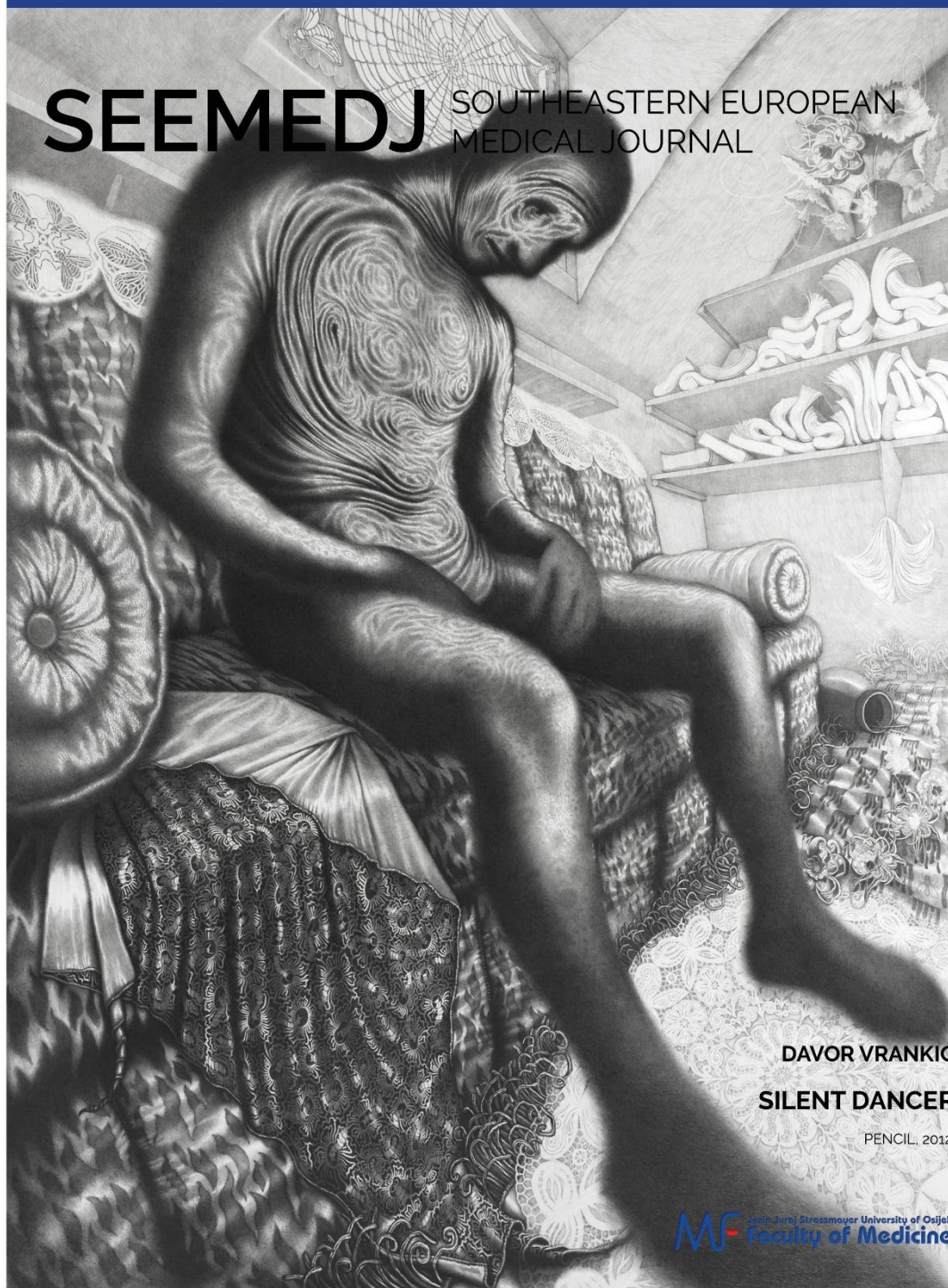


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MEDICAL JOURNAL



DAVOR VRANKIĆ
SILENT DANCER

PENCIL, 2012.

MF Josip Juraj Strossmayer University of Osijek
Faculty of Medicine

Davor Vrankić, born in Osijek, Croatia in 1965 (collection of the Museum of Fine Arts in Osijek)

Silent Dancer, 2012

Pencil drawing

"For the last twenty years I've been making drawings in graphite 0.9 mm lead 2B pencil, mostly large drawings. By using this basic technique, I try to maximize its effect to the fullest extent. Without using any model or sketch, I go about creating some kind of virtual image by using all the visual experiences that were instilled in me by classical art, cartoons, cinematography, videography and photography. I draw connections between the frame of a movie, distorted camera lenses and Flemish painting. While at the same time evoking the characteristics of old engravings, the small strokes of the pencil also refer to black and white photography or cinematography. The result is an image that seems almost real, but it is completely fictional, created by combining the logic of synthetic imagery with classical drawing. I develop my technique towards achieving an almost photorealistic expression, making my drawings as realistic as possible. This approach is intended to analyse and critically evaluate the role that images play in modern-day life and to point out to their ambiguous nature."

(Author's comment on his work)

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Original article

Assessment of Nutritional Status of Elderly People in a Family Medicine Practice in Relation to MNA Test, Comorbidity and Chronic Therapy

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Abstract

Introduction: Nutrition assessment is one of the biggest challenges in family medicine practice because of the increasing number of older people with more comorbidities and chronic therapy. The MNA (Mini Nutritional Assessment) test has proven to be the most sensitive and exact tool for this type of research. The aim of this study was to assess whether there is a difference in the nutritional status of elderly people, over 65 years of age, with respect to sociodemographic characteristics, number and type of chronic diseases, and number of medications used in chronic therapy.

Materials and methods: Research subjects were 207 patients at the age of 65 treated at the Medical Centre Slavonski Brod during a period of 3 months. During the visit, the nutritional status was examined by using the MNA test. The information on chronic diseases and number of medications the patients were using has been collected from the Medicus computer program.

Results: According to the MNA test results, 62 subjects (30%) showed risk of malnutrition, average age of the subjects was 72 years and the median of MNA test results was 25.50. Also, multimorbidity is present in 64.73% of the subjects and 42% of them take more than three medications in chronic therapy. No statistically significant difference was found in the results of the MNA test regarding the number of chronic diseases ($p = 0.89$) and number of medications ($p = 0.87$).

Conclusion: It is important to regularly monitor the nutritional status in order to prevent progression of chronic diseases and reduce additional cost of treatment.

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KEYWORDS: nutritional assessment, comorbidity, polypharmacy

Introduction

According to the latest epidemiological data, there is a negative demographic trend in the Republic of Croatia that is evident by the increased number of older people (1,2). Demographic aging has affected the Republic of Croatia, with particular focus on people over 65 years of age who represent the fastest-growing population segment in the world (3,4). According to the 2011 population census data for the Republic of Croatia, 24.1% persons were older than 60 and 17.7% of persons were over 65 years of age. According to the World Health Organization (WHO), the Republic of Croatia is among the countries with a high percentage of population over 65 (3). According to data of the Croatian Institute for Public Health (HZJZ), life expectancy for elderly people has increased from 71.0 years in total (66.1 for men, 76.2 years for women) in the year 1991, to 77.9 years in total (74.7 for men, 81 for women) in the year 2014 (4). With the increase of the percentage of older population, there is also a significant increase in the number of medical examinations, consumption of medicinal products and the number of hospitalizations, which requires better socioeconomic awareness and new strategies in treatment of patients.

Aging weakens the integrative functions of the endocrinological and immune systems. It also causes the accumulation of free radicals, which, in turn, leads to morphological and functional changes in the body and shortens the cellular life span. Morphological changes are observable in all organs. These changes are characterized by reduction in cell volume, atrophy and progressive loss of cells (5, 6, 7). Also, changes in the cardiovascular system imply lower heart rate, decrease in catecholamine sensitivity and in myofibril contractility (6, 7). There are also changes in the respiratory function, which are characterized by an increased residual volume, decreased parenchyma elasticity and higher risk of developing atelectasis.

Chronic disease is defined by WHO as a long-lasting and slow-progressing condition. Today it is the most common and most expensive health

care problem. There are numerous factors which contribute to its development. These are, in addition to the medical ones, socioeconomic factors and political, cultural and environmental aspects (8). Therefore, comorbidity represents one of the greatest challenges in 21st century medicine, because it describes the simultaneous occurrence of two or more diseases. This presents a challenge in both scientific research and daily clinical practice and treatment of patients. Sometimes treatment for one disease leads to the appearance or exacerbation of another disease, including potentially a fatal outcome and premature death. Furthermore, the presence of more diseases and conditions concurrently is directly related to higher mortality, deficient functioning, lower quality of life and more frequent hospitalizations.

Malnutrition can be defined as a nutrient imbalance in which the intake of energy and other nutritional factors is lower than their consumption. This leads to the development of chronic diseases. Malnourished patients are reported to be prone to infections, which lead to prolonged hospitalizations and increased costs of healthcare (10, 11). Also, numerous diseases of different organ systems can lead to malnutrition. This means that malnutrition is caused by changes in intake, digestion or absorption of food but also by changes in the metabolism and excretion and/or metabolic requirements for energy, protein and other nutrients (12). In addition, malnutrition can also be a result of low socioeconomic level, inadequate nutritional support as well as the nature of the disease itself (loss of appetite in various acute and chronic diseases).

Older age is associated with the presence of chronic diseases. This, due to various pathophysiological mechanisms, such as an increased degree of chronic inflammation and oxidative stress, leads to muscular wasting, but also to other changes related to malnutrition (e.g. loss of some micronutrients). Multimorbidity, malnutrition and muscular wasting (sarcopenia) increase the risk of negative health outcomes, such as

hospitalizations, dependence on others to perform daily activities and premature death (13). Important indicators of nutritional status are biochemical methods based on blood and urine tests, where serum protein levels are an especially important factor. Albumin is the most prominent in the serum proteins and also the most cited biochemical parameter mentioned in literature as an indicator of malnutrition (14, 15).

Questionnaires for nutrition status testing are the most useful tools because they are more comprehensive than other measures (based on multiple measured parameters) used in the assessment. Furthermore, the literature describes many different questionnaires that have been used so far in clinical practice. The MNA-SF (Mini Nutritional Assessment - Short Form) test is a widely used screening tool designed to examine the nutritional status of the elderly, whether they are hospitalized, housed in nursing homes or living independently in a community. This test is used by healthcare professionals and it is based on recording the BMI, food intake, weight loss in the last three months, mobility and the presence of psychological stress and neuropsychological problems in the last three months. Screening of the elderly for malnutrition is easier to carry out in general/family medicine practice because it is easier to retrieve general population data there. For this purpose, simple but comprehensive and accurate screening tools are required. The MNA test has proven to be one of the most appropriate tools (16, 17).

The aim of this study was to assess whether there is a difference in the nutritional status of the elderly, at the age of 65 or over, with respect to sociodemographic status, number and type of chronic diseases, number of medications in chronic therapy and the achievement on the MNA test.

Patients and methods

The study was conducted on 207 patients (N=207), aged 65 and over, who were treated at the family medicine practice in the Health Centre of Slavonski Brod (Dom zdravlja Slavonski Brod). This was done during a period of three months (from January to March 2019). Research subjects were treated for various reasons, except those listed as exclusion criteria (patients suffering from acute illnesses and sudden health problems, patients with malignancies, patients with limb amputations, patients examined during home visits, patients on chronic haemodialysis program). When it comes to gender, 90 of the research subjects were men (N=90, 43.47%) and 117 were women (N= 117, 56.52%).

A Medicus computer program was used to obtain information on chronic diseases and the number of medications in chronic therapy. During the patients' ambulatory visit, a nutritional assessment was performed using the MNA test. The longer version of this test was used. It consisted of 18 questions, which examined patients' eating habits, type of food they consume, the number of medications in chronic therapy and patients' personal opinion about their own health condition. The maximum number of points that could be scored in the MNA test was 30. The score ranging from 24 to 30 points indicates a good degree of nutrition, 17 to 23.5 indicates a risk of malnutrition and less than 17 points indicates malnutrition (16, 17).

Clinical characteristics of patients are presented descriptively (categorical variables as absolute and relative frequency, and numerical variables as mean and standard deviation and as interquartile range and median). The chi-square test was used to examine the difference between categorical variables. Fischer's exact test was also used. All p-values are two-sided. The significance level will be set to $\alpha = 0.05$. The IBM SPSS 23 software package (IBM Corp. (2015) IBM SPSS Statistics for Windows, Version 23.0. Armonk, New York: IBM Corporation) was used for statistical analysis.

Results

According to the MNA test results, 62 patients (30%) showed malnutrition risk and only 2

patients (0.9%) had malnutrition. Personal history of 134 subjects (64.73%) showed they suffered from more than three chronic diseases and 87 subjects (42%) took more than three medications (Table 1).

Table 1. Descriptive data of nutritional status (number and relative frequency) of the categorical variables used in the study

		N	Relative frequency
Gender	male	90	43.47%
	female	117	56.52%
Nutritional status	well-nourished	143	69.1%
	risk of malnutrition	62	30%
	malnutrition	2	0.9%
	stage 4	2	1%
Number of chronic diseases	< 3	73	35.26%
	≥ 3	134	64.73%
Number of drugs in chronic therapy	< 3	120	58%
	≥ 3	87	42%

The average age of the research subjects was 72 years (interquartile range 69 to 76 years) and the median MNA test result was 25.50 (interquartile range 23 to 27). Overall, both genders had three or more chronic illnesses present. Hypertension

was most prevalent as a chronic disease in both genders. Musculoskeletal disorders were more common in women, especially osteoporosis. Diabetes and COPD were equally present in both genders (Table 2).

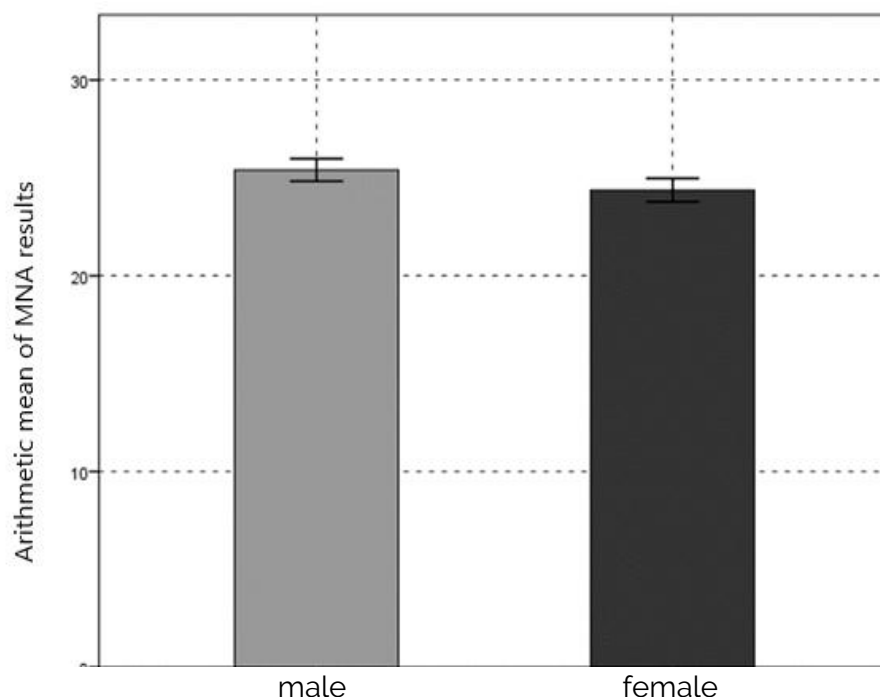
Table 2. Descriptive data (absolute and relative frequencies) on the type and number of chronic diseases depending on gender

	Number of respondents			
	Male		Female	
	N	Relative frequency	N	Relative frequency
> 3 chronic diseases	57	63.33%	77	65.8%
< 3 chronic diseases	33	36.7%	40	34.2%
Diabetes	17	18.9%	22	18.8%
Hypertension	79	87.8%	108	92.3%
Gastrointestinal diseases	27	30%	45	38.5%
COPD	7	7.8%	6	5.1%
Musculoskeletal disorders	34	37.8%	61	52.1%
Osteoporosis	1	1.1%	20	17.1%
Arthritis	11	12.2%	19	16.2%

The analysis of nutrition with respect to gender, showed a lack of significant difference in the frequency of nutrition status, $2(1) = 2.04$, $p = 0.15$. The result would be somewhat different if the achievement in the MNA test was measured by the average number of points, rather than the

categories of malnutrition. Accordingly, the results in the Student's t-test show a significant difference between the genders ($t(205) = 2.40$, $p = 0.02$), with men having a higher score ($M = 25.41$, $SD = 2.77$) than women ($M = 24.38$, $SD = 3.24$). These results are shown in Figure 1.

Figure 1. Arithmetic mean of MNA scores and associated confidence intervals (95%) in relation to gender



There was no difference in nutrition when taking into consideration the number of chronic diseases (<3 , ≥ 3), $2(1) = 0.02$, $p = 0.89$. Moreover, most of the men who are suffering from three or more diseases, showed good nutritional status.

On the other hand, further difference in nutritional status was examined regarding the presence of a single chronic disease (hypertension, musculoskeletal diseases, COPD, osteoporosis, arthritis). No significant statistical difference was observed in the distribution of frequencies of a specific chronic disease between well-nourished patients and patients at risk of malnutrition.

When it comes to examining the nutritional status of older women, regarding the number of

chronic diseases, it should also be mentioned that most women suffering from three or more diseases showed good nutritional status. The nutritional status with respect to the presence of an individual disease did not show a significant statistical difference in the nutritional status between well-nourished elderly women and women at risk of malnutrition.

Apart from gender, differences in nutritional status were examined considering the age factor. Subjects were divided into four categories according to their age; 65 to 69, 70 to 72, 73 to 76 and 77 to 91 years of age. The first age group (65-69 years) was the one with the highest percentage of three or more chronic diseases (Table 3).

Table 3. Distribution of respondents by age categories and nutritional status

P

		Number (%) of respondents			P
		Well-nourished	Insufficient nutrition	Total	
Number of chronic diseases (65 – 69)	< 3	22 (33.3)	6 (9.1)	28	0.56*
	≥ 3	32 (48.5)	6 (9.1)	38	
	total	54	12	66	
Number of chronic diseases (70 – 72)	< 3	14 (31.8)	3 (6.8)	17	>0.99†
	≥ 3	22 (50)	5 (11.4)	27	
	total	36	8	44	
Number of chronic diseases (73–76)	< 3	8 (16.7)	5 (10.4)	13	0.73†
	≥ 3	24 (50)	11 (22.9)	35	
	total	32	16	48	
Number of chronic diseases (77 – 91)	< 3	6 (12.2)	9 (18.4)	15	0.79*
	≥ 3	15 (30.6)	19 (38.8)	34	
	total	21	28	49	

-statistical significance, * - Chi-square test, † - Fisher's exact test

Examining the difference in nutritional status with regard to the number of medications a subject was taking, the chi-square had no significant use, $\chi^2(1) = 0.02$, $p = 0.87$. To check the potential direction of the difference, Student's t-test was again performed on the MNA nutritional assessment, comorbidity, polypharmacy etc, showing no significant difference ($t(205) = 0.59$, $p = 0.55$). However, upon examining the degree of malnutrition considering patients' age and score on the MNA test, it was observed that well-nourished patients were younger ($M = 72.02$, $SD = 5.38$) than malnourished patients ($M = 75.64$, $SD = 6.12$).

Discussion

One of biggest challenges for a family medicine doctor is to recognize and prevent malnutrition due to negative demographic situations and a

large number of elderly people. Also, there are other factors that make this work and the objectivity of clinical judgment more difficult. These include a large number of outpatient examinations, lack of medical staff and working as a substitute in different outpatient clinics.

The results obtained in our research showed that elderly people are often diagnosed with two or more chronic diseases. However, the results also show that there is no significant correlation between the number of chronic diseases and nutritional status. It should be emphasized that elderly men and elderly women show signs of multimorbidity equally (Table 1).

One of the biggest challenges was to choose a proper screening tool for malnutrition (18, 19). Reasons for that are multimorbidity and a relatively high number of medications used in

chronic therapy, which are associated with higher mortality and a lower quality of life.

