysteine is a naturally occurring amino acid produced within the methylation process. It is a derivative of protein that is found in blood plasma when body chemistry is out of balance. It is a homologue of the amino acid cysteine, with the differences of an additional methylene (-CH2-) group. Homocysteine is not obtained

from the diet, instead, it is biosynthesized from methionine via a multi-step process.

Methionine is an amino acid and is found primarily in meats, eggs, dairy products, chicken, fish, nuts and some vegetables. Methionine is activated to S-adenosylmethionine (SAM) via the methionine adenosyltransferase enzyme. Circulating levels of homocysteine are generally low because of its rapid metabolism via one of two pathways: a pyridoxal 5' phosphate (PLP, vitamin B6) dependent trans-sulphuration pathway that transform homocysteine into cysteine or a cobalamin (vitamin B12) and folate dependent re-methylation pathway that recompose methionine (12-14).

The complex metabolism of homocysteine depends on vitamin derived cofactors, and deficiencies in folic acid, vitamin B12 and B6 are associated with hyperhomocysteinaemia. The reason of cell damage and the onset of major disease, caused by homocysteine accumulation in the body, is because the biochemical transformation process is not working properly, generally due to lack of needed vitamins.

The possible effect of hyperhomocysteinaemia that cause harm such as vascular damage, cognitive impairment, neurological complications, congenital defects and pregnancy complications are common to all these conditions. It was indicated that; raised homocysteine is related to damage in the arteries and one mechanism explaining of this mechanism is by interfering with the way cells use oxygen, resulting in a build-up of damaging free radicals.

What Causes Raised Homocysteine Levels?

Alot of different factors are thought to cause raising of homocysteine levels; among them are poor diet, poor lifestyle especially alcohol intake, smoking and high coffee, some prescription drugs, rheumatoid arthritis, diabetes and poor thyroid function. The age triggeres the rising homocyteine levels and higher levels are seen mostly in men than women. As with cholesterol, family history and genetic make-up can play a partly role in raising of levels as well as obesity and lack of exercise.

Several different genes that regulate the enzymes that are involved in methionine metabolism have been determined. A decrease of these genes activity like one of them that regulates the

enzyme methyl-enetetrahydrofolate reductase (MTHFR) increases mean homocysteine levels (14-16).

The most important nutrients that help lower homocysteine levels are folate, the vitamins B12, B6 and B2, zinc and trimethylglycine (TMG).

The aim of treatment of classic homocysteinuria is to decrease the accumulation of homocysteine. The first idea for this treatment based on the insufficient methionine diet. After that; come forward treating with pyridoxine as the cofactor of CβS, a subclass of this disease. Another alternative method is using of Betain which seem to be the most effective and usable without side effect compare to most others (16,19).

Use of Betain in Classical Homocysteine

In the case of classical HHcy, it is better to use betaine in most cases against to methione treatment method. For example in most cases, methionine-restricted diet are quite difficult; is mostly anadaptive with diet; can cause to some health problems and purchising of these special diets can be difficult. Against to all these negative effect of Methionine restricted diets alternatively, using betaine as an treatment may provide partial control of Hcy levels in these patients, and suggested as an alternative for these patients (12-15,19).

İt is important to know the relationship between AD and homocysteine mechanism and found the right treatment aginst to homocysteine level in case of AD possibility. For this aim some of these similar research and studies are summarized in this part.

Literature Review

On the basis of all these informations; it was understood that there is close relationship between elavated homocyctein levels and Alzheimer and Dementia. So to support this indication and opinion several different studies were searched and summarized.

In one study; A total of 1092 subjects without dementia (667 women and 425 men; mean age, 76 years) were used and the relationship between plasma total homocysteine level and Dementia cases or dementia-related nutritional and vitamin deficiencieswere searched. The multivariable proportional-hazards regression were used to adjust for age, sex, apolipoprotein E

genotype, vascular risk factors other than homocysteine, and plasma levels of folate and vitamins B12 and B6.

On the result; in a period of eight years, dementia developed in 111 subjects, including 83 given a diagnosis of Alzheimer's disease. The multivariable-adjusted relative risk of dementia was 1.4. The relative risk of Alzheimer's disease was 1.8 with a plasma homocysteine level greater than 14 micromol per liter, the risk of Alzheimer's disease nearly doubled. This study was summarized that an increased plasma homocysteine level is a strong, independent risk factor for the development of dementia and Alzheimer's disease (20).

In another study; to understand the exact cause of Alzheimer's disease especially, focusing to high plasma concentration of homocysteine (Hcy) a possible cause to Dementia this study was carried out. For this aim; rat model of global forebrain ischemia (IRI) combined with the experimentally induced hHcy were demontrated . The results showed remarkable neural cell death induced by hHcy in the brain cortex and neurodegeneration is further aggravated by global IRI. They obtained degeneration of cortical neurons, alterations in number and morphology of tissue astrocytes and dysregulation of oxidative balance with increased membrane protein oxidation. Complementary to, an immunohistochemical analysis of tau protein and β-amyloid peptide showed that combination of hHcy with the IRI might lead to the progression of AD-like pathological features. According to these findings they suggest that combination of risk factor hHcy with IRI aggravates neurodegeneration processes and leads to development of AD-like pathology in cerebral cortex (21).