Previous research has shown that taking six different medications increases the risk of adverse effects up to 80%. Also, taking eight medications increases the risk of medication interactions up to 100% (19, 20). In our research, 87 participants (42%) took more than three medications (Table 1). Based on the given results, in order to prevent adverse effects, it is highly important to be aware of the number and type of medications used in chronic therapy. This study did not show any statistical difference between the number of medications and the nutritional status of elderly people.

In our research, only 62 (30%) participants out of 207 were at risk of malnutrition. These results confirm a good nutritional status of elderly people (Table 1). According to the results they achieved in the MNA test, research subjects were further examined based on differences in gender and age with regard to their nutritional status. It has been observed that men achieve a slightly higher score on the MNA test than women, which means that women are more at risk of malnutrition. These results are shown in Figure 1. On the other hand, it should be noted that the data obtained by the MNA result indicate a good degree of nutritional status in both cases (16, 17).

Results of this study do not differ significantly from the results found in the research by Kalan U. et al., who studied the connection between the MNA test, nutritional status and the potential factors that lead to malnutrition. Comparing our results to the results of the study conducted by Tavassoli et al., 30% of the results of participants at risk of malnutrition in our research are slightly lower than those for malnutrition according to the MNA test (21). In relation to age, we separated our participants into four groups. Patients at the age of 77 to 91, who make up 19.4% of our research subjects, showed risk for malnutrition. The adverse impact of multimorbidity on nutritional status is more manifested in older age groups (> 77 years), and the number of chronic disease (presence of 3

and > chronic diseases) is also increased (Table 3).

Overall, hypertension was the most prevalent chronic disease in both genders (Table 2). When it comes to good nutritional status of elderly people, it is expected that the majority of them suffer from a cardiovascular disease. This can be explained by the generally high prevalence of hypertension in elderly people, where three out of four people suffer from hypertension (19). Despite the presence of hypertension in both genders, there was no significant difference in nutritional status between research subjects, when hypertension and number of chronic diseases are taken into consideration.

Similar results were obtained by Ivana Platuzic in her research, as a part of her graduate work at the Faculty of Food Technology in Osijek (22). When compared to other chronic diseases, musculoskeletal disorders are more common in women (Table 2). Osteoporosis and arthritis were the disorders that were most presented in our research. These kinds of diseases are associated with degenerative changes and carry the risk of falls. Furthermore, it is important to be aware of the development of the physical disability syndrome, also known as the frailty syndrome. It is a common clinical syndrome in older adults that carries an increased risk for poor health outcomes that include disability, hospitalization and mortality. That is why this syndrome is of great interest to scientific circles.

Despite the greater distribution of osteoporosis in older women, there was no significant connection between nutritional status, presence of musculoskeletal diseases and the number of chronic diseases. However, the presence of musculoskeletal disorders and multimorbidity (> 3 chronic diseases) may have an effect on malnutrition only in the third and fourth age group (>73 and >77 years, respectively).

Furthermore, in future research, more attention should be paid to the diagnosis of painful back. This is important because more and more people perform sedentary work, which, over time, leads to the development of painful back. Moreover, it is important to make a stratification of diagnosis of painful back by the severity of the

symptoms and the clinical manifestation in order to evaluate degenerative changes.

In our research, occurrence of diabetes mellitus is very similar in both genders (Table 2). Moreover, there was no significant difference in nutritional status between men and women if we take into consideration the presence of diabetes and the number of chronic diseases.

Ursulin-Trstenjak et al. studied the relationship between obesity, hypertension and diabetes mellitus in elderly people. They have tried to prove a direct link between obesity and chronic diseases (23). In previous studies, malnutrition was evident in situations where chronic respiratory diseases were present (24). According to the small number of participants who suffered from chronic respiratory diseases, the data obtained showed a similar distribution of disease in both genders, and there was no significant statistical difference between nutritional statuses. In future research, for a better understanding of the connection between chronic respiratory diseases and nutritional status, it is important to have more research subjects involved.

Even though the previous studies have proven there is a connection between malnutrition and chronic gastrointestinal diseases, the results of this study showed no significant difference in the nutritional status of elderly men and women. While we did not isolate gastrointestinal diseases as specific factors, in future research for better understanding of nutritional status, it will be useful to isolate participants who suffer

from inflammatory bowel disease and multimorbidity.

The aim of this study was also to find a connection between age and nutritional status. Obtained data found a significant difference in the degree of nutrition with respect to age. It was observed that patients with normal nutrition were younger than those with poor nutritional status.

Even though there are many available screening tools for conducting research, the MNA test is still the most efficient one, because of its simplicity. According to the results of this cross-sectional study, as well as the results of previous studies, we can state that MNA is the optimal, accessible ambulatory tool for conducting research in family medicine practice.

This research has some limitations as it was conducted only in the Health Centre in Slavonski Brod. For more accurate data, it would be best to extend this research to other Health Centres in other counties and compare the results. One of the biggest problems that will affect family medicine practice in the next 40 years is an increased number of people over 60 years of age. It is expected that the number of elderly people will increase by 50%. Therefore, in future research, more attention should be focused on a comprehensive approach to nutrition monitoring in elderly people. To conclude, it is important to educate elderly people and raise their awareness of their own nutritional status in order to prevent malnutrition and improve their quality of life.

References

1. The Census of Population, Households and Dwellings 2011. Croatian Bureau of Statistics, Zagreb, 2011. Available at: <http://www.dzs.hr/>. Accessed: 13 June 2019.
2. Croatian Health Statistics Yearbook 2017. Available at: [https://www.hzjz.hr/wp-](https://www.hzjz.hr/wp-content/uploads/2019/03/Ljetopis_2017.pdf)
3. Nejašmić I, Toskić A. Starenje stanovništva u Hrvatskoj- sadašnje stanje i perspektive. Croatian Geographical Bulletin, 2013;75/1, 89 – 110.
4. Croatian Institute of Public Health. Usporedba pokazatelja o vodećim javnozdravstvenim problemima u Republici Hrvatskoj i Europskoj uniji.

- Available at:
https://www.hzjz.hr/wp-content/uploads/2017/01/Pokazatelj_RH_EU.pdf. Accessed: 13 June 2019.
5. Damjanov I, Jukić S, Nola M. Patologija, 3rd reworked and supplemented edition. Zagreb: Medicinska naklada; 2011. pp. 41-42.
 6. Vrندیć O, Kostić I. Patofiziološki mehanizam procesa starenja. Medicinski časopis. 2010;3, 30-36.
 7. Gamulin S, Marušić M. Patofiziologija, 7th updated and modified edition. Zagreb: Medicinska naklada. 2011; pp. 24- 27.
 8. Vukelić M. Percepcija bolesti i terapije u bolesnika s kroničnim bolestima. [Graduate thesis]. Zagreb: Faculty of Pharmacy and Biochemistry. 2016.
 9. Perko G, Tomek- Roksandić S, Mihok D, Puljak A, Radašević H, Tomić B. Vodeći multifaktorijski gerijatrijski sindrom u starijih osoba ("4N" u gerijatriji). Hrvatski časopis za javno zdravstvo. 2006; 20-22.
 10. Krznarić Ž. Klinička prehrana u gastroenterologiji. Medicus [Internet]. 2006 [accessed: 18 August 2019];15(1_Gastroenterologija):169-181. Available at: <https://hrcak.srce.hr/18845>.
 11. Vranešić Bender D, Krznarić Ž. Malnutrition - Undernutrition of Hospital Patients. Medicus. 2008. Volume 17, 71-79.
 12. Jeejeebhoy KN. Hospital malnutrition: is a disease or lack of food? Clin Nutr. 2003;22: 219.
 13. Haehling S von. The wasting continuum in heart failure: from sarcopenia to cachexia. Proceedings of the Nutrition Society. 2015;74:367-377.
 14. Fuhrman MP, Charney P, Mueller CM. Hepatic proteins and nutrition assessment. J Am Diet Assoc. 2004;104:1258-64.
 15. Fuhrman MP. The albumin-nutrition connection: separating myth from fact. Nutrition. 2002;18:199-200.
 16. Kalan U, Arik F, Isik AT, Soysal P. Nutritional profiles of older adults according the Mini-Nutritional Assessment. Aging Clin Exp Res. 2019.
 17. Soysal P, Veronese N, Arik F, Kalan U, Smith L, Isik AT. Mini Nutritional Assessment Scale-Short Form can be useful for frailty screening in older adults. Clin Interv Aging. 2019;14:693-699.
 18. Hien H, Berthé A, Drabo MK, Meda N, Konaté B, Tou F i sur. Prevalence and patterns of multimorbidity among the elderly in Burkina Faso: cross-sectional study. Trop Med Int Health. 2014;19 (11):1328-33.
 19. Katić M, Švab I et al. Obiteljska medicina. Zagreb 1st edition. Alfa; 2013.
 20. Zadak Z, Hyspler R, Ticha A, Vlcek J. Polypharmacy and malnutrition. Current Opinion in Clinical Nutrition & Metabolic Care. 2013;16 (1):50-55.
 21. Tavassoli N, Guyonnet S, Abellan Van Kan G, Sourdet S, Krams T, Soto MF et al. Description of 1,108 older patients referred by their physician to the "Geriatric Frailty Clinic" for assessment of frailty and prevention of disability at the gerontopole. J Nutr Health Aging. 2014;18:457-64.
 22. Platužić Ivana. Procjena statusa uhranjenosti starijih osoba. [Graduate thesis]. Osijek: Faculty of Food Technology Osijek. Josip Juraj Strossmayer University of Osijek, 2018

23. Uršulin-Trstenjak N, Levanić D, Hasaković-Felja M. Pretilost kao faktor rizika za nastajanje kardiovaskularnih-koronarnih bolesti. Tehnički glasnik. 2015;9:230-234.
24. Ezzell L, Jensen GL. Malnutrition in chronic obstructive pulmonary disease. The American Journal of Clinical Nutrition, Volume 72, Issue 6. 2000;1415-1416.

Original article

Do Nutrition Habits Influence the Clinical Presentation of Parkinson's Disease?

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Abstract

Introduction: Parkinson's disease (PD) is the second most common neurodegenerative disorder characterized with alpha-synuclein pathology. For the majority of patients, except for some genetic forms, etiology is still unknown. There are some implications that food intake and gut microbiota could contribute to PD.

Aim: The aim of this paper is to analyze the influence of protein, fruit and vegetable intake on the clinical presentation of idiopathic Parkinson disease

Patients and methods: Patients with idiopathic PD were surveyed for demographic data and nutritional habits in regards to protein, fruit and vegetable intake. Motor symptoms were evaluated using the Unified Parkinson Disease Rating Scale (UPDRS) part III and IV, cognitive impairment using Mini Mental State Examination (MMSE) and depression using Beck Depression Inventory (BDI).

Results: We have analyzed data of 96 patients. Patients using fewer dairy products have more often tremor type of PD ($p < 0.040$). We did not find any differences in severity of motor symptoms, disease stage, age when disease start, frequency of motor complications and fluctuation of therapy, depression and cognitive impairment according to protein, fruit and vegetable ingestion.

Conclusion: Higher intake of dairy products could influence the appearance of less favorable forms of Parkinson's disease (rigor type). Protein, fruit and vegetable intake do not influence the disease appearance, severity of motor symptoms, motor fluctuation and complication of therapy, disease stage, the appearance of cognitive impairment nor depression in Parkinson's disease patients.

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KEYWORDS: Parkinson's disease, nutrition, dairy products, protein, fruit, vegetables

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder characterised by alpha-synuclein pathology [1]. For the majority of patients, the etiology of the disease is still unknown. Some recent studies in PD patients are addressing food and its influence on gut microbiota [2]. It is known that PD patients have altered gut microbiota with abundance in proinflammatory and reduction in anti-inflammatory microbes [3]. Those changes can promote alpha-synuclein pathology in the enteric nervous system, which could spread in a prion-like manner to the brain [4]. Many studies have been done in order to explore the influence of various types of nutrition on the risk of Parkinson's disease. There have been papers reporting an increased risk associated with diets rich in animal fat [5,6], dairy foods [7,8], raw meat [9], and carbohydrates [10], while some other studies have not found a strong correlation between nutrition and the risk of PD [2, 11-13]. It has been shown that some nutrients could decrease the risk of developing PD in many ways. Monounsaturated (MUFAs) and polyunsaturated fatty acids (PUFAs) are known to have anti-inflammatory effects and they can reduce oxidative stress and inhibit apoptosis [14,15]. Vitamin A, B6, B9, B12, D and E have been proven to have protective effects and decrease the risk of PD [16-20]. Early post-treatment (after 6- hydroxydopamine toxicity) with retinoic acid in the animal model is able to provide protection from neurodegeneration in nigrostriatal dopaminergic neurons [16]. Decreased levels of vitamins B6, B9 and B12 lead to elevated levels of homocysteine. Hyperhomocysteinemia damages the DNA, depletes energy reserves and subsequently induces neuron apoptosis [21]. Calcitriol (vitamin D) reduces neuronal toxicity, while vitamin E has the ability to reduce MPTP-induced (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) toxicity in dopaminergic neurons [22,23]. Using food with anthocyanin- and proanthocyanidin-rich substances improves the mitochondrial function and reduces the level of neurodegeneration [24].

This paper aims to analyse the influence of protein, fruit and vegetable intake on the clinical presentation of idiopathic Parkinson's disease observed through several parameters: the age when the disease was diagnosed, severity of motor symptoms, type of Parkinson's disease, appearance of motor fluctuations and complication of therapy, depression and cognitive impairment.

Patients and Methods

The study was conducted on patients with idiopathic Parkinson's disease diagnosed during a regular check-up at the outpatient clinic at Osijek Clinical Hospital Centre. Their consent of participation in this study was obtained and the study was approved by the local Ethics Committee. The patients were surveyed for age, sex, disease duration, the age when the disease was diagnosed and nutrition habits pertaining to protein, fruit and vegetable intake for 3 months prior to the examination (part of the Mini Nutritional Assessment, source Nestlé Nutrition Institute). Motor symptoms were evaluated using the Unified Parkinson Disease Rating Scale (UPDRS) Part III (range from 0 to 103 points) and IV (range from 0 to 23 points), cognitive impairment symptoms were evaluated using the Mini Mental State Examination (MMSE; range from 0 to 30 points) and depression was evaluated using the Beck Depression Inventory (BDI; range from 0 to 63 points). According to the UPDRS Part III, patients were divided into 2 groups – rigor-dominant and tremor-dominant. Categorical data were presented as absolute frequencies and percentages, while the differences between nominal variables were tested by the Fisher's exact test. Numerical data were tested with the Shapiro-Wilk test for normality of data distribution. Afterwards, numerical data were presented with the mean and standard deviation in the case of normal, and with the median and interquartile range in the case of abnormal distribution. The comparison between nominal and numerical variables with normal distribution was tested using the One-way ANOVA or Student's t-test,

while for numerical variables with abnormal distribution, the Mann-Whitney and Kruskal-Wallis tests were used. Statistical significance was defined as $\alpha = 0.05$, while the statistical analysis was conducted with STATISTICA 13 (StatSoft Inc., Tulsa, Oklahoma, USA).

Results

A total of 96 patients were analysed, of whom 57 (59.4%) males and 39 (49.6%) females, with the mean age of 70.22 ± 8.598 . Regarding the type of Parkinson's disease, 50 (52.1%) patients had the tremor-dominant type, while 46 (47.9%) patients had the rigor-dominant type. Table 1 shows the data about disease duration, disease stage, the age of onset, UPDRS III, MMSE and BDI score.

Table 1. Demographic data, UPDRS III, MMSE, BDS data

	mean/median	std. dev./25th- 75th	min/max
Age	70.22	± 8.598	48/80
Disease duration	4.00	(2.00-10.00)	1/16
Age when disease started	64.64	± 9.730	36/81
Updrs lii	16.50	(10.25-23.75)	3/83
Mmse	26.00	(23.00-28.00)	15/30
Bds	13.60	± 8.992	0/44

UPDRS III – Unified Parkinson's Disease Rating Scale part III; MMSE – Mini Mental State Examination; BDS – Beck

Table 2 presents the frequency of nutrition intake. The majority of the patients eat meat every day (40.6%) or every other day (37.5%). More than two-thirds (71.9%) of the patients consume dairy products every day, while 68.8% of them consume two or more legumes and eggs per week. Half of them eat meat, fish and poultry every day and more than 2 pieces of fruit and vegetable per day (Table 2).

Table 2. Frequency of protein, fruit and vegetable intake

Food	N	%
Protein intake		
• once per week	4	4.2
• twice per week	17	17.7
• every other day	36	37.5
• everyday	39	40.6
Dairy products one per day		
• yes	69	71.9
• no	27	28.1
Legumes or eggs two or more per week		
• yes	66	68.8
• no	30	31.2
Meet, fish, poultry every day		
• yes	46	47.9
• no	50	52.1
Fruit or vegetable ≥ 2 per day		
• no	43	44.8
• yes	53	55.2

The UPDRS III and IV results were compared with the nutrition habits of PD patients, but no

significant difference was found. The comparison is shown in Table 3.

Table 3. Difference in UPDRS part III and motor complications and fluctuations of therapy according to protein, fruit and vegetable intake

	UPDRS III		„OFF“		DYSKINESIA	
	median	p	yes/no (N)	p	yes/no (N)	p
Protein intake						
• once per week	19.50		1/3		0/4	
• twice per week	22.00		10/7		2/15	
• every other day	17.00		15/21		5/31	
• everyday	15.00	0.580	17/22	0.572*	9/30	0.614*
Dairy products one per day						
• yes	17.00		30/39		11/58	
• no	16.00	0.925	13/14	0.820*	5/22	0.766*
Legumes or eggs two or more per week						
• yes	17.00		29/37		11/55	
• no	14.50	0.351	14/16	0.828*	5/25	1.000*
Meet, fish, poultry every day						
• yes	15.00		20/26		10/36	
• no	18.50	0.334	23/27	0.840*	6/44	0.275*
Fruit or vegetable ≥ 2 per day						
• no	17.00		19/25		6/37	
• yes	16.00	0.487	24/28	1.00*	10/42	0.656*

Differences in the age of disease diagnosis, MMSE and BDI score regarding the patients'

nutrition habits were also observed, but there were no statistically significant differences, as shown in Table 4.

Table 4. Difference in age when disease start, type of Parkinson's disease (tremor vrs rigor), MMSE and BDI according to protein, fruit and vegetable intake

	Age when disease started		Type of PD		MMSE		BDI	
	mean	p	t/r (N)	p	median	p	mean	p
Protein intake								
• once per week	68.00		2/2		25.50		18.50	
• twice per week	68.71		8/9		24.00		16.00	
• every other day	64.86		22/14		26.00		12.53	
• everyday	62.31	0.126	18/21	0.574*	26.00	0.179	13.05	0.274
Dairy products one per day								
• yes	65.29		31/38		26.00		14.45	
• no	62.96	0.295	19/8	0.040*	25.00	0.993	11.44	0.072
Legumes or eggs two or more per week								
• yes	65.27		35/31		25.00		12.82	
• no	63.23	0.344	15/15	0.828*	27.00	0.348	15.33	0.388
Meet, fish, poultry every day								
• yes	62.24		22/24		26.00		13.28	
• no	65.00	0.704	28/22	0.540*	25.00	0.323	13.90	0.991
Fruit or vegetable ≥ 2 per day								
• no	63.60		23/21		26.00		14.09	
• yes	65.31	0.399	27/25	0.835*	25.00	0.219	12.56	0.383

PD – Parkinson's disease; t/r – tremor vrs. rigor type; MMSE – Mini Mental State Examination; BDI – Beck Depression Inventory

The analysis of influence of nutrition habits of PD patients showed that the tremor-dominant group of PD patients consumed dairy products less frequently, while there were no statistically

significant differences in other nutrition habits of patients with tremor-dominant and rigor-dominant Parkinson's disease (Table 5).

Table 5. Comparison between type of Parkinson disease and nutritional habits of Parkinson disease patients

		Type of PD
	t/r (N)	p
Protein intake		
• once per week	2/2	0.574*
• twice per week	8/9	
• every other day	22/14	
• everyday	18/21	
Dairy products one per day		
• yes	31/38	0.040*
• no		
	19/8	
Legumes or eggs two or more per week		
• yes	35/31	0.828*
• no		
	15/15	
Meet, fish, poultry every day		
• yes	22/24	0.540*
• no		
	28/22	
Fruit or vegetable ≥2 per day		
• yes	23/21	0.835*
• no		
	27/25	

Discussion

Nutrition habits of 96 PD patients were surveyed for the purpose of analysing their influence on the clinical presentation of the disease. The majority of the patients ingested protein in the form of dairy products, eggs and legumes and half of them in the form of meat, fish and poultry on a daily basis. No difference in the age when

the disease was diagnosed, severity of motor symptoms, disease stage, frequency of motor fluctuations and complication of therapy, nor depression and cognitive impairment associated with protein, fruit and vegetable intake was found. It was only found that the patients consuming fewer dairy products more frequently suffer from tremor-dominant PD, which is a form of the disease with a favourable outcome [25]. Neuropathological studies have

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shown that the rigor-dominant type compared to the tremor type of PD exhibits a higher level of neuronal loss of the locus coeruleus, lateral and medial part of the substantia nigra with more severe gliosis, extra-neuronal melanin deposits and neuroaxonal dystrophy in the substantia nigra [26]. Many papers have reported a relation between dairy products and PD [27-30]. There are several possible explanations of how dairy products influence neurodegeneration and the risk of PD. One of the possible explanations is the influence of milk fat on gut microbiota. Milk fat (MF) and PUFA-rich fat had similar effects on Bacteroidetes and Firmicutes, but besides this, MF has the ability to greatly increase *Bilophila wadsworthia*. An increased level of *Bilophila wadsworthia* was associated with the pro-inflammatory T helper type 1 (T(H)1) immune response [31]. Dairy products also have the ability to reduce the uric acid level, which could cause a greater PD incidence and faster PD progression [32,33]. It is also known that they can induce insulin resistance and that this has an impact on the development of not only PD, but also of Alzheimer's disease [34,35]. People suffering from lactose intolerance and consuming dairy products are at the risk of intestinal inflammation and increased intestinal permeability. Besides that, milk could be contaminated with neurotoxic pesticides [36]. Finally, the ingestion of bovine microbiota could affect human microbiota through small intestinal bacterial overgrowth (SIBO), which could increase the risk of PD [37-39]. Marczevska et al. found in 45 advanced-stage PD patients that patients with high protein intake experience moderate to severe disease motor symptoms more frequently [40]. Serum carotenoid, retinol and tocopherol concentrations were lower in PD patients with severe motor symptoms and a more advanced stage of the disease [41]. Many studies have proved that high protein intake affects the motor response to levodopa therapy, causing the appearance of motor fluctuations [42], and that the use of a protein-redistribution diet helps with the amelioration of „on-off“ fluctuations [43]. On the other hand, a protein-restricted diet (PRD) has proven to worsen the fluctuations with the worsening of dyskinesia

[44]. This negative influence of proteins on the motor function is not present in early stages of PD and usually appears after 13 years of disease duration, or 8 years after levodopa was introduced in therapy [45]. No influence of protein ingestion on motor symptoms, motor fluctuations and complication of therapy was found, probably due to the fact that the study group of patients was mostly in the early stage of the disease (the median was 4.00 years), during which there is no such negative influence. The ingestion of saturated fatty acids, lower consumption of milk and dairy products and consumption of full-fat dairy products have a negative impact on age-related cognitive decline, mild cognitive impairment and vascular dementia [46]. There is limited data about the protective role of fruit and vegetable ingestion on cognitive decline, dementia and vascular dementia [46]. No differences in nutrition habits and cognitive impairment were found. The majority of our patients were diagnosed with mild cognitive impairment (MMSE median was 24.00) and were a rather homogeneous group (MMSE interquartile range from 23.00 to 28.00). Besides this, MMSE is not very sensitive to the subcortical type of cognitive impairment that is present in Parkinson's disease [47]. Therefore, a more heterogenous patient group with more sensitive tests for subcortical cognitive impairment should be used for more conclusive results. The MIND diet (the Mediterranean-DASH Intervention for Neurodegenerative Delay diet) that emphasises intake of fresh fruit, vegetables, and legumes was not associated with the reduction of depression risk, in contrast to the Mediterranean diet [48]. Consumption of full-fat yogurt was related to a lower risk of depression, but only in women, in the study of Pernez-Cornago et al [49]. There is evidence (in large-scale and well-conducted observational studies) that the ingestion of seafood, vegetables, fruit and nuts reduces the risk of depression [50]. Unfortunately, no significant differences between nutrition habits and depression were found in this study.

Higher intake of dairy products could influence the appearance of less favourable forms of Parkinson's disease (rigor-dominant type). This

study did not find any influence of protein, fruit and vegetable intake on the age of disease diagnosis, severity of motor symptoms, disease stage, motor fluctuations and complications of therapy, appearance of cognitive impairment or depression in Parkinson's disease patients. The limitation of this study is a small sample size. Furthermore, only the source of protein intake (meat, legumes or eggs, dairy) was analysed, while there are no evaluated sources regarding fruit and vegetables. For that reason, the data about the ingestion of fruit and vegetables producing antioxidant effects are limited. Therefore, the interpretation of our study results

must be taken with caution. Ethical approval: "All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards."

Informed consent: "Informed consent was obtained from all individual participants included in the study. Additional informed consent was obtained from all individual participants for whom identifying information is included in this article."

References

- Goedert M. Alpha-synuclein and neurodegenerative diseases. *Nat Rev Neurosci*. 2001; 2(7):492-501.
- Erro R, Brigo F, Tamburin S, Zamboni M, Antonini A, Tinazzi M. Nutritional habits, risk, and progression of Parkinson disease. *J Neurol*. 2018; 265(1):12-23.
- Scheperjans F, Aho V, Pereira PA, Koskinen K, Paulin , Pekkonen E, Haapaniemi E, Kaakkola S, Eerola-Rautio J, Pohja M, Kinnunen E, Murros K, Auvinen P. Gut microbiota are related to Parkinson's disease and clinical phenotype. *Mov Disord*. 2015; 30(3):350-8.
- Braak H, de Vos RA, Bohl J, Del Tredici K. Gastric alpha-synuclein immunoreactive inclusions in Meissner's and Auerbach's plexuses in cases staged for Parkinson's disease-related brain pathology. *Neurosci Lett*. 2006; 396(1):67-72.
- Anderson C, Checkoway H, Franklin GM, Beresford S, Smith-Weller T, Swanson PD. Dietary factors in Parkinson's disease: the role of food groups and specific foods. *Mov Disord*. 1999; 14(1):21-7.
- Logroscino G, Marder K, Cote L, Tang MX, Shea S, Mayeux R. Dietary lipids and antioxidants in Parkinson's disease: a population-based, case-control study. *Ann Neurol*. 1996; 39(1):89-94.
- Jiang W, Ju C, Jiang H, Zhang D. Dairy foods intake and risk of Parkinson's disease: a dose-response meta-analysis of prospective cohort studies. *Eur J Epidemiol*. 2014; 29(9):613-9.
- Hughes KC, Gao X, Kim IY, Wang M, Weisskopf MG, Schwarzschild MA, Ascherio A. Intake of dairy foods and risk of Parkinson disease. *Neurology*. 2017; 89(1):46-52. doi: 10.1212/WNL.0000000000004057.
- Hellenbrand W¹, Seidler A, Boeing H, Robra BP, Vieregge P, Nischan P, Joerg J, Oertel WH, Schneider E, Ulm G. Diet and Parkinson's disease. I: A possible role for the past intake of specific foods and food groups. Results from a self-administered food-frequency questionnaire in a case-control study. *Neurol*. 1996; 47(3):636-43.
- Hellenbrand W, Boeing H, Robra BP, Seidler A, Vieregge P, Nischan P, Joerg J, Oertel WH, Schneider E, Ulm G. Diet and Parkinson's disease II. A possible role for the past intake of specific nutrients: Results from a self-administered food-frequency questionnaire in a case-control study. *Neurol*. 1996; 47:644-650.
- Powers KM, Smith-Weller T, Franklin GM, Longstreth WT Jr, Swanson PD, Checkoway H. Parkinson's disease risks associated with dietary iron, manganese, and other nutrient intakes. *Neurol*. 2003; 60(11):1761-6.
- Logroscino G, Marder K, Cote L, Tang MX, Shea S, Mayeux R. Dietary lipids and antioxidants

in Parkinson's disease: a population-based, case-control study. *Ann Neurol.* 1996; 39(1):89-94.

13. Miyake Y, Tanaka K, Fukushima W, Sasaki S, Kiyohara C, Tsuboi Y, Yamada T, Oeda T, Miki T, Kawamura N, Sakae N, Fukuyama H, Hirota Y, Nagai M; Fukuoka Kinki Parkinson's Disease Study Group. Lack of association of dairy food, calcium, and vitamin D intake with the risk of Parkinson's disease: a case-control study in Japan. *Parkinsonism Relat Disord.* 2011; 17(2):112-6.

14. Fritsche KL. The Science of Fatty Acids and Inflammation. *Adv Nutr.* 2015; 6(3): 293S-301S. doi: 10.3945/an.114.006940.

15. Schapira AHV. Mitochondrial dysfunction in Parkinson's disease. *Cell Death and Differentiation.* 2007; 14(7):1261-1266. doi: 10.1038/sj.cdd.4402160.

16. Yin LH, Shen H, Diaz-Ruiz O, Bäckman CM, Bae E, Yu SJ, Wang Y. Early post-treatment with 9-cis retinoic acid reduces neurodegeneration of dopaminergic neurons in a rat model of Parkinson's disease. *BMC Neurosci.* 2012; 13:120. doi: 10.1186/1471-2202-13-120.

17. Miyake Y, Fukushima W, Tanaka K, Sasaki S, Kiyohara C, Tsuboi Y, Yamada T, Oeda T, Miki T, Kawamura N, Sakae N, Fukuyama H, Hirota Y, Nagai M. Dietary intake of antioxidant vitamins and risk of Parkinson's disease: a case control study in Japan. *Eur J Neurol.* 2011; 18(1):106-113.

18. Shen L. Associations between B vitamins and Parkinson's disease. *Nutrients.* 2015; 7(9): 7197-7208.

19. Lv Z, Qi H, Wang L, Fan X, Han F, Wang H, Bi S. Vitamin D status and Parkinson's disease: a systematic review and meta-analysis. *Neurol Sci.* 2014; 35(11):1723-30. doi: 10.1007/s10072-014-1821-6.

20. Golbe LI, Farrell TM, Davis PH. Follow-up study of early-life protective and risk factors in Parkinson's disease. *Mov Disord.* 1990; 5(1):66-70.

21. Kruman Il1, Culmsee C, Chan SL, Kruman Y, Guo Z, Penix L, Mattson MP. Homocysteine elicits a DNA damage response in neurons that promotes apoptosis and hypersensitivity to excitotoxicity. *J Neurosci.* 2000; 20(18):6920-6926.

22. Wang JY, Wu JN, Cherng TL, Hoffer BJ, Chen HH, Borlongan CV, Wang Y. Vitamin D(3) attenuates 6-hydroxydopamine-induced neurotoxicity in rats. *Brain Res.* 2001; 904(1):67-75.

23. Akaneya Y, Takahashi M, Hatanaka H. Involvement of free radicals in MPP+ neurotoxicity against rat dopaminergic neurons in culture. *Neurosci Lett.* 1995; 193(1):53-56. doi: 10.1016/0304-3940(95)11668-M.

24. Strathearn KE, Yousef GG, Graceetal MH. Neuroprotective effects of anthocyanin-and proanthocyanidin-rich extracts in cellular models of Parkinson's disease. *Brain Res.* 2014; 1555:60-77.

25. Marras C, Rochon P, Lang AE. Predicting motor decline and disability in Parkinson disease: a systematic review. *Arch Neurol.* 2002; 59(11):1724-8.

26. Paulus W, Jellinger K. The neuropathologic basis of different clinical subgroups of Parkinson's disease. *J Neuropathol Exp Neurol.* 1991; 50(6):743-55.

27. Park M, Ross GW, Petrovitch H, White LR, Masaki KH, Nelson JS, Tanner CM, Curb JD, Blanchette PL, Abbott RD. Consumption of milk and calcium in midlife and the future risk of Parkinson disease. *Neurol.* 2005; 64:1047-1051. doi: 10.1212/01.WNL.0000154532.98495.BF.

28. Jiang W, Ju C, Jiang H, Zhang D. Dairy foods intake and risk of Parkinson's disease: a dose-response meta-analysis of prospective cohort studies. *Eu J Epidemiol.* 2014; 29:613-619. doi: 10.1007/s10654-014-9921-4.

29. Chen H1, O'Reilly E, McCullough ML, Rodriguez C, Schwarzschild MA, Calle EE, Thun MJ, Ascherio A. Consumption of dairy products and risk of Parkinson's disease. *Am J Epidemiol.* 2007; 165:998-1006. doi: 10.1093/aje/kwk089.

30. Chen H, Zhang SM, Hernán MA, Willett WC, Ascherio A. Diet and Parkinson's disease: a potential role of dairy products in men. *Ann Neurol*. 2002; 52:793–801.
31. Devkota S, Wang Y, Musch MW, Leone V, Fehlner-Peach H, Nadimpalli A, Antonopoulos DA, Jabri B, Chang EB. Dietary-fat-induced taurocholic acid promotes pathobiont expansion and colitis in *Il10^{-/-}* mice. *Nature*. 2012; 5:487(7405):104–8. doi: 10.1038/nature11225.
32. Dalbeth N, Ames R, Gamble GD, Horne A, Wong S, Kuhn-Sherlock B, MacGibbon A, McQueen FM, Reid IR, Palmero K. Effects of skim milk powder enriched with glycomacropeptide and G600 milk fat extract on frequency of gout flares: a proof-of-concept randomised controlled trial. *Ann Rheum Dis*. 2012; 71:929–934. doi: 10.1136/annrheumdis-2011-200156.
33. Vieru E, Koksál A, Mutluay B, Dirican AC, Altunkaynak Y, Baybas S. The relation of serum uric acid levels with L-dopa treatment and progression in patients with Parkinson's disease. *Neurol Sci*. 2016; 37:743–747. doi: 10.1007/s10072-015-2471-z.
34. Tucker LA, Erickson A, LeCheminant JD, Bailey BW. Dairy consumption and insulin resistance: the role of body fat, physical activity, and energy intake. *J Diabetes Res*. 2015;2015:206959. doi: 10.1155/2015/206959.206959
35. Duarte AI, Candeias E, Correia SC, Santos RX, Carvalho C, Cardoso S, Plácido A, Santos MS, Oliveira CR, Moreira PI. Crosstalk between diabetes and brain: glucagon-like peptide-1 mimetics as a promising therapy against neurodegeneration. *Biochimica Biophysica Acta* 2013; 1832:527–541. doi: 10.1016/j.bbadis.2013.01.008.
36. Bertron P, Barnard ND, Mills M. Racial bias in federal nutrition policy, part I: the public health implications of variations in lactase persistence. *JAMA*. 1999; 91:151–157.
37. Tan AH, Mahadeva S, Thalha AM, Gibson PR, Kiew CK, Yeat CM, Ng SW, Ang SP, Chow SK, Tan CT, Yong HS, Marras C, Fox SH, Lim SY. Small intestinal bacterial overgrowth in Parkinson's disease. *Parkinsonism Relat Disord*. 2014; 20:535–540. doi: 10.1016/j.parkreldis.2014.02.019.
38. Sandyk R, Gillman MA. Motor dysfunction following chronic exposure to a fluoroalkane solvent mixture containing nitromethane. *Eur Neurol*. 1984; 23:479–481.
39. Makhani M, Yang J, Mirocha J, Low K, Pimentel M. Factor analysis demonstrates a symptom cluster related to methane and non-methane production in irritable bowel syndrome. *J Clin Gastroenterol*. 2011; 45:40–44. doi: 10.1097/MCG.0b013e3181f423ea.
40. Marczevska A, De Notaris R, Sieri S, Barichella M, Fusconi E, Pezzoli G. Protein intake in Parkinsonian patients using the EPIC food frequency questionnaire. *Mov Disord*. 2006; 21(8):1229–31.
41. Kim JH, Hwang J, Shim E, Chung EJ, Jang SH, Koh SB. Association of serum carotenoid, retinol, and tocopherol concentrations with the progression of Parkinson's Disease. *Nutr Res Pract*. 2017; 11(2):114–120. doi: 10.4162/nrp.2017.11.2.114.
42. Pincus JH, Barry KM. Plasma levels of amino acids correlate with motor fluctuations in parkinsonism. *Arch Neurol*. 1987; 44(10):1006–9.
43. Barichella M, Cereda E, Cassani E, Pinelli G, Iorio L, Ferri V, Privitera G, Pasqua M, Valentino A, Monajemi F, Caronni S, Lignola C, Pusani C, Bolliri C, Faierman SA, Lubisco A, Frazzitta G, Petroni ML, Pezzoli G. Dietary habits and neurological features of Parkinson's disease patients: Implications for practice. *Clin Nutr*. 2017; 36(4):1054–1061.
44. Pincus JH, Barry K. Influence of dietary protein on motor fluctuations in Parkinson's disease. *Arch Neurol*. 1987; 44(3):270–2.
45. Wang L, Xiong N, Huang J, Guo S, Liu L, Han C, Zhang G, Jiang H, Ma K, Xia Y, Xu X, Li J, Liu JY, Wang T. Protein-Restricted Diets for Ameliorating Motor Fluctuations in Parkinson's Disease. *Front Aging Neurosci*. 2017; 9:206. doi: 10.3389/fnagi.2017.00206.

46. Solfrizzi V, Panza F, Frisardi V, Seripa D, Logroscino G, Imbimbo BP, Pilotto A. Diet and Alzheimer's disease risk factors or prevention: the current evidence. *Expert Rev Neurother.* 2011; 11(5):677-708. doi: 10.1586/ern.11.56.
47. Skorvanek M, Goldman JG, Jahanshahi M, Marras C, Rektorova I, Schmand B, van Duijn E, Goetz CG, Weintraub D, Stebbins GT, Martinez-Martin P; members of the MDS Rating Scales Review Committee. Global scales for cognitive screening in Parkinson's disease: Critique and recommendations. *Mov Disord.* 2018; 33(2):208-218. doi: 10.1002/mds.27233.
48. Fresán U, Bes-Rastrollo M, Segovia-Siapco G, Sanchez-Villegas A, Lahortiga F, de la Rosa PA, Martínez-Gonzalez MA. Does the MIND diet decrease depression risk? A comparison with Mediterranean diet in the SUN cohort. *Eur J Nutr.* 2019; 58(3):1271-1282. doi: 10.1007/s00394-018-1653-x.
49. Perez-Cornago A, Sanchez-Villegas A, Bes-Rastrollo M, Gea A, Molero P, Lahortiga-Ramos F, Martínez-González MA. Intake of High-Fat Yogurt, but Not of Low-Fat Yogurt or Prebiotics, Is Related to Lower Risk of Depression in Women of the SUN Cohort Study. *J Nutr.* 2016; 146(9):1731-9. doi: 10.3945/jn.116.233858
50. Martínez-González MA, Sánchez-Villegas A. Food patterns and the prevention of depression. *Proc Nutr Soc.* 2016; 75(2):139-46. doi: 10.1017/S0029665116000045.

Original article

Self-Determined Engagement in Physical Activity and Sedentary Behaviour of College Students in Eastern Croatia - Does the Major Subject of Study Make a Difference?

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Abstract

Aim: The aim of this study was to investigate physical activity and sedentary behaviour of college students who study health sciences (physiotherapy) and students who study non-health-related majors (law and economics) at the same college to find out if there is any impact of their major subject of study on how they spend their leisure time, as well as to examine sex differences in physical activity and sedentary behaviour.

Methods: A cross-sectional study was conducted during the winter semester of 2017. A total of 112 students volunteered to participate in the study, of whom there were 42 males (37%) and 70 females (63%). Physical activity was measured by using a short form of IPAQ (International Physical Activity Questionnaire) and sedentary behaviour by an SBQ (Sedentary Behaviour Questionnaire). Additionally, some general questions were included, such as sex, body height, body weight and field of study. Study participants were divided into two groups, according to their major: 1. students of physiotherapy (55 participants); and 2. students of law and economics (57 participants).