Different study was carried out to determination of endothelin receptor against β-amyloid induced AD type of vascular dementia. This disease was applied by combine administration of single ICV (intracerebroventricle) infusion of β-amyloid (Aβ) once and chronic oral administration of l-Methionine for 21 days. Bosentan (dual endothelin receptor antagonist) was administered for 21 days. Behavioral alterations were observed in different time of the study. Oxidative parameters, acetylcholinesterase activity, neuro-inflammatory markers, amyloid beta levels were obtained from hippocampus and cortex while serum homocysteine, serum nitrite carotid artery superoxide anion level were also determined. According to finding; significant development of cognitive and vascular endothelial deficits, manifested in terms of increase in

serum homocysteine level, endothelial dysfunction, impairment of learning and memory, enhanced brain acetylcholinesterase activity and marked mito-oxidative damage were obtained in rats. The results of this study concluded that bosentan give a possibility in protection against β-amyloid-induced vascular dementia in rats (22).

Another study based on investigation of the effects of simultaneous supplement of betaine on Alzheimer-like pathological changes and memory deficits in hyperhomocysteinemic rats after a 2-week induction by vena caudalis injection of homocysteine (Hcy). It was obtained from the result that supplementation of betaine could ameliorate the Hcy-induced memory deficits, enhance long-term potentiation (LTP) and increase dendritic branches numbers and the density of the dendritic spines, with up-regulation of NR1, NR2A, synaptotagmin, synaptophysin, and phosphorylated synapsin I protein levels. Supplementation of betaine also attenuated the Hcy-induced tau hyperphosphorylation at multiple AD-related sites and also decreased Aβ production with decreased presenilin-1 protein levels. These findings suggest that betaine could be a promising candidate for arresting Hcy-induced AD-like pathological changes and memory deficits (3).

Similar study was conducted for searching of HC plasma levels in a group of Alzheimer's (AD) patients and compared with a group of age-matched patients. It has been confirmed that a positive correlation exists between age and HC plasma levels in the control group, but not in the AD patients. These results may indicate that in AD patients high HC plasma levels (possibly associated with high glycine levels and/or excessive glutamate release) have an significant neurodegeneration and, once this process has been triggered off, the plasma HC levels become independent from the age related increased HC plasma levels (23).

Another study based on the determination of folic acid deficiency and AD link. For this aim; in this study the hypothesis that impaired one-carbon metabolism resulting from folic acid deficiency and high homocysteine levels promotes accumulation of DNA damage and sensitizes neurons to amyloid beta-peptide (Abeta) toxicity were tested. According recent findings; persons with low folic acid levels and elevated homocysteine levels are at increased risk of Alzheimer's disease (AD). Their finding indicate that folic acid deficiency and homocysteine impair DNA repair in

neurons, which sensitizes them to oxidative damage induced by Abeta (24).

Another review study indicate that; according to several different epidemiological studies there is a close relationship between hyperhomocysteinaemia and both histologically confirmed AD and disease progression and hyperhomocysteinaemia to be a strong, independent risk factor for dementia and AD. Thus, hyperhomocysteinaemia and AD could be linked by stroke or microvascular disease. Also there is known relations between B-group-vitamin deficiency and both hyperhomocysteinaemia and neurological dysfunction, give a possiblity for prevention of AD with dietary modification or food fortification (25).

Another study was carried out in USA. This study included 340 participants with a diagnosis of probable AD. Active treatment was daily 5 mg folic acid, 1 mg B12, and 25 mg B6 for 18 months, which lowered tHcy by 26% (from 9.2 to 6.78 μmol/L). These results suggest that B vitamin treatment may be effective in patients with mild AD but not in those in whom the disease has progressed to the moderate stage (26).

Conclusion

The complex metabolism of homocysteine within the body is highly dependent on vitamin derived cofactors, and deficiencies in vitamin B12, folic acid and vitamin B6 and it is associated with raised homocysteine levels. Raised levels of homocysteine are also linked to Alzheimer's, dementia, declining memory, poor concentration, judgment and lowered mood. The reason homocysteine accumulates in the body causing cell damage and the onset of major disease, is because the biochemical transformation process is not working properly, usually due to lack of these needed vitamins. Homocysteine has therefore been shown to play a crucial role as a key marker for disease development determining longevity and health throughout a person's life. Results from human and animal studies suggest that moderate Hcy elevation especially in the elderly population is a potential risk factor for AD. When the Hcy level is higher than 14 μM, the risk of AD almost reach to twice in people over 60 years of age. Hyperhomocysteinemia (HHcy), the abnormal elevation of blood levels of homocysteine (Hcy), has been proposed to be a modifiable risk factor for AD. The most important nutrients that

help lower homocysteine levels are folate, the vitamins B12, B6 and B2, zinc and trimethylglycine (TMG) and it is very important to keep homocyteine level in lower grade to reduce or eliminate AD possibility. It was reported that folate, pyridoxine and betaine combination could be used in these patients as an treatment packet.

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