Results: The participants reported a high physical activity level, but also a significant amount of time spent on sedentary activities. Results showed that there was no difference in physical activity levels, but that there was a slight difference in sedentary behaviour between physiotherapy students and students of law and economics with regard to the following: total time spent in sedentary activities during weekdays ($p=0.006$), involvement in sitting and driving/riding in a car, bus or train on weekdays, and time spent playing computer/video games on weekend days ($p=0.046$).

Conclusion: Presented results lead to the conclusion that the majority of students are sufficiently active, but still spend much time on sedentary activities. Students with different preferences also differ in how they spend their leisure time, but do not differ in physical activity level.

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Introduction

Physical inactivity is the fourth leading risk factor responsible for 6% of deaths around the world, according to the World Health Organization (WHO) (1). It presents a threat to global health due to its great prevalence among all age groups and correlation with weight gain, cardiovascular diseases, diabetes and many other medical conditions (2). Current international physical activity (PA) guidelines recommend that an adult must engage in at least 150 minutes of moderate-intensity aerobic activity or 75 minutes of vigorous-intensity activity (600 MET-min) weekly (3). When it comes to inactivity, young adults are one of the vulnerable age groups since they are at a stage of life when their habits and lifestyle are forming. In the past decade, there has been a growing number of studies investigating physical activity and inactivity among young adults, mostly university and college students. Studies have measured physical activity mostly by self-evaluation on the basis of questionnaires, with the IPAQ (international physical activity questionnaire) being one of the most popular due to its good metric properties (4-10). Most of the studies investigating physical activity among university and college students reported low physical activity, with a minority of them meeting physical activity guidelines (11, 12). Also, sedentary behaviour is fairly widespread among young adults (13), measured by screen-time or the use of mobile phones. Sedentary behaviour is also regarded as a risk factor for many diseases and it is affecting health independently of physical inactivity (14).

Physical inactivity should be differentiated from sedentary behaviour. People can be both highly active and highly sedentary (15). For those reasons, sedentary behaviour and physical activities should be investigated as two distinct modes of behaviour. Female students are usually more inactive than male (16,17), but that does not necessarily mean that they are spending more time in sedentary activities.

However, we found that there is a lack of studies investigating the difference between students

from different study groups. Yang and collaborators reported that a 7-week course on knowledge, attitude and practice of health behaviour improved health-related behaviour in Chinese college students, including an increase in high physical activity involvement and a decrease in screen-time (18). This led to an increase in interest for examining the differences between students of health sciences and students majoring in non-health-related studies. Students of health sciences should be better informed about the benefits of physical exercise and the effects of sedentary behaviour on health than the students who study non-health related majors. Physical therapy students should be especially aware of physical activity benefits, as well as of adverse effects of sedentary behaviour, considering that, after graduation, their profession should include active lifestyle promotion and safeguarding of health.

The main hypothesis of this paper was developed based on the aforementioned and states as follows: students of physiotherapy are more active, with higher physical activity levels, and spend less time in sedentary activities, compared to students who study law or economics at the same college. We also examined sex differences in physical activity levels and sedentary behaviour.

Participants and methods

Participants

A cross-sectional study was conducted during the winter semester of 2017. All first-year students at the College of Applied Sciences in Vukovar were invited to participate in the study. One hundred and twelve students volunteered to participate. Among them, there were forty-two males (37%) and 70 females. The participants' age was between 18 and 22 years (median age 19). Study participants were divided into two groups, according to their major subject of study:

1. students of physiotherapy (55 participants); and

2. students of law and economics (57 participants).

All participants signed informed consent forms.

Measures

The survey included a short form of IPAQ (International Physical Activity Questionnaire) (19) and an SBQ (Sedentary Behaviour Questionnaire) (20). Additionally, some demographic items were included, such as sex, body height, body weight and field of study.

The short form of IPAQ consists of seven items. Six items measure three levels of physical activity (light (walking), moderate and vigorous) and one measures daily sitting time. According to Craig and colleagues (21), IPAQ is characterized by a good test-retest reliability coefficient (ICC) ranging between 0.81 and 0.89 and criterion validity (Spearman coefficient) ranging from 0.26 to 0.27. Metabolic equivalent minutes (MET min/wk) and time spent in physical activity per week were calculated by following the scoring protocol (22). Time spent in physical activity (PA) per week was converted into time spent in physical activity per day (min PA/7).

SBQ measures time spent in 9 sedentary activities during weekdays and weekend days separately. There are 9 items that determine the amount of time spent doing 9 sedentary activities during weekdays and weekend days: watching television, playing computer/video games, sitting while listening to music, sitting and talking on the phone, doing paperwork or office work, sitting and reading, playing a musical instrument, doing arts and crafts, sitting and driving/riding in a car, bus, or train. According to Rosenberg and colleagues (23), the ICCs were acceptable for all items and the total scale (range=0.51-0.93). For men, there were significant relationships of SBQ items with IPAQ sitting time and BMI. For women, there were relationships between the SBQ and accelerometer inactivity minutes, IPAQ sitting time, and BMI.

The participants gave their answers by selecting the amount of time they spend performing the relevant sedentary activity on a typical weekday in the first part, and on a typical weekend day in the second part of the SBQ (from when they wake up until they go to bed). Frequencies of answers were compared between the tested groups.

BMI (body mass index) was calculated based on self-reported height and weight.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 20.

Numerical variables: BMI value, time spent in sitting, walking, and in moderate and vigorous activities were tested for normal distribution. Normally distributed data were presented as a mean and standard deviation, while non-normally distributed data were presented as median and range. The difference between study types (majors) was tested by applying the Mann-Whitney U-test for independent samples. It was used to compare IPAQ results.

The difference in frequency of answers in the SBQ was tested by using the chi-square test, as well as the difference in frequency between physical activity levels according to IPAQ score, and the difference in frequency between BMI categories. Level of significance was set at $p=0.05$.

Results

Total engagement in physical activities reported by the participants was from 0 to 630min/day, with the median being 120min/day, and mode being 60min/day. There was no statistically significant difference between physiotherapy students and students of law and economics ($p=0.183$), or between male and female students ($p=0.204$). Table 1. shows the reported physical activity engagement levels during one typical day for physiotherapy students and for students of law and economics.

Table 1. Difference in time (min/day) spent in physical activities between physiotherapy students and students of social sciences

Type of physical activity	Time spent in physical activity (min/day)								p*
	physiotherapy students (N=55)				students of social sciences (N=57)				
	min	max.	median	mean	min	max.	median	mean	
Vigorous PA	0	120	20	24.4	0	200	30	45.2	0.161
Moderate PA	0	180	30	40	0	300	30	30	0.061
Walking	0	420	30	78	0	240	60	84	0.707

* statistical significance of difference derived from the Mann-Whitney U-test

The reported sitting time (IPAQ) in a typical day is between min. 30min and max. 720min, with the median being 360min, and mode being 300min. There was no statistical difference between males and females ($p=0.29$), but the difference between physiotherapy students and students of law and economics was statistically significant, indicating that physiotherapy students spend more time in sitting activities in comparison to students of law and economics ($p<0.0001$). Physiotherapy students reported between 120 and 720min of sitting per day, with median value being 420min/day, while the students of law and economics reported that they sit between 30 and 600min/day, with median value being 300min/day.

Reported physical activity converted to MET-min/week yielded results presented in Table 2. Physical activity of 74% participants (83 of 112 participants) was high, with their MET-min/week being over 3000 (68% of physiotherapy students and 81% of students of social sciences), while 6 (5%) participants reported physical activity lower than 600 MET-min/week, which represents low physical activity (7% of physiotherapy students, and 3% of students of law and economics). Pearson Chi-square revealed no significant difference between physiotherapy students and students of law and economics in terms of physical activity levels ($p=0.345$).

Table 2. Difference in physical activity level expressed in MET-min/week between physiotherapy students and students of social sciences

Type of physical activity	MET-min/week								p*
	physiotherapy students (N=55)				students of social sciences (N=57)				
	min	max.	median	mean	min	max.	median	mean	
Vigorous PA	0	960	160	195.5	0	1600	240	362.1	0.161
Moderate PA	0	1440	200	280	0	2400	280	521	0.061
Walking	0	1386	198	287	0	792	198	253	0.707
TOTAL	0	2994	677	743	0	4330	640	1105	0.202

* statistical significance of difference derived from the Mann-Whitney U-test.

The SBQ results revealed that participants were involved in sedentary activities between 60 and 720min/day on weekdays, with median value being 300min/day, and between 15 and 720 min/day on weekend days, with median value being 300min/day. There was no statistically significant difference between males and

females in terms of total time spent engaging in sedentary activities during weekdays ($p=0.591$) or weekend days ($p=0.788$). A statistically significant difference was noted between physiotherapy students and students of law and economics in terms of their sedentary behaviour during weekdays, as could be seen in Table 3..

Table 3. Difference in total time spent in sedentary activities (min/day) between physiotherapy students and students of social sciences during weekdays and weekend days

	Time spent in sedentary activities (min/day)								p*
	physiotherapy students (N=55)				students of social sciences (N=57)				
	min	max.	median	mean	min	max.	median	mean	
Weekdays	60	720	240	246	60	600	300	340	0.006
Weekend days	30	600	300	300.5	15	720	330	332.5	0.372

* statistical significance of difference derived from the Mann-Whitney U-test.

Students of social sciences are more involved in sedentary activities during weekdays. The total time spent on engaging in sedentary activities is a sum of all reported times spent on engaging in sedentary activities. All those activities, along with the distribution of reported times spent in each activity, are presented for students with different majors in Table 4., as are the results of the Pearson Chi-square test used to determine differences among groups.

Table 4. Difference in frequency of answers on time spent in each sedentary activity/day between physiotherapy students and students of social sciences (p = statistical significance derived from the chi-square test).

		0 min /day	up to 15 min /day	15-30 min/day	30-60 min /day	1-2 hours /day	2-3 hours /day	3-4 hours /day	4-5 hours /day	6 or more hours/day	p
Weekdays	watching TV	physioth (N=55)	13	8	1	17	10	3	2	1	0.238
		soc sci (N=57)	7	5	9	15	13	4	2	2	
	playing computer /video games	physioth (N=55)	27	3	7	10	6	2			0.379
		soc sci (N=57)	29	7	6	6	4	1	1	3	
	sitting while listening to music	physioth (N=55)	1	10	4	20	5	6	4	1	0.257
		soc sci (N=57)		3	8	14	11	6	5	2	
	using phone	physioth (N=55)	1	9	3	12	10	6	4	4	0.657
		soc sci (N=57)	5	8	5	10	8	6	2	7	
	doing paperwork or office work	physioth (N=55)	3	6	3	18	18	4	1	2	0.174
		soc sci (N=57)	7	8	11	15	13	1	1	1	
	sitting and reading	physioth (N=55)	22	13	6	7	6		1		0.742
		soc sci (N=57)	23	14	5	11	1	1	1	1	
	playing a musical instrument	physioth (N=55)	49	3	2	1					0.221
		soc sci (N=57)	55		1					1	
	doing arts and crafts	physioth (N=55)	26	6	2	11	9	1			0.095
		soc sci (N=57)	28	2	7	5	9	5		1	
Weekend days	sitting and driving/riding in a car, bus, or train	physioth (N=55)	13	8	13	13	8				0.009
		soc sci (N=57)	2	5	7	26	12	2	2	1	
	watching TV	physioth (N=55)	8	6	5	10	12	7	4	1	0.983
		soc sci (N=57)	7	4	6	15	13	7	3	1	
	playing computer /video games	physioth (N=55)	29	4	3	4	7	6	1		0.522
		soc sci (N=57)	28	5	5	9	5	4	0	2	

Continued											
		0 min/ day	up to 15 min/ day	15-30 min/d ay	30- 60 min/ day	1-2 hours/ day	2-3 hours/ day	3-4 hours/d ay	4-5 hours/ day	6 or more hours /day	p
sitting while listening to music	<i>physioth</i> (N=55)	5	4	5	14	9	2	5	3	6	0.046
	<i>soc sci</i> (N=57)		1	4	10	16	7	5	1	13	
using phone	<i>physioth</i> (N=55)	2	10	5	10	8	7	2	2	8	0.193
	<i>soc sci</i> (N=57)	7	3	8	10	7	7	5	6	5	
doing paperwork or office work	<i>physioth</i> (N=55)	8	8	6	15	11	5	0		1	0.121
	<i>soc sci</i> (N=57)	22	3	6	15	8	2	1		1	
sitting and reading	<i>physioth</i> (N=55)	26	8	5	9	3	2	1			0.935
	<i>soc sci</i> (N=57)	25	9	9	7	3	2	1		1	
playing a musical instrument	<i>physioth</i> (N=55)	49	2		3						0.119
	<i>soc sci</i> (N=57)	56		1						1	
doing arts and crafts	<i>physioth</i> (N=55)	23	1	7	5	14	3	1			0.438
	<i>soc sci</i> (N=57)	28	0	5	11	8	3	2		1	
sitting and driving/riding in a car, bus, or train	<i>physioth</i> (N=55)	11	7	14	14	5	2			1	0.262
	<i>soc sci</i> (N=57)	6	8	8	17	11	5	2		1	

The difference between physiotherapy students and students of law and economics was statistically significant in terms of sitting and driving/riding in a car, bus, or train during weekdays, and in terms of sitting while listening to music on weekend days. Physiotherapy students reported a maximum of 1-2 hours/day spent sitting and driving/riding in a car, bus, or train during weekdays, while some students of law and economics reported that they travel by car, bus or train for over 2-3 or more hours/day. Students of law and economics also reported longer times spent sitting while listening to music on weekend days in comparison to physiotherapy students.

There is a greater difference in distribution of time spent in sedentary activities between sexes. Females spend more time in sedentary

activities: using the phone ($p=0.041$ for weekend days, and $p=0.009$ for weekdays), doing paperwork or office work ($p=0.046$ for weekend days and $p=0.004$ for weekdays) and sitting and reading ($p=0.003$ for weekend days and $p=0.045$ for week days), while males spend more time playing computer/video games compared to females both during weekdays ($p<0.001$) and weekend days ($p<0.001$). Also, females reported spending more time in doing arts and crafts on weekdays in comparison to males ($p=0.036$).

BMI ranged between 17 and 35kg/m², with mean value being 22.4 ± 3.13 kg/m². Most participants (86 of them, or 77%) were of normal weight (BMI from 18.5 to 24.9kg/m²), 7 (6%) were underweight, and 19 (17%) were overweight, with 4 overweight participants being in the obese category (BMI>30kg/m²). There was no

statistical difference between physiotherapy students and social sciences students ($p=0.073$) in terms of frequency distribution by their BMI categories.

Discussion

The main finding of this study was that there was no difference in the physical activity level, but there was a slight difference in sedentary behaviour between physiotherapy students and students of law and economics. Participants reported high physical activity levels, but also a significant amount of time spent in sedentary activities.

Most students reported high physical activity, while only 5% of them reported low physical activity (<600 MET-min/wk) and did not meet the physical activity recommendations. Studies with similar objectives presented various results. Some reported low physical activity levels and great amounts of time spent in sedentary activities (11-13, 24-26), while others reported results similar to ours with high prevalence of sufficiently active students (15, 27-29). The reasons for such discrepancies are still to be determined. Differences in research methodology could be affecting the results and could be one of the reasons for occurrence of such discrepancies. Smetaniuk and co-workers (30) identified the main themes related to the facilitators of and barriers to physical activity and sedentary behaviour in Master of Physical Therapy students: 1) priorities and life balance; 2) commitment and accountability; 3) environment; and 4) Master of Physical Therapy programming. Variations in results pertaining to physical activity levels of participants in different studies in different places probably could be partially explained by differences in the aforementioned facilitators and barriers. In their study conducted among college students from the Mid-Atlantic Region, US, Vainshelboim and cooperatives (29) reported results similar to ours. They reported that 84-94% of examined students met the physical activity recommendations. Another similarity pertains to sedentary behaviour. Our results showed that approximately half of the questioned students spend 6 hours/day in

sedentary activities, while they reported that 69% females and 46% males are highly sedentary. Those individuals who are highly active and highly sedentary at the same time are known as "active couch potatoes" (31). They regularly exercise and meet the physical activity recommendations, but still spend great amounts of time in sedentary activities. Barkley and Lepp (32) reported that cell phone use is a significant positive predictor of being an "active couch potato". Mobile phones use was shown to be associated with sedentary behaviour of college students (32). However, Penglee and associates examined the correlation of smartphone use and physical activity among college students in the United States and in Thailand (33), and reported that greater smartphone use per day is inversely related to days per week of engaging in physical activity among Thai students, but not among US students. It is common belief that sedentary behaviour is displacing physical activity, so when sedentary behaviour increases, physical activity should decrease. However, this does not have to be the case when it comes to mobile phone use. There are some smartphone functions and applications that can encourage physical activity. There are many ways in which mobile phones can be used, and if someone is a "heavy" user, their use does not have to necessarily represent time spent in sedentary behaviour. In our study, only 6 participants reported not using phones during weekdays, and 9 reported not using them on weekend days, while others use phones during the greater part of the day (Table 4). We also found that there was no difference between males and females in terms of total time spent in sedentary behaviour. However, there was a difference between sexes regarding the distribution of that total time in terms of time spent on different sedentary activities. This is probably a consequence of sex differences in terms of preferences and interests. According to the review of Castro et al. (34), these results differ from the results of other studies. They found that sex has no association with total sedentary time, with screen-time, or with preferences to any type of sedentary activity. We ascertained that females use phones more than males, they also spend more time doing paperwork or office work and sitting and reading, as well as doing

arts and crafts on weekdays, while males spend more time playing computer/video games compared to females, both during weekdays and weekend days. However, there is no difference between males and females in terms of total time spent in sedentary activities.

As for the differences regarding sedentary activities between physiotherapy students and students of law and economics, we ascertained a significant difference in the total amount of time spent in sedentary activities during weekdays, but no difference in the total amount of time spent in sedentary activities during weekend days. During weekdays, students of law and economics reported more time spent performing the listed sedentary activities compared to physiotherapy students, even though, in the IPAQ, the physiotherapy students reported more time spent sitting. This discrepancy in the results could stem from the differences pertaining to class schedule, because sitting in a classroom was not listed as sedentary behaviour in the SBQ. Doing paperwork and office work was included, but that could easily be understood for doing homework, preparing for class or performing other activities at home, after classes. Physiotherapy students are more oriented towards practical lessons that require their involvement. This means that they do not always sit and listen during their classes, but are required to move and be physically active, unlike students who study law and economics, where classes, in general, require the students to sit and listen. In addition, other variables could also affect the differences pertaining to total time spent in sedentary behaviour during weekdays and weekend days, e.g. the distance between a student's residence and college, which could affect the total time that a student spent sitting while driving to class.

Weight status of the participants was mostly within normal weight thresholds (BMI between 18.5 and 24.99 kg/m²), but every fifth participant was overweight. Physical inactivity is strongly correlated to BMI, and regular exercise and an active lifestyle are the best way to reduce weight and reach a healthy weight status. There were no differences between physiotherapy

students and students of law and economics in terms of distribution across weight categories. Young adults in general should be more educated about the risk of health problems connected to high BMI.

The limitations of the study include the use of subjective measures, although valid and reliable. Although researchers tried to explain the questions to the participants and help them understand and answer them as accurately as they can, the answers are still a subjective evaluation and a memory of past events, as they remember them. Objective measures of physical activity and sedentary behaviour are warranted for future studies. Also, the cross-sectional design of the study could represent a limitation due to the inability to track changes in physical activity and sedentary behaviour, as well as their interaction, or to investigate potential facilitators and barriers that affect physical activity and/or sedentary behaviour. Of course, we must take into consideration the limitation of use of IPAQ. IPAQ is a questionnaire that requires participants to record only physical activities (vigorous, moderate and walking) that lasted at least 10 minutes at a time. In our opinion, this is the reason why the results included 0 min of walking. This result is not within the 5% of extremes, because all participants who live near the college and walk, e.g., 5 min to get to their classes, or those who drive to college by car or bus and do not walk around for more than 10 min do not record this brief amount of time that they spent walking. On the other hand, some students work while studying and they spend a great amount of time walking to their workplace.

All presented results lead to the conclusion that the majority of students are sufficiently active, but they still spend much time in sedentary activities. Our hypothesis was partially disproved, because we found no significant difference in physical activity between physiotherapy students and students of law and economics. On the other hand, physiotherapy students reported more time spent sitting, while students of social sciences reported more time spent in sedentary behaviour during weekdays. This could lead to the conclusion that, in this

case, a major affects what kind of lifestyle the students adopt and in which leisure activities they engage in. Students with different preferences also differ in terms of how they spend their leisure time.

References

1. World Health Organization. Global Health Risks: Mortality and Burden of Disease Attributable to Selected Major Risks. Geneva, Switzerland: WHO; 2009.
2. Gaetano A. Relationship between physical inactivity and effects on individual health status. *J Physical Education Sport*. 2016; 16(2): 1069-1074.
3. World Health Organization. Global Recommendations on Physical Activity for Health. Geneva, Switzerland: WHO; 2010.
4. Ballard M, Gray M, Reilly J, Noggle M. Correlates of video game screen time among males: body mass, physical activity, and other media use. *Eating Behav* 2009; 10: 161-167.
5. Bauman A, Ainsworth BE, Sallis JF, et al. The descriptive epidemiology of sitting. A 20-country comparison using the International Physical Activity Questionnaire (IPAQ). *Am J Prev Med* 2011; 41(2): 228-235.
6. Sugiyama T, Healy GN, Dunstan DW, Salmon J, Owen N. Joint associations of multiple leisure-time sedentary behaviours and physical activity with obesity in Australian adults. *Int J Behav Nutr Phys Act* 2008; 35(5):1-6.
7. Abu-Omar K, Rutten A. Relation of leisure time, occupational, domestic, and commuting physical activity to health indicators in Europe. *Prev Med* 2008; 47:319-23.
8. Azevedo MR, Araujo CL, Cozzensa da Silva M, Hallal PC. Tracking of physical activity from adolescence to adulthood: a population-based study. *Rev Saude Publica* 2007; 41:69-75.
9. Bauman AB, Chey T, Craig CL. The IPS Group The International Prevalence Study on Physical Activity: results from 20 countries
- International journal behavioral nutrition and physical activity 2009; 31:21.
10. D'Angelo E, Di Blasio A, Di Donato F, Di Gregorio S, Di Renzo D, Ripari P. Relationships between physical exercise practice, dietary behaviour and body composition in female university students. *J Sports Med Phys Fitness* 2010; 50:311-7.
11. Haase A, Steptoe A, Sallis JF, Wardle J. Leisure-time physical activity in university students from 23 countries: associations with health beliefs, risk awareness, and national economic development. *Prev Med* 2004; 39:182-90.
12. Irwin JD. Prevalence of university students' sufficient physical activity: a systematic review. *Percept Mot Skills* 2004; 98:927-43.
13. Felez-Nobrega M, Hillman CH, Dowd KP, Cirera E, Puig-Ribera A. ActivPAL™ determined sedentary behaviour, physical activity and academic achievement in college students. *J Sports Sciences* 2018; 36(20):2311-2316.
14. Biswas A, Oh PI, Faulkner GE et al. sedentary time and its association with risk for disease incidence, mortality, and hospitalization in adults: a systematic review and meta-analysis. *Ann Intern Med* 2015; 162:123-132.
15. Peterson NE, Sirard JR, Kulbok PA, DeBoer MD, Erickson JM. Sedentary behavior and physical activity of young adult university students. *Res Nurs Health* 2018; 41(1): 30-38.
16. Varela-Mato V, Cancela JM, Ayan C, Martín V, Molina, A. Lifestyle and Health among Spanish University Students: Differences by Gender and Academic Discipline. *Int J Environ Res Public Health* 2012; 9: 2728-2741.

17. Felez FM, Nikolaidis PT, Martins FML, Mendes RS. Physical Activity Patterns in University Students: Do They Follow the Public Health Guidelines? PLoS ONE 2016; 11(3): e0152516.
18. Yang XH, Yu HJ, Liu MW, Zhang J, Tang BW, Yuan S, Gasevic D, Paul K, Wang PG, He QQ. The impact of a health education intervention on health behaviors and mental health among Chinese college students. J Am Coll Health 2019. DOI: 10.1080/07448481.2019.1583659.
19. International Physical Activity Questionnaire short version. www.ipaq.ki.se/downloadable/questionnaire (15.09.2019.)
20. Sedentary behavior questionnaires. www.sedentarybehaviour.org (15.09.2019)
21. Craig CL, Marshall AL, Sjoström M, Bauman AE, Booth ML, Ainsworth BE, Pratt M, Ekelund U, Yngve A, Sallis JF, Oja P. International physical activity questionnaire 12-country reliability and validity. Med Sci Sports Exerc 2003; 35(8):1381-1395.
22. International Physical Activity Questionnaire scoring protocol. www.ipaq.ki.se/scoring-protocol (15.09.2019)
23. Rosenberg DE, Norman GJ, Wagner N, Patrick K, Calfas KJ, Sallis JF. Reliability and validity of the Sedentary Behavior Questionnaire (SBQ) for adults. J Phys Act Health 2011; 7(6):697-705.
24. Varela-Mato, V.; Cancela, J.M.; Ayan, C.; Martín, V.; Molina, A. Lifestyle and Health among Spanish University Students: Differences by Gender and Academic Discipline. Int J Environ Res Public Health 2012; 9:2728-2741.
25. Alzamil HA, Alkhakbamy MA, Alfadda NA, Alnusallam SM, Al-Hazza HM. A profile of Physical Activity, Sedentary Behaviours, Sleep and Dietary Habits of Saudi College Female Students. J Family Community Ed 2019; 26(1):1-8.
26. Wu X, Tao S, Zhang S, Tao F. Low Physical Activity and High Screen Time Can Increase the Risks of Mental Health Problems and Poor Sleep Quality among Chinese College Students. PLOS ONE 2015. 10(3):e0119607
27. Mašina T, Kraljić V, Musil V. Physical activity and health-promoting lifestyle of first and second year medical students. Pedijatrija danas 2016; 12(2):160-168.
28. Haase A, Steptoe AD, Sallis JF, Wardle J. Leisure time physical activity in university students from 23 countries: associations with health beliefs, risk awareness, and national economic development. Prev Med 2004; 39(1):182-190.
29. Vainshelboim B, Brennan GM, LoRusso S, Fitzgerald P, Wisniewski KS. Sedentary behavior and physiological health determinants in male and female students. Physiol Behav 2019; 204:277-282.
30. Smetaniuk T, Johnson D, Creurer J, Block K, Schlegel M, Burcher S, Oosman SN. Physical activity and sedentary behavior of Master of Physical Therapy Students: An exploratory study of Facilitators and Barriers. Physiotherapy Canada 2017; 69(3):260-270.
31. Owen N, Healy GN, Matthews CE, Dunstan DW. Too much sitting: the population health science of sedentary behavior. Exerc Sport Sci Rev 2010; 38:105-113.
32. Barkley JE, Lepp A, Salehi-Esfahami S. College students mobile telephone use is positively associated with sedentary behavior. Am J Lifestyle Med. 2015; 10(6):437-441.
33. Penglee N, Christiana RN, Battista RA, Rosenberg E. Smartphone use and physical activity among college students in health science related majors in the United States and Thailand. Int J of Environ Res Public Health 2019; 16:1315.
34. Castro O, Bennie J, Vergeer I, Bosselut G, Biddle SJH. Correlates of sedentary behavior in university students: A systematic review. Prev Med 2018; 116:194-202.

Original article

Influence of Work Motivation, Work Environment and Job Satisfaction on Turnover Intention of Croatian Nurses: A Qualitative Study

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Abstract

Aim: The purpose of this study was to examine, identify and describe the factors that influence the turnover intention of nurses in Croatia.

Methods: A qualitative descriptive phenomenological study was conducted in June 2018. The participants were 20 registered nurses working full time who were employed in different cities in the Republic of Croatia, working in different healthcare institutions and in different medical fields. The data were obtained from interviews and were analysed and interpreted using the content analysis method.

Results: During data analysis, four main ideas emerged as follows: job satisfaction, work motivation, psychological factors (individual) and structural factors – work environment. Job satisfaction has been identified as a key factor with direct impact in nurses' turnover intention. Work motivation, psychological factors (individual) and structural factors – work environment does not have a direct influence on the nurses' intention to leave their job, but they have a significant indirect impact through job satisfaction.

Conclusion: Recognizing nursing challenges in the healthcare system and the factors which influence the intention of nurses to leave their workplace can help with the development of a clear strategy and retention measures based on the factors that influence the nurses' turnover intention.

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Introduction

The last decade has been marked by a steady increase in the proportion of the elderly, which has in turn increased the need for healthcare (1). The increasing need for healthcare is accompanied by globalization, which, in addition to increased information mobility, also enables greater mobility of people (2). The effects of employees leaving their workplace have caught the attention of many professionals who consider it to be one of the most expensive and difficult challenges faced by modern organizations (3).

International migration of nurses in recent years has become a major issue in international political circles (4). Croatia's accession to the European Union in 2013 opened a way to other European countries for many Croatian professionals, including healthcare professionals. Like other European countries, the Republic of Croatia is currently facing a shortage of nurses and nurse technicians, which has attracted the attention of the Croatian media for several years (5-7). Another phenomenon that is covertly present, in addition to the lack of professionals with qualifications, is that a great number of nurses do not want to work in the current working conditions. The studies conducted so far indicate a lack of empirical knowledge about the predictors of the intention to leave the workplace. This paper focuses on the influence of certain factors on the intention of nurses to leave their workplace, institution, or country.

The phenomenon of abandonment of the nursing profession, resulting in a decline in the number of educated nurses, poses a significant problem for the functioning of healthcare systems in many countries (2, 8), and especially in the less developed countries of the European Union (EU) (9, 10). The financial crisis, limitations of the national budget, reforms of the healthcare system, the workload of healthcare professionals, the decrease (or stagnation) of personal incomes and unpaid overtime

represent just some of the factors that have affected the nursing profession both all over the world and in Croatia (2).

The results of numerous studies conducted on the topic indicate that a growing number of nurses are leaving their workplace (11, 12), going to a different institution, or even leaving the nursing profession altogether. Employee's intention to leave the primary workplace is defined as the deliberate, voluntary and self-initiated change of job or institution. The intention to leave actually reflects an employee's attitude toward their current workplace or organization (13). From the employee's perspective, the intention to leave can be seen as a positive phenomenon. Reasons for positive perception of the above relate to better job offers that include higher income and/or intangible benefits, such as greater autonomy and new challenges (14). Moyce, Lash and de Leon Siantz (2016) cite the so called "push and pull" factors as reasons why nurses leave their workplace. "Push" factors are the factors that encourage nurses to leave and "Pull" factors are the factors that attract them to new opportunities and challenges (2). Among the most common factors that drive nurses to leave are dissatisfaction with the working conditions, stress and emotional exhaustion, while the factors that attract them are higher income, greater autonomy, recognition and respect within a team of healthcare professionals (2).

In a study conducted in Singapore on a sample of 814 nurses, Goh and Lopez (2016) describe leadership skills and work environment as the most important predictors of the nurses' intention to leave (15). An individual's statement of the intention to leave has, in previous research, been proved to be a significant predictor of their leaving the workplace (16). Simply put, an individual who verbally expresses their intention to leave a job is significantly more likely to leave the job than others. The validity of the above predictor has been highlighted in several studies of nurses' intention to leave (17-19). Brewer and Kovner (2014) propose and describe the concept of nurse turnover based on

a model that includes job satisfaction, organizational commitment, intention to leave and intention to seek a new position.

Official data on Croatian nurses who have left the workplace or migrated are not available; however, according to Kovačević Barišić and Lepan Stefančić (2015), around 400-500 nurses left Croatia shortly after Croatia joined the EU, in 2014 and 2015.

Identifying and understanding the factors that significantly affect job satisfaction and the level of nurses' work motivation is useful for preventing dissatisfaction and decreasing the intention of nurses to leave their current workplace or profession (20). Barać et al. (2015) performed a study to that effect on Croatian nurses, but it focused on job satisfaction, which is a predictor of nurses leaving the workplace (21). Smokrović et al. (2019) conducted a quantitative study, where the impacts of work motivation, organisation, and absenteeism on job satisfaction and intention to leave were considered (22). However, the aforementioned studies assessed the impact of predefined factors identified in a review of the literature on job satisfaction and turnover intention. The participants did not have the option of adding extra factors.

Hence, the goal of this study was to identify, through the use of the qualitative research method, potential factors that have an impact on job satisfaction and turnover by considering the opinions of Croatian nurses. We posed the following research question: Which factors influence the turnover intention of Croatian nurses?

Methods

A descriptive qualitative study was conducted in accordance with the guidelines on qualitative research (23).

Study Design

A qualitative approach was applied in order for us to gain a profound understanding of the nurses' opinions and attitudes in the context of

work motivation, work environment, job satisfaction and intention to leave. After a thorough review of the available literature and clearly defined ideas, certain claims/situations were established based on the existing theories and insights gained into each particular construct. The central phenomenon which was examined was the experience of nurses related to work motivation, job satisfaction and work environment, and the importance and impact of these concepts on turnover intention were examined as well.

Participants

In order to obtain a heterogeneous sample of participants, the study was conducted in different Croatian cities: Rijeka (five participants), Osijek (five participants), Zadar (five participants), and Našice (five participants); in different healthcare institutions (primary – five participants, secondary – 10 participants, and tertiary – five participants); 15 participants were employed in public, and five in private healthcare institutions; and in different nursing fields: 15 were working in healthcare centres, four were employed in departments of internal medicine, four were surgical nurses, two were employed in gynaecology departments, two were from paediatrics, one was employed in the department of neurology, one was employed in the department of oncology and one was working in the department of urology.

Nurses were randomly selected from the list of nurses employed in each of the participating healthcare institutions. The list of nurses was formed in accordance with the following predefined inclusion criteria: 1) a registered nurse with a valid license, 2) a minimum of five years of work experience in the profession in the institution of current employment, 4) full-time employment, 5) open-ended employment contract, 6) voluntary participation in the study. A total of 20 nurses were selected who met the above criteria and who expressed their consent to participate in the study.

Data collection

Data were collected using a semi-structured face-to-face interview conducted between 4 June 2018 and 22 June 2019. Interviews were conducted by seven experts in the field of clinical and medical sciences, nursing sciences in collaboration with psychology and information science experts.

Participants were interviewed in a room outside of their usual work environment, without external interference and without the presence of others. Just before conducting the interview, the researchers were reminded of the importance of using comprehensible language in communication, interactivity, changing the order of questions/statements or asking additional questions to get to the essence of the topic, and of the obligation to verify that they understood their interviewees' statements.

Prior to each interview, the purpose of the study and the reasons for conducting it were explained to the participants. The participants' anonymity was guaranteed. Participants voluntarily agreed to participate either verbally or in writing. Likewise, with prior permission given by the participants, for the purpose of clearer understanding and more detailed processing of data, the interviews were recorded and transcribed verbatim.

During the interview, each researcher presented a total of nine possible (fictional) situations with fictional characters – nurses. The fictional situations were designed by considering everyday real-life/work situations. After the individual statement/situation was read and presented to the participants, they had the opportunity to reflect on their position and think of a possible solution to the situation and then verbalize their opinion. After the presentation of the situations, it was left to the participants to seek further clarification regarding the presented situation.

After each participant responded to the situation, a mandatory additional question was asked: *Do you think the reasons would be different for male nurses?* The interviews lasted between 30 and 60 minutes and there was no need to repeat any of them.

Data analysis

Data saturation was achieved in the 11th interview. Four additional interviews were processed to increase the quality of the study, and in total 15 interviews were analysed. All interviews were carefully transcribed and analysed, where the researchers analysed each sentence in detail according to Van Manen's (2002) detailed analysis approach (24).

Colaizzi's (1978) seven-step approach was also used to ensure an in depth analysis of interview data using a clear and systematic approach (25). Each interview was separately coded by at least two experts. In the first step, a naive reading of interview transcripts was performed, followed by axial coding, where codes were refined, and selective coding, where the final coding was performed. After revising each transcript, the researchers consulted one another and performed the final categorization, i.e. they repeated selective coding. The researchers extracted illustrative quotes, which were classified into separate categories.

For example: "... *She is primarily satisfied because she loves her job, loves helping people who need help: it makes her feel happy, satisfied, fulfilled because helping someone who needs it is of great importance for her personal satisfaction. Interpersonal relationships and the atmosphere in the department where she works are good, as are the overall working conditions ...*" (Participant 5, female, 7 years of service).

Individual ideas were identified and a detailed description of each idea was then drawn up. To verify the accuracy of interpretation, interview transcripts were read three times. In the final step, there was no need to include any further changes based on feedback from the research participants.

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Ethical aspects

All participants, after being properly informed of the purpose of the research, voluntarily agreed to participate in the research. All of them signed a consent form for participating in the survey or expressed their consent orally. The interviewee's name was not mentioned at any time during the interview to protect the privacy of the participants. All participants were made aware of the fact that they had the right and the option to refuse to give an answer to or opinion on a particular statement/situation before the start of the interview and they were aware of the

fact that they could stop the interview at any time.

Results

Demographic data

All participants included in this study were female, employed full time and were registered nurses. The youngest participant was 27 and the oldest was 48 years old. The average age of the participants was 33, with 6.5 to 28 years of work experience. They all worked and lived in Croatia and were native speakers of Croatian.

Thematic analysis and categorization

Thematic analysis of the content by code group resulted in a division into four categories. Each category contained a number of subcategories, all of which have a significant impact on the main idea (Table 1). Participants' opinions for each category were further expanded and compared with other studies conducted in Europe and the rest of the world that have been published and made available so far, which will be presented in the Discussion section.

Table 1. Nurses' intention to leave – Thematic content analysis by category and subcategory

Category	Subcategory
Job satisfaction	<i>Positive attitudes *</i>
	<i>Autonomy *</i>
	<i>Acknowledgment of a job well done *</i>
	<i>Stress **</i>
	<i>Possibility of advancement *</i>
Work motivation	<i>Wrong choice of profession **</i>
	<i>Identification with the job *</i>
	<i>Intrinsic motivation *</i>
	<i>Extrinsic motivation (material) *</i>
	<i>Family factors *</i>
Psychological factors (individual)	<i>Younger age *</i>
	<i>Change of residence *</i>
	<i>Family migration *</i>
	<i>Working conditions **</i>
Structural factors – work environment	<i>Availability of materials, sufficient time and employees **</i>
	<i>Conflict in the workplace **</i>
	<i>Managers' ability to manage and support *</i>

*positive effect; **negative effect

Presentation of participants' responses

Job satisfaction was most influenced by: good interpersonal relationships, complexity of the work, team atmosphere and positive team attitudes (N = 13); doing the job you love (N = 9); good organization and working conditions, job security, regular income (N = 7); and identifying with nursing as a profession because it makes me happy, satisfied and fulfilled (N = 5). The participants cite positive internal motivation, capabilities and accessibility of their superiors as other reasons.

Thirteen participants believe that there is no difference in the factors of job satisfaction between men and women; however, two participants state that by acquiring the skills, a male nurse changes jobs more quickly and easily and their opinions are more respected than the opinions of female nurse.

Job dissatisfaction was most influenced by: dissatisfaction with the work environment, organization of work, night shifts, performing tasks outside the scope of the job, low salaries, non-recognition of professional qualifications, conflicts in the work environment (N = 15); personal participation in internal conflicts in the work environment (N = 12); privileged positions of superiors and inequality (N = 4); choosing the wrong profession (N = 2). Other reasons indicated were that the superior is not a good manager and that the nursing profession is not appreciated enough.

The majority of participants (N = 10) feels that there is no difference in job dissatisfaction factors between males and females; however, some participants state that men would switch jobs if they were not satisfied, especially if better pay was involved.

Change of workplace within an institution is most often due to: poor interpersonal relationships and communication in the department (N = 9); advancement (N = 5); health problems (N = 5); being tired of one's job (N = 3); compromised position and protection (N = 2).

The opinion of 11 participants is that there are no differences of opinion between men and women, but other participants state that men have to face new challenges in their desire for promotion and a better workplace.

Nurses decide to change the institution where they work because of: better working conditions and interpersonal relationships (N = 9); proximity to work (e.g. relocation) and therefore more family time (N = 9); financial situation, as well as non-recognition of a higher education degree (N = 6).

The majority of participants (N = 10) believe that there is no difference in reasoning between male and female nurses; however, some say that male nurses would be looking for new challenges and better pay.

Leaving the nursing profession is most often due to: wrong choice of profession, poor working conditions, interpersonal relationships and financial situation (N = 9); stress (N = 3).

Eleven participants believe that there are no differences of opinion between males and females, while other participants note financial problems as a reason for changing their profession.

Nurses do not intend to leave their department, institution or profession because they are: satisfied with their job, working conditions, interpersonal relationships and superiors (N = 14); in addition to the above assertion, five participants state that they have a fear of a new environment. Two participants cite status as a reason.

Fifteen participants feel that there are no differences between the opinions of male and female persons.

Nurses decide to go abroad for: financial reasons (N = 12); better working conditions and healthcare system (N = 11). As for other reasons, they state that younger people are more likely to choose to leave, as are those who have already

family abroad, and that the profession is more appreciated abroad.

Thirteen participants feel that there are no differences between male and female persons; however, two participants state that it is easier for men to leave.

The most common reasons for nurses only doing their job enough to "satisfy the form" are: there are no rewards or praise, which is demotivating (N = 12); routine and saturation (N = 6). Participants also indicate selection of the wrong profession and early retirement of employees.

A total of fifteen participants believe that there are no differences between the opinions of male and female persons.

Nurses are pleased with their superiors because of: systematization and regulated scope of work and good organization in the department;

leadership, good communication skills, understanding of team needs and teamwork, managing the department professionally and responsibly (N = 15).

Thirteen participants are of the opinion that there are no differences between male and female persons; however, two participants note that more tolerance is shown for male than female nurses.

Presentation of the main category relationships on nurses' intention to leave

By further analysing the results obtained regarding the defined main categories and subcategories, we detected categories that have a direct impact on nurses' intention to leave. Additionally, we also present the categories that directly affect job satisfaction and indirectly affect the nurses' intention of leaving. The results are shown in Figure 1..

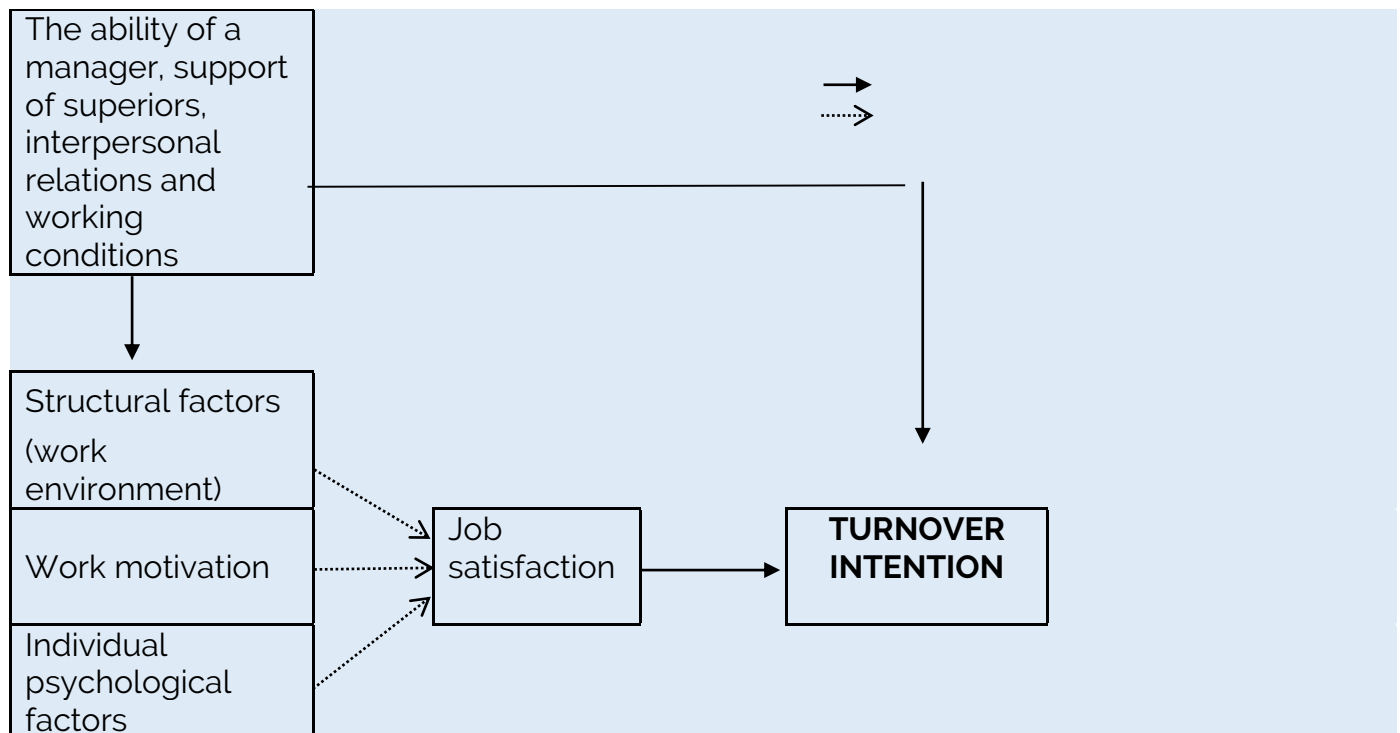


Figure 1. Main category and subcategory influences on nurses' turnover intention

Discussion

The results of the study indicate that four main categories of factors are important for nurses' intention of quitting their jobs in Croatia. The first category is job satisfaction, which has been

identified as a key factor in nurses' turnover intention, as has been confirmed in a number of previous studies conducted in Croatia and worldwide (3, 16, 22, 26). The results indicate that dissatisfaction with work and the work environment is a clear indication that nurses will leave their jobs in the future. A survey conducted in Turkey in 2015 recognizes job satisfaction as an important factor and states that 61% of nurses intending to leave their job register a moderate level of satisfaction (12). Positive attitudes, autonomy, recognition of a job well done, and the ability to advance in the workplace were highlighted as subcategories of job satisfaction, which has been confirmed in previous research. In a recent Croatian survey, Barać et al. (2017) also describe nurses' job satisfaction and cite that nurses who are more committed to their work have greater job satisfaction (27).

The level of job satisfaction is closely related to work motivation (27, 28), which represents the second category in our research. Work motivation does not have a direct influence on the nurses' intention to leave their job, but it has a significant indirect impact on job satisfaction. Similar results were previously reported in a study conducted in Croatia (22). Singh and Tiwari also found a correlation between job satisfaction and work motivation in their research. They claim that increasing job satisfaction increases work motivation and vice versa. Employee satisfaction thus increases work motivation, while dissatisfaction effects motivation decline (27).

The results indicate a significant impact of work motivation through the subcategories of identification, intrinsic motivation, and extrinsic (material) goals. Gagné et al. (2015) state that an autonomous type of motivation, especially intrinsic, which is also the preferred type of motivation, is related to job satisfaction and the intention to leave (29). The same results were also found in a study conducted in the Netherlands (30), which aimed to examine the connection between work stressors and the reactions of employed nurses. In another study, Singh and Tiwari (2007) describe that lack of job satisfaction is a predictor of leaving, driven by an individual's motivation (27). Goh and Lopez (2016)

especially emphasize the impact of intrinsic and extrinsic factors on employee satisfaction, which is also highlighted in our results in the category of work motivation (15).

In contrast with the results of Smokrović et al. (2019), where nurses who identified with the profession felt lower job satisfaction, our results indicate a positive relationship between identifying with the profession, intrinsic and extrinsic motivation and work motivation. Since extrinsic motivation plays a significant role in overall satisfaction, the impact of a system of support, rewards and bonuses on employee motivation should not be neglected. If the nurse is acknowledged and supported by the staff and superiors, their self-esteem and satisfaction at work will grow. This reduces the possibility that the nurse will consider leaving the workplace. In a study conducted in Jordan, Mahmoud Al-Hussami (2008) also cites a strong relationship between job satisfaction and support from superiors (31). The same results were found in a study conducted in Croatia, where the authors said that managers' support is a valid predictor of job satisfaction (22).

The majority of participants emphasize extrinsic material motivation and inadequate material income in their responses as a reason for dissatisfaction and demotivation. They feel that material motivation has a significant impact on the intention to leave the country and the workplace. In previous research, material welfare was also recognized as a significant factor (8).

Job satisfaction is also closely related to employees' personal characteristics (29, 32) and the work environment (28, 29, 33, 34). Our results show that individual psychological factors of employees, work environment and work motivation are important for achieving the level of ultimate satisfaction. In their literature review, Lu, While and Louise Barriball (2005) highlight working conditions, working relationships, salary, promotion opportunities, job security, accountability, recognition by superiors and overtime as the most common factors that have a direct impact on satisfaction.

Additionally, Toode, Routasalo and Suominen (2011) state that personal characteristics and priorities, in addition to the internal psychological state, influence work motivation. The results of this study reveal that personal characteristics of employees are extremely important predictors of their intention to leave. The study implies that the intention to leave is not necessarily related to the institution of employment, work organization, collective or motivation, and we believe that personal characteristics need to be singled out and emphasized as a separate factor in the intention to leave. In this study, we categorized individual psychological factors that have a significant indirect impact on the intention to leave, such as family, age, change of residence, and family migration; this was also partially confirmed in a previous study (22). Employees report that the choice to leave is easier for younger people, as well as for those whose family members have previously migrated. Different results specific for some EU countries have also been published in a study conducted in 10 EU countries that aimed to discover the factors that influence leaving the workplace (1).

As the last category which, in addition to indirect influence through job satisfaction, also has a direct impact on nurses' intention to leave, the work environment was also found to be a factor in our study, and it was also highlighted in studies mentioned above (1, 22, 28, 31, 34). Masum et al. (2016) conducted their research in private healthcare facilities in Turkey and, in addition to the factors mentioned above, specifically emphasized the importance of the work environment and the relationship with colleagues and superiors. Our results also confirm that a strong correlation exists between the characteristics and quality of the work environment and the decision to leave the workplace.

The participants stressed material and human resources, e.g. availability of materials, working conditions, sufficient time and number of employees, as important determinants of the work environment. As in previous studies, the possibility of further advancement and qualities of the manager were classified under the

category of work environment (1, 34). A Chinese study conducted by Wang et al. (2015) examined the impact of nurses' work environment on job satisfaction and considered the work environment to be a key factor in an organization. They found that it has a stronger impact on job satisfaction than any other organizational or personal factor. The same results were obtained in a study conducted in the United States of America (33). As stated by Latham, Hogan and Ringl (2008), work environment is highlighted as a crucial factor in the intention to leave or remain in the workplace, along with job satisfaction (35). Employees will find it much more difficult to leave the workplace if they work in a good, positive environment where they do not encounter daily conflict situations. The ability to advance, the superiors' ability to lead and manage, and support by the superiors are the factors that are most commonly mentioned as factors that influence the decision to leave in this category.

In conclusion, the departure of nurses from Croatia or the workplace poses a major challenge to the healthcare system. The results of this study are thus aimed at managers who, in the present-day migration of all healthcare professionals, including nurses, should prioritize the development of a clear strategy and measures for retention of nurses based on the factors that influence their intention to leave. Decision makers in healthcare must take all steps that are necessary for creating a positive work environment and stimulating employee motivation and satisfaction.

This research was conducted on a relatively small sample of nurses, and we believe that in the near future a detailed and extensive combined examination of the reasons for the turnover intention of nurses in the Republic of Croatia, covering all territorial regions, will be required. The proposed research would certainly provide detailed insight into the above factors, which would lead to a deeper understanding of this phenomenon.

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References

1. Heinen MM, van Achterberg T, Schwendimann R, Zander B, Matthews A, Kózka M, et al. Nurses' intention to leave their profession: A cross sectional observational study in 10 European countries. *Int J Nurs Stud*. 2013;50(2):174–84.
2. Moyce S, Lash R, de Leon Siantz M Lou. Migration Experiences of Foreign Educated Nurses: A Systematic Review of the Literature. *J Transcult Nurs*. 2016;27(2):181–8.
3. Rizwan M. Determinants of Employees intention to leave. Determinants employees Intent to leave [Internet]. 2014;4(3):1–19. Available from: <http://www.macrothink.org/journal/index.php/ijhrs/article/viewFile/5871/4760>
4. Brewer CS, Kovner CT. Intersection of migration and turnover theories-What can we learn? *Nurs Outlook* [Internet]. 2014;62(1):29–38. Available from: <http://dx.doi.org/10.1016/j.outlook.2013.09.002>
5. Kovačević Barišić R, Lepan Stefančić S. Consequences of Turnover and Retirement: Hospitals are seeking nurses and doctors. *Večernji list* [Internet]. 2015 Jul 9; Available from: <https://www.vecernji.hr/vijesti/bolnice-traze-medicinske-sestre-i-doktore-1033453>
6. Rimac Lesički I. In five years, 926 nurses left country. *Večernji list* [Internet]. 2018; Available from: <https://mojohrvatska.vecernji.hr/vijesti/u-pet-godina-otislo-1829-medicinskih-sestara-1244266>
7. Gugić M. The nurses are leaving. *Zadarski list* [Internet]. 2019; Available from: <https://www.zadarskilist.hr/clanci/02042019/s>
8. Dimaya RM, McEwen MK, Curry LA, Bradley EH. Managing health worker migration: A qualitative study of the Philippine response to nurse brain drain. *Hum Resour Health*. 2012;10:1–8.
9. Lesniowska J. Poland's Nursing Brain Drain To The West. *Health Aff*. 2008;27(2):593–593.
10. Paina L, Ungureanu M, Olsavszky V. Implementing the Code of Practice on International Recruitment in Romania - exploring the current state of implementation and what Romania is doing to retain its domestic health workforce. *Hum Resour Health* [Internet]. 2016;14(Suppl 1). Available from: <http://dx.doi.org/10.1186/s12960-016-0119-6>
11. Toode K, Routasalo P, Helminen M, Suominen T. Hospital nurses' work motivation. *Scand J Caring Sci*. 2015;29(2):248–57.
12. Masum AKM, Azad MAK, Hoque KE, Beh L-S, Wanke P, Arslan Ö. Job satisfaction and intention to quit: an empirical analysis of nurses in Turkey. *PeerJ*. 2016;4:e1896.
13. Ngo-Henha PE. A Review of Existing Turnover Intention Theories. *Int J Econ Manag Eng*. 2017;3(11):2734–41.
14. Schyns B, Torka N, Gössling T. Turnover intention and preparedness for change: Exploring leader-member exchange and occupational self-efficacy as antecedents of two employability predictors. *Career Dev Int*. 2007;12(7):660–79.
15. Goh YS, Lopez V. Acculturation, quality of life and work environment of international nurses in a multi-cultural society: A cross-

estre-odlaze-vec-u-svibnju-medicinskih-sestara-nece-bit-na-birou-i-nastat-ce

This paper is part of a seminar project of students at the Postgraduate Doctoral Study in Biomedicine and Health at the Faculty of Medicine in Osijek.

sectional, correlational study. *Appl Nurs Res.* 2016;30:111–8.

16. Basak E, Ekmekci E, Bayram Y, Bas Y. Analysis of Factors That Affect the Intention to Leave of White-collar Employees in Turkey Using Structural Equation Modelling. *Proc World Congr Engineering Comput Sci* 2013 [Internet]. 2013;11(April):23–5. Available from: <http://www.doaj.org/doaj?func=fulltext&ald=1970134>

17. Yildiz Z, Ayhan S, Erdoğan Ş. The impact of nurses' motivation to work, job satisfaction, and sociodemographic characteristics on intention to quit their current job: An empirical study in Turkey. *Appl Nurs Res.* 2009;22(2):113–8.

18. Mxenge S V, Dywili M, Bazana S. Job Engagement and Employees' Intention To Quit Among Administrative Personnel At the University of Fort Hare in South Africa. *Int J Res Soc Sci.* 2014;4(5):129–44.

19. Zhang L feng, You L ming, Liu K, Zheng J, Fang J bo, Lu M min, et al. The association of Chinese hospital work environment with nurse burnout, job satisfaction, and intention to leave. *Nurs Outlook* [Internet]. 2014;62(2):128–37. Available from: <http://dx.doi.org/10.1016/j.outlook.2013.10.010>

20. Toode K, Routasalo P, Suominen T. Work motivation of nurses: A literature review. *Int J Nurs Stud* [Internet]. 2011;48(2):246–57. Available from: <http://dx.doi.org/10.1016/j.ijnurstu.2010.09.013>

21. Barać I, Plužarić J, Kanisek S, Dubac Nemet L. Job satisfaction of nurses in relation to workplace. *Sestrin Glas J.* 2015;20(1):27–32.

22. Smokrović E, Frencl Žvanut M, Bajan A, Radić R, Žvanut B. The effect of job satisfaction, absenteeism, personal motivation, nursing practice environment and personal characteristics on job quitting: a survey of Croatian nurses. *J East Eur Manag Stud.* 2019;24:396–420.

23. Ajduković M, Laklija M. How to report qualitative research? Guidelines for researchers,

mentors and reviewers. *Annu Soc Work.* 2017;21(2):263–93.

24. Van Manen M. Writing in the dark: Phenomenological studies in interpretative inquiry. Ontario, Canada: Althouse Press; 2002.

25. Morrow R, Rodriguez A, King N. Colaizzi's descriptive phenomenological method. *Psychologist.* 2015;28(8):643–4.

26. Lu H, While AE, Louise Barriball K. Job satisfaction among nurses: A literature review. *Int J Nurs Stud.* 2005;42(2):211–27.

27. Singh SK, Tiwari V. Relationship between motivation and job satisfaction of the white collar employees: A Case study. *J Educ Policy.* 2007;2(7):1–10.

28. Lorber M, Skela Savič B. Job satisfaction of nurses and identifying factors of job satisfaction in Slovenian Hospitals. *Croat Med J.* 2012;53(3):263–70.

29. Gagné M, Forest J, Vansteenkiste M, Crevier- L, Broeck A Van Den, Aspel AK, et al. The Multidimensional Work Motivation Scale: Validation evidence in seven languages and nine countries The Multidimensional Work Motivation Scale: Validation evidence in. 2015;0643(January 2016).

30. Jantschek N, Jantschek I, Kunzendorf S, Blomhoff S, Malt UF, Jahnsen J. The INSPIRE study: Do personality traits predict general quality of life (Short form-36) in distressed patients with ulcerative colitis and Crohn ' s disease? *Scand J Gastroenterol.* 2008;(0027):1505–13.

31. Mahmoud Al-Hussami. A Study of Nurses' Job Satisfaction: The Relationship to Organizational Commitment, Perceived Organizational Support, Transactional Leadership, Transformational Leadership, and Level of Education. *Eur J Sci Res.* 2008;22(2):286–95.

32. Dywili M. The Relationship between Occupational Stress and Intentions to Quit among Employees at Nkonkobe Municipality, South Africa. *Bus Econ J* [Internet]. 2015;06(02). Available from:

<https://www.omicsonline.com/open-access/the-relationship-between-occupational-stress-and-intentions-to-quitamong-employees-at-nkonkobe-municipality-south-africa-2151-6219-1000146.php?aid=48714>

33. Choi J, Flynn L, Aiken LH. Nursing practice environment and registered nurses' job satisfaction in nursing homes. *Gerontologist*. 2012;52(4):484-92.

34. Sojane JS, Klopper HC, Coetzee SK. Leadership, job satisfaction and intention to leave among registered nurses in the North West and Free State provinces of South Africa. *Curationis*. 2016;39(1):1-10.

35. Latham CL, Hogan M, Ringl K. Nurses Supporting Nurses. *Nurs Adm Q*. 2008;32(1):27-39.

Original article

Representation of Topics Regarding Clinical Supervision in Nursing in National and International Journals

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Abstract

Aim: The aim of this paper was to examine the representation of topics of clinical supervision in nursing in national and international journals.

Methods: A Databases Medline, EBSCO and Hrčak were retrospectively researched. The research encompassed nursing journals published from 2011 to 2015. MeSH keywords were used as well. The availability of articles in full text was examined by PubMed Central and by using PERO, a search engine for electronic resources online, which is an online source of journals with articles available in full text to the Croatian scientific and academic community. A total of 168 articles and 54 journals were included in this research.

Results: The topic of clinical supervision in nursing has not been found in any of the papers published in Croatian journals. There were 168 scientific papers about clinical supervision in nursing in 54 international journals. In the "Journal of Nursing Management" there was a trend of a decreasing number of published scientific papers (Cochran–Armitage test $p < 0.0001$). In the Medline database there were 43 journals. Most journals were published in the USA, 23 of them. A total of 29 articles are available in full form. OvidSP enables access to the highest number of articles, 18 (62.1%), while PERO search engine found no articles in full form.

Conclusion: In national journals in Croatia there are no topics regarding clinical supervision in nursing, but there are some in international journals.

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Introduction

Definition of the word "supervise" is to watch somebody or something to make sure that work, etc is being done properly and that people are behaving correctly (1). That is why nurses very often have a negative attitude towards clinical supervision (CS). Smith highlighted that it is not about controlling somebody; instead, it is about empowering staff. Sabrage said it has been described in literature as "time for me" (2). In addition to that, Fowler stated that nurses should sometimes put themselves before others (3), which gives CS a completely different meaning.

There have been many attempts to define CS. According to the Care Quality Commission, "the purpose of CS is to provide a safe and confidential environment for staff to reflect on and discuss their work, personal and professional response to their work. The focus is on supporting staff in their personal and professional development and in reflecting on their practice" (4).

Furthermore, the Royal College of Nursing states that the term "clinical supervision" is used to describe a formal process of professional support and learning which enables practitioners to develop knowledge and competence, assume responsibility for their own practice and enhance consumer protection and the safety of care in complex clinical situations. It is central to the process of learning and to the expansion of the scope of practice and should be seen as a means of encouraging self-assessment and analytic and reflective skills (5).

Bishop and Sweeney described it as "designated interaction between two or more practitioners within a safe and supportive environment, that enables a continuum of reflective critical analysis of care, to ensure quality patient services and the wellbeing of the practitioner" (6).

Despite these and numerous other definitions, many authors state that definition of clinical supervision is still unclear (7,8).

Butterworth et al justify this by explaining that there are many different definitions, especially among states because of socio-cultural impact (9). Fowler explains that "the practice of clinical supervision will and should vary because the practice of nursing varies across different environments and patient groups" (10). Except those, he describes some more factors, such as ward culture and organisation, ratio of the number of employees, employees' needs and management (11).

Clinical supervision can be implemented in different ways. It can be implemented as a one-to-one relationship or group supervision. The other consideration is whether supervision is among peers, in a team or multidisciplinary. One-to-one is a fairly common model, where a more experienced nurse supervises a less experienced one. Experienced specialist nurses can be involved in "peer supervision", whereby staff of similar experience and profession "co-supervise" each other. However, a specialist nurse can also receive supervision from someone with greater experience, but who is not a nurse. There are three types of CS groups: peer, team and multidisciplinary groups. In peer CS groups, all staff members are of similar qualifications and experience (e.g. nurses, clinical managers, healthcare assistants, clinical nurse specialists). Team supervision occurs within the established hierarchical clinical team. Multidisciplinary supervision tends to occur where multidisciplinary staff work closely together (12).

One of the three most frequently cited models was reported by Winstanley and White – Proctor's interactive model, highlighting the normative (managerial), formative (educative) and restorative (supportive) functions of supervision (13). The aim of the normative component is to support reflection on practice with an awareness of local policy and codes of conduct. Formative component focuses on the development of skills, knowledge, attitudes and understanding. Restorative component fosters resilience through nurturing supportive relationships that offer motivation and encouragement and that can also be drawn

upon in times of stress (14). That model has become the most used model (15).

Although the principles of clinical supervision are simple, its implementation is more difficult. It requires time, commitment, openness to self-reflection, admission of areas of weakness and a wiliness to develop and grow (3). Many authors describe lack of time as the main barrier to clinical supervision implementation (16-20). Fowler states that we must make time for clinical supervision, it needs to be viewed in the same way as mandatory training, days off or annual leave (21).

There are many benefits of CS, some of them are: improved employee retention, better motivation and commitment to the organisation, maintenance of clinical skills and quality practice, improved communication among workers, increased job satisfaction, self-critique of clinical and cultural practice in a safe environment, development of strategies to address issues raised as part of critiquing and reflecting on practice, identification of strengths in practice, identification of learning opportunities to enhance further development of nursing practice, prevention of burnout, nursing leadership development (22).

The aim of this paper was to examine the representation of clinical supervision topics in nursing in national and international journals.

Material and methods

Databases Medline, EBSCO and Hrčak were retrospectively researched. The research encompassed nursing journals published from 2011 to 2015. MeSH keywords "Organization and Administration" and "Nursing, supervisory" were used for searching the Medline database. Subheading "Standards" was used to restrict the heading "Organization and Administration" and searching was restricted to nursing journals. Subheadings "Standards", "Organization and Administration" and "Statistic & Numerical Data" were used to restrict the heading "Nursing, supervisory" (Figure 1).

For searching the EBSCO database, the title "clinical supervision" and subject term "nursing" were combined with Boolean operator AND (Figure 1).

Keyword "supervizija"/ "supervision" was used for searching the database Hrčak. Results were restricted to the area of "Biomedicine and Healthcare" (Figure 1).

Results in all databases were restricted to nursing journals (Figure 1).

Nursing journals which did not have access to all or some parts of journal volumes were excluded from research.

In all included journals, the main focus was on looking for all published articles and all articles about clinical supervision in the period from 2011 to 2015.

The availability of articles in full text was examined by PubMed Central and by using PERO. A total of 168 articles and 54 journals were used in this research (Figure 1).

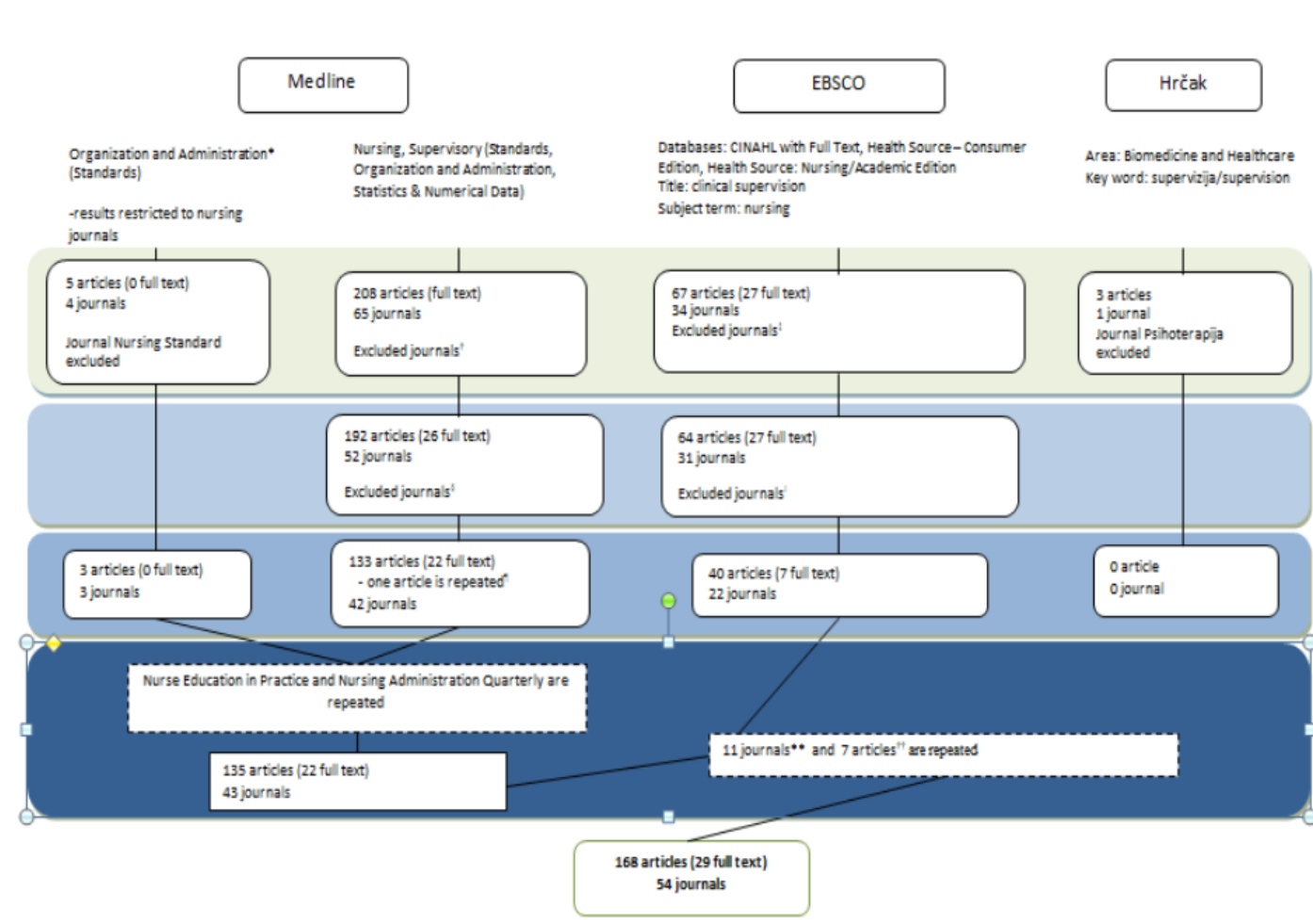


Figure 1. Flow chart

* Use the keyword 'supervision' then continue to search Heading Organization & Administration

† Global Health Action; Global Journal of Health Science; Palliative Medicine; Studies in Health Technology and Informatics; Health Service Journal; Advances in Health Care Management; Advances in Neonatal Care; Giornale Italiano di Medicina del Lavoro ed Ergonomia; Journal of the Medical Association of Thailand; Critical and Resuscitation; Journal of Intellectual and Developmental Disability; International Journal of Evidence-Based Health Care; Journal of Occupational Rehabilitation

‡ Journal of Intellectual Disabilities and Offending Behaviour; Scandinavian Journal of Caring Sciences; Research on Social Work Practice

§ Nursing Standard; Australian Nursing & Midwifery Journal; Mental Health Nursing; British Journal of Nursing; American Journal of Nursing; Insight; Nursing Times; Nursing New Zealand (Wellington); Tar Heel Nurse; RCM Midwives

|| JARNA; Nursing Standard; Mental Health Nursing; Community Practitioner; Nosileftiki; British Journal of Nursing; Communicating Nursing Research; Practice Nurse; Australian Nursing & Midwifery Journal

¶ Miller A, Buerhaus PI. The changing nature of ICU charge nurses' decision making: from supervision of care delivery to unit resource management. Joint Commission Journal on Quality & Patient Safety. 2013;39:38-47.

** Perspectives in Psychiatric Care; Nursing & Health Sciences; Journal of Advanced Nursing; Nurse Education Today; Nurse Education in Practice; Journal of Psychiatric & Mental Health Nursing; Journal of Clinical Nursing; Journal of Nursing Management; Issues in Mental Health Nursing; Australian Critical Care; International Journal of Mental Health Nursing

¶¶ Gonge H, Buus N. Model for investigating the benefits of clinical supervision in psychiatric nursing: A survey study. International Journal of Mental Health Nursing. 2011;20:102-11.

Cross WM, Moore AG, Sampson T, Kitch C, Ockerby C. Implementing clinical supervision for ICU Outreach Nurses: A case study of their journey. *Australian Critical Care*. 2012;25:263-70.

Kenny A, Allenby A. Implementing clinical supervision for Australian rural nurses. *Nurse Education in Practice*. 2013;13:165-9.

Koivu A, Hyrkas K, Saarinen PI. Who attends clinical supervision? The uptake of clinical supervision by hospital nurses. *Journal of Nursing Management*. 2011;19:69-79.

Gonge H, Buus N. Is it possible to strengthen psychiatric nursing staff's clinical supervision? RTC of meta-supervision intervention. *Journal of Advanced Nursing*. 2015;71:909-21.

Sharrock J, Javen L, McDonald S. Clinical supervision for transition to advanced practice. *Perspectives in Psychiatric Care*. 2013;49:118-25.

Carver N, Clibbens N, Ashmore R, Sheldon J. Mental health pre-registration nursing students' experiences of group clinical supervision: a UK longitudinal qualitative study. *Nurse Education in Practice*. 2014;14:123-9.

Results

The topic of clinical supervision in nursing has not been found in any of the papers published in Croatian journals. There were 168 scientific papers about clinical supervision in nursing in international journals. The biggest number of

journals about CS were published in 2011, a total of 46. The fewest were published in 2014, only 25. The "Journal of Nursing Management" contained the most scientific papers about CS in 2011, specifically 19 of them. In that journal there was also a trend of reduced number of published articles in the period from 2011 to 2015 (Cochran – Armitage test $p < 0,0001$) (Table 1)..

Table 1. Representation of topics regarding clinical supervision in nursing in international journals

Journal	Total number of published articles (proportion of articles dealing with clinical supervision)					P*
	2011	2012	2013	2014	2015	
BMC Nursing	24 (0)	28 (0)	29 (0)	50 (0)	85 (1)	0.34
Nordic Journal of Nursing Research & Clinical Studies /Vard i Norden	36 (0)	41 (0)	40 (2)	43 (0)	38 (0)	0.97
Perspectives in Psychiatric Care	32 (0)	30 (0)	35 (1)	35 (0)	35 (0)	0.96
Nursing & Health Sciences	76 (1)	71 (1)	75 (1)	73 (0)	71 (1)	0.74
International Journal of Nursing Studies	166 (1)	163 (0)	168 (0)	170 (0)	198 (1)	0.93
Journal of Advanced Nursing	253 (0)	256 (2)	266 (0)	267 (2)	253 (1)	0.53
Nurse Education Today	182 (0)	191 (1)	282 (3)	268 (0)	270 (2)	0.6
Nurse Education in Practice	105 (1)	114 (1)	170 (3)	120 (3)	93 (1)	0.56
Journal of Psychiatric & Mental Health Nursing	136 (0)	111 (1)	122 (1)	113 (2)	96 (0)	0.58
Journal of Clinical Nursing	395 (1)	385 (2)	358 (0)	368 (1)	368 (0)	0.32
CONNECT: The World of Critical Care Nursing	25 (0)	26 (0)	17 (0)	20 (1)	19 (0)	0.41
British Journal of Midwifery	149 (0)	169 (0)	150 (0)	168 (1)	162 (0)	0.49
Journal of Nursing Education Scholarship	28 (0)	26 (1)	36 (0)	18 (0)	20 (0)	0.54
Contemporary Nurse: A Journal for the Australian Nursing Profession	88 (0)	84 (0)	84 (1)	73 (0)	49 (0)	0.86

Table 1a. Representation of topics regarding clinical supervision in nursing in international journals

Journal	Total number of published articles (proportion of articles dealing with clinical supervision)					P*
	2011	2012	2013	2014	2015	
Journal of Nursing Management	109 (19)	205 (3)	106 (0)	100 (0)	112 (4)	<0.0001
Australian Critical Care	102 (0)	80 (1)	79 (0)	97 (0)	90 (0)	0.49
International Journal of Mental Health Nursing	52 (2)	68 (0)	63 (3)	65 (0)	64 (0)	0.16
Journal of Nursing Measurement	14 (0)	17 (0)	34 (0)	43 (1)	46 (0)	0.74
Obzornik Zdravstvene Nege	37 (1)	28 (0)	30 (0)	26 (0)	26 (0)	0.98
Klinisk Sygepleje	29 (0)	31 (1)	34 (0)	28 (0)	29 (0)	0.48
Assistenza Infermieristica e Ricerca:Air	25 (0)	34 (2)	28 (0)	30 (0)	27 (1)	1.00
Practising Midwife	99 (1)	118 (3)	113 (3)	110 (7)	114 (6)	0.05
Nursing Economics	42 (0)	48 (0)	39 (0)	34 (0)	46 (1)	0.16
Health Care Manager	43 (0)	37 (0)	41 (1)	38 (0)	47 (1)	0.35
JOGNN – Journal of Obstetric, Gynecologic, & Neonatal Nursing	100 (0)	100 (0)	92 (2)	89 (0)	98 (1)	0.39
Nursing Management (Harrow)	171 (1)	148 (3)	74 (2)	176 (1)	111 (1)	0.82
Professioni Infermieristiche	23 (0)	27 (0)	26 (0)	27 (0)	28 (1)	0.17
Soins; La Revue de Reference Infirmiere	255 (0)	185 (0)	172 (0)	156 (1)	140 (0)	0.37
CIN: Computers, Informatics, Nursing	132 (0)	106 (0)	104 (0)	97 (1)	99 (0)	0.43
Women & Birth: Journal of the Australian College of Midwives	26 (0)	35 (0)	72 (0)	60 (1)	72 (0)	0.66
The Gerontologist	73 (0)	91 (0)	107 (0)	115 (1)	121 (0)	0.58
Worldviews on Evidence-Based Nursing	26 (2)	25 (0)	19 (1)	48 (1)	46 (0)	0.11
Queensland Nurse	53 (0)	53 (0)	59 (1)	63 (0)	45 (0)	0.99
Nursing Administration Quarterly	43 (3)	46 (0)	57 (2)	55 (0)	60 (1)	0.14

Table 1b. Representation of topics regarding clinical supervision in nursing in international journals

Journal	Total number of published articles (proportion of articles dealing with clinical supervision)					P*
	2011	2012	2013	2014	2015	
Journal of Nursing Administration	106 (1)	112 (3)	122 (3)	116 (0)	121 (1)	0.38
Nursing Forum	32 (1)	33 (0)	34 (3)	32 (0)	35 (0)	0.45
Canadian Nurse	209 (0)	206 (1)	205 (2)	203 (0)	167 (0)	0.76
Joint Commission Journal on Quality & Patient Safety	69 (0)	65 (0)	70 (1)	71 (0)	72 (0)	0.98
Journal of Nursing Care Quality	45 (0)	51 (0)	45 (2)	48 (0)	53 (0)	0.96
Midwifery	154 (0)	117 (0)	177 (1)	156 (0)	146 (0)	0.98
MCN, American Journal of Maternal Child Nursing	85 (0)	81 (1)	87 (0)	82 (0)	92 (0)	0.47
Krankenpflege – Soins Infirmiers	158 (0)	163 (1)	147 (0)	171 (0)	202 (0)	0.44
Online Journal of Issues in Nursing	28 (1)	26 (1)	24 (0)	22 (0)	24 (0)	0.16
Research in Nursing & Health	40 (0)	52 (1)	47 (0)	45 (0)	43 (0)	0.47
Nursing leadership (Toronto, Ont)	33 (2)	45 (0)	44 (0)	30 (0)	18 (0)	0.05
Issues in Mental Health Nursing	127 (1)	133 (0)	142 (1)	128 (0)	138 (0)	0.30
Public Health Nursing	64 (1)	63 (0)	62 (0)	62 (0)	75 (0)	0.15
Journal of Cardiovascular Nursing	74 (1)	60 (0)	72 (0)	82 (0)	84 (0)	0.14
Journal of Emergency Nursing	137 (1)	159 (0)	154 (0)	150 (0)	140 (0)	0.15
Journal of the American Medical Directors Association	107 (1)	183 (0)	200 (0)	150 (0)	213 (0)	0.10
AAOHN Journal	73 (1)	95 (0)	93 (0)	91 (0)	88 (0)	0.13
International Nursing Review	92 (1)	103 (0)	81 (0)	74 (0)	74 (0)	0.19
Journal of the American Association of Nurse Practitioners	82 (0)	86 (0)	89 (0)	83 (0)	112 (1)	0.19
Mental Health Practice	220 (1)	206 (0)	185 (1)	177 (1)	186 (0)	0.78
Total	5084 (46)	5216 (30)	5261 (41)	5216 (25)	5261 (26)	0.01

* Cochran – Armitage test

Most of the journals in which scientific papers about CS were published were found in the Medline database, specifically 43 of them. In the Hrčak database there were no journals containing articles about CS in nursing (Table 2).

Table 2. Representation in databases Medline, EBSCO and Hrčak of journals in which articles about clinical supervision in nursing were published

Database	Number (%)	
	Total number of journals	Journals in which articles about CS were published
Medline	1235 (100)	43 (3.5)
EBSCO	15337 (100)	22 (0.1)
Hrčak	437 (100)	0

In total, there were 54 journals in which articles about CS in nursing were published. Most of the journals were published in USA, 23 (42,5 %) of

them. Slovenia, France, Switzerland and Denmark each had only one journal with articles about CS in nursing published (Table 3).

Table 3. List of countries publishing journals in which articles about CS in nursing were published

Country publishing journal	Number (%) of journals in which articles about CS in nursing were published
USA	23 (42.5)
Great Britain	19 (35.1)
Australia	4 (7.4)
Canada	2 (3.7)
Italia	2 (3.7)
Slovenia	1 (1.9)
France	1 (1.9)
Switzerland	1 (1.9)
Denmark	1 (1.9)
Total	54 (100)

Most of the articles were published in UK, specifically 105 (62,5 %) of them.

In 2015, there were 19 articles (73,1 %) (Table 4).

Table 4. List of countries where articles about CS in nursing were published between 2011 and 2015

Country publishing journal	Number (%) of articles					Total N (%)	P*
	2011.	2012.	2013.	2014.	2015.		
USA	12 (26.1)	7 (23.4)	17 (41.4)	5 (20)	5 (19.2)	46 (27.4)	0.18
UK	31 (67.4)	17 (56.7)	20 (48.8)	18 (72)	19 (73.1)	105 (62.5)	0.19
Australia	0	1 (3.3)	2 (4.9)	1 (4)	0	4 (2.4)	0.51
Canada	2 (4.3)	1 (3.3)	2 (4.9)	0	0	5 (2.9)	0.67
Italy	0	2 (6.7)	0	0	2 (7.7)	4 (2.4)	0.09
Slovenia	1 (2.2)	0	0	0	0	1 (0.6)	0.62
France	0	0	0	1 (4)	0	1 (0.6)	0.19
Switzerland	0	1 (3.3)	0	0	0	1 (0.6)	0.33
Denmark	0	1 (3.3)	0	0	0	1 (0.6)	0.33
Total	46 (100)	30 (100)	41 (100)	25 (100)	26 (100)	168 (100)	

*2 test

In total, 29 articles about CS in nursing are available in full text to the Croatian Academic Community through the Academic and Biomedical Consortium. OvidSP provides access

to the largest number of articles, 18 (62.1 %) of them, while PERO alone does not provide access to any article in full form (Table 5).

Table 5. Available articles about CS in nursing in full text

Browser (interface)	Number (%) of articles in full text
Only PERO	0
Only PubMed Central	1 (3.5)
Only OvidSP	18 (62.1)
EBSCOhost, PERO	7 (24.1)
OvidSP, PERO	3 (10.3)
Total	29 (100)

Discussion

After searching for articles about CS, it can be concluded that many articles give a review of that topic, especially of a specific topic within CS, for example CS evaluation (9), the effectiveness of group CS in reducing stress (23), organization of CS in nursing (24), empirical research on CS in psychiatric care (7), concept and definition of CS (25), administrative CS (26).

In order to find papers about CS, most of the authors searched databases such as Medline (PubMed) and CINAHL (7, 27, 15, 23, 26). Some of them searched PsycINFO (7, 15), MEDIC, LINDA (26), Pre-CINAHL, and Academic Elite (27) as well.

It can be seen that authors who searched the EBSCO database also searched databases CINAHL and PsycINFO. For the purposes of this research, apart from the CINAHL database, databases Health Source-Consumer Edition and Health Source: Nursing/Academic Edition were searched. Database PsycINFO was not searched.

The most commonly used keyword was "clinical supervision" (27, 15, 23). In one case, "clinical supervision" was combined with the keyword

"nurse" (27). Keywords "supervision" and "nursing supervisory" were used as well (15).

It is interesting that only one author used the MeSH term "Nursing Supervisory" (15). None of them used the MeSH term "Organization and Administration", which is synonymous with the term "Supervision" (28).

This research showed that articles about CS were published in a lot of journals (if we consider the number of articles). But if we look closer, it is obvious that more than half of the journals, 29 to be precise, published only one article in a period of five years. The rest of the journals did not publish more than ten articles. The journal "Practising Midwife" published 20 articles and the "Journal of Nursing Management" published 26 articles.

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References

- (1) Hornby AS, Wehmeier S, McIntosh C, Turnbull J, Ashby M. Oxford Advanced Learner's Dictionary. 7. ed. UK: OUP Oxford, 2005.
- (2) Salvage J. Speaking out. Nurs Times 1998;94:24.
- (3) Fowler J. Advancing practice: from staff nurse to nurse consultant. Part 4: Using clinical supervision. BJN 2013;22:941.
- (4) Care Quality Commission. Supporting Information and Guidance: Supporting Effective Clinical Supervision. London: Care Quality Commission, 2013.
- (5) Royal College of Nursing. Clinical Supervision in the Workplace: Guidance for Occupational Health Nurses. London: Royal College of Nursing, 2002.

- (6) Bishop V. Clinical Supervision in Practice. 2. ed. Basingstoke: Palgrave-Macmillan, 2007.
- (7) Buus N, Gonge H. Empirical studies of clinical supervision in psychiatric nursing: a systematic literature review and methodological critique. IJMHN 2009;18:250-64.
- (8) White E, Winstanley J. A randomised controlled trial of clinical supervision: selected findings from a novel Australian attempt to establish the evidence base for causal relationships with quality of care and patient outcomes, as an informed contribution to mental health nursing practice development. JRN 2010;15:151-67.
- (9) Butterworth T, Bishop V, Carson J. First steps towards evaluating clinical supervision in nursing health visiting. I. Theory, policy and practice development. A review. JCN 1996;5:127-32.

- (10) Fowler J. Clinical supervision: from staff nurse to nurse consultant. Part 1: What is clinical supervision?. BJN 2013;22:786.
 - (11) Fowler J. Supporting self and others: from staff nurse to nurse consultant. Part 5: Clinical supervision. BJN 2011;20:830.
 - (12) Fowler J. Clinical supervision: from staff nurse to nurse consultant. Part 9: models of Implementation. BJN 2013;22:1261.
 - (13) Watkins EC, Milne DL. The Wiley International Handbook of Clinical Supervision. 1. ed. UK: Wiley Blackwell, 2014.
 - (14) Helen & Douglas House. Clinical Supervision Toolkit. Oxford: Helen & Douglas House, 2014.
 - (15) Dilworth S, Higgins I, Parker V, Kelly Brian, Turner J. Finding a way forward: A literature review on the current debates around clinical supervision. CN 2013;45:22-32.
 - (16) Chilvers R, Ramsey S. Implementing a clinical supervision programme for nurses in a hospice setting. IJPN 2009;15:615-9.
 - (17) Cleary M, Freeman A. The cultural realities of clinical supervision in an acute inpatient mental health setting. Issues ment. health nurs 2005;26:4889-505.
 - (18) Deery R. An action-research study exploring midwives' support needs and the affect of group clinical supervision. Midwifery 2005;21:161-76.
 - (19) Kenny A, Allenby A. Implementing clinical supervision for Australian rural nurses. NURSE EDUC PRACT 2013;13:165-9.
 - (20) White E, Winstanley J. Implementation of clinical supervision: Educational preparation and subsequent diary accounts of the practicalities involved, from an Australian mental health nursing innovation. J Psychiatr Ment Health Nurs 2009;16:895-903.
 - (21) Fowler J. Clinical supervision: from staff nurse to nurse consultant. Part 10: prioritising and making time. BJN 2013;22:1322.
 - (22) Blisshen M. 'Why we need supervision'. KAI TIAKI NURS NZ 2016;22:30-1.
 - (23) Graham WR, Dodds S. The effectiveness of a group approach to clinical supervision in reducing stress: a review of the literature. JCN 1999;8:338-44.
 - (24) Fowler J. The organization of clinical supervision within the nursing profession: A review of the literature. J ADV NURS 1996;23:471-8.
 - (25) Wright J. Clinical supervision: a review of the evidence base. Nurs Stand 2012;27:44-9.
 - (26) Sirola-Karvinen P, Hyrkas K. Clinical supervision for nurses in administrative and leadership positions: a systematic literature review of the studies focusing on administrative clinical supervision. J Nurs Manag 2006;14:601-9.
 - (27) Butterworth T, Bell L, Jackson C, Pajnkihar M. Wicked spell or magic bullet? A review of the clinical supervision literature 2001-2007. Nurse Educ Today 2008;28:264-72.
- U.S. National Library of Medicine. MeSH Browser. Available at: <https://meshb.nlm.nih.gov/record/ui?ui=D009934>. Date last accessed: 3.6.2017.

Review article

Open Approach in Rhinoplasty

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Abstract

The aim of this study was to present the advantages and disadvantages of open approach in rhinoplasty. In it, we also present the development of this technique in Croatia and examine its application in the last five years at the Department of Otorhinolaryngology and Head and Neck Surgery of the Clinical Hospital Centre Osijek.

Retrospectively, from January 2008 to August 2012, 400 patients with septal deviation and/or deformities of the nasal pyramid who underwent open rhinoplasty at the Department of Otorhinolaryngology, Head and Neck Surgery of the Clinical Hospital Centre of Osijek, Croatia were identified. The clinical diagnosis was based on a detailed medical history of the patient and nasal endoscopy. The patients were photographed in six projections before and after the surgery, and followed up on two occasions.

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Introduction

Rhinoplasty is a procedure in plastic surgery of the nose which solves functional and aesthetic problems of nasal soft tissue. Rhinoplasty includes repositioning of nasal cartilage and bone as well as of soft tissue structures for the purpose of improving the function and aesthetic appearance of the nose (1). It is often necessary to do both rhinoplasty and septoplasty (surgery of the nasal septum which facilitates breathing) at the same time. Such combined surgery is called rhinoseptoplasty. Nasal deformities affect the aesthetics of the face, and rhinoplasty affects the individual functionally, aesthetically, artistically and psychologically. Rhinoplasty is one of the most complex and most challenging interventions in aesthetic surgery, where precision is down to a fraction of a millimetre. Anatomy of the nose is very complex, with challenging bone and cartilage structure, as well as variable thickness of the skin, with the thickest skin found on the apex. It is necessary to precisely determine how a certain procedure will affect the appearance of the nose (2).

History of medicine notes that the first successful aesthetic surgery of the nose was performed by the Brancas (father and son) in the 15th century, in the Italian province of Catania (3). At the beginning, rhinoplasty was considered to be a surgical part of psychotherapy, which is confirmed by the fact that at the start of the 20th century, depression was one of the indications for rhinoplasty. The father of modern techniques of rhinoplasty is Jacques Joseph, who lay the foundation of the surgical technique in 1928 (4). At the same time, in 1921, an otolaryngologist from Budapest named Aurel Rethy developed a new surgical technique, the so-called open approach or decortication. Rethy's technique was first modified by prof. Ante Šercer, and his modified technique is still being applied all over the world today. Professor Ante Šercer was born in Požega, completed his studies in Graz and Prague, and worked at the two biggest Clinical Hospital Centres (CHC) after World War II: "Šalata" (CHC Zagreb) and CHC Sestre

Milosrdnice. He is recognized as the greatest Croatian expert in otorhinolaryngology. His student, prof. Ivo Padovan, presented a new open approach technique (so-called decortication) in 1970 at the first international symposium of the American Academy of Facial Plastic and Reconstructive Surgery in New York, showing the results of the procedure conducted on 400 patients, who were operated at the Department of Otorhinolaryngology of the CHC "Sestre Milosrdnice" (5).

According to the claims of prof. Gunther, a famous American plastic surgeon, who is the organizer of one of the most popular international symposia for plastic and reconstructive head and neck surgery in Dallas, that method was not accepted in the USA until the 1970's. Today, a lot of ENT specialists and specialists and subspecialists of plastic and reconstructive head and neck surgery use decortication all over the world. As we can see from the available data, 98% of patients are operated on by surgeons using this approach at the Clinical Hospital in Dallas. The respected prof. Toriumi from Chicago uses the open approach for more than 85% of all rhinoplasty procedures. In the USA, surgeons perform over 100 000 aesthetic rhinoplasties annually (6).

The nose is located at the centre of the face; it is also the most protruding part of the face, which is why it is the most exposed part of the face for trauma. It can be changed as a result of trauma, genetic factors or disease. Nasal trauma is the most common cause of aesthetic deformities of the septum and of the external part of the nose. Aesthetic nose correction is the most challenging surgery in aesthetic surgery. The spectrum of deformities of the external part of nose is varied and because of that, the approach and planning of surgical procedure must be done on a case-by-case basis. Typical nose deformities include: dorsal hump, saddle nose, crooked nose, overprojected nose, wide nose and combinations of the above. The goal of rhinoplasty is to create the nose shape that would best fit the face, because every face is different, and the nose needs to be adjusted

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accordingly. Rhinoplasty may be primary (correction for the first time) or secondary (reoperation). There are two main approaches to rhinoplasty: intranasal and open (decortication). Deformities may be located in the bone and/or cartilage. In the open approach, a small incision is performed on the columella and along the front edge of alar cartilage, and in that way, deformities may be corrected. Open approach is indicated in severe deformity of the apex, or for noses that have been operated multiple times or have suffered trauma multiple times, since they cannot be operated on using the intranasal approach. In the open approach, a small scar is left in the shape of the letter V at the columella (the fleshy part that divides the nostrils). Skin haematoma of the apex lasts

longer than when the intranasal technique is used, which depends mostly on the type of skin on the apex. Breathing normally through the nose should never be sacrificed to achieve the desired aesthetic nose shape (7).

Patients and methods

This retrospective analysis was made at the Department of Otorhinolaryngology and Head and Neck Surgery of the Clinical Hospital Centre Osijek.

A total of 400 patients with functional and/or aesthetic nose surgeries performed in the period from January 2008 to August 2012 were included (Table 1).

Table 1. Functional and aesthetic rhinoplasty performed at the Department of Otorhinolaryngology and Head and Neck Surgery of the Clinical Hospital Centre Osijek from 2008 to 2012.

Type of surgery	2008	2009	2010	2011	8/2012	Total
Septoplasty	44	56	57	67	55	279
Rhynoseptoplasty (open and intranasal approach)	12	17	18	32	21	100 (28, 72)
Reconstruction of nasal valve	0	4	8	5	4	21
Total						400

Study design

Before surgery, after taking the patient's anamnesis, the patient was photographed and

analysed from six different angles. Attention was drawn to the nasolabial angle, which is 90-110 degrees in women, and 80 to 90 degrees in men, while the nasofrontal angle is generally about 150 degrees in both sexes (Figure 1).

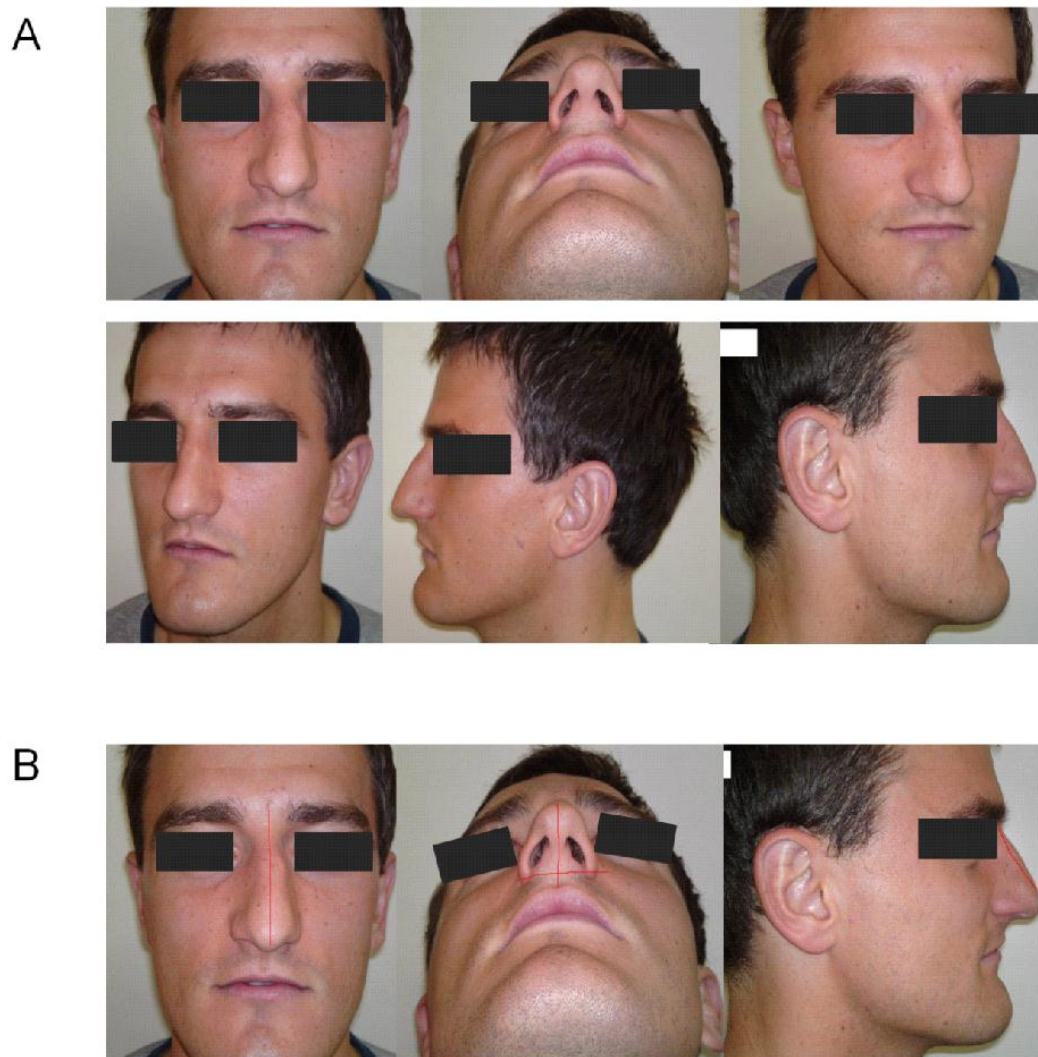


Figure 1. Preoperative photo

After thorough anamnesis was taken, the preoperative patient was photographed and analysed from six different angles (Figure 1A) (5). Attention is drawn to the nasolabial angle, which is 90-110 degrees in women, and 80 to 90 degrees in men, while the nasofrontal angle is generally about 150 degrees in both sexes. Figure 1B shows deviations from the median plane and clearance of the nose and preoperative planning of the operation.

Functional and/or aesthetic nose surgeries performed were septoplasty, rhinoseptoplasty (open or intranasal approach) and reconstruction of the nasal valve. After the surgery was

completed, the results were monitored and documented by repeated photographing from the same six angles (Figure 2).



Figure 2. Postoperative photo

The results of the operation are monitored and documented by repeated photographing from six angles. Figure 2 shows the same patient after rhinoseptoplasty was performed; the increase in the nasolabial angle is noticeable, as is the corrected nasal dorsum.

Results

We noted 279 septoplasties, 100 rhinoseptoplasties and 21 reconstructions of the nasal valve (Table 1). From the presented data, it is evident that the number of surgical interventions at the annual level is constantly increasing, which is in line with the increase in the number of ENT surgeons employed at our hospital, who were educated at other hospitals in Croatia, as well as in world-renowned centres for plastic reconstructive surgery.

Discussion

In addition to the functional dimension, the nose has an essential aesthetic dimension. In functional terms, the nose is the initial and extremely important part of the respiratory system. Apart from the "air conditioning" the inhaled air, the nose also contains nerve endings that are responsible for distinguishing odours (5).

Generally, the appearance, i.e. the anatomic material, reflects the function of the breathing dynamics. It is therefore clear that any plastic surgery performed on the nose is also a functional surgery. Along with the aforementioned "technical" aspect, the appearance of the nose is affected by race, ethnic characteristics and individual heritage. Within each race, there are typical characteristics. In the black race, for example, the nose is wider than the nose in the white race; it is lower in the bony part, with a predominance of wide noses, and the columella is shorter, with horizontal nostrils. In the white race, we differentiate the Greek, the Latin, the Galician, the Germanic nose, etc. (8). Finally, the appearance of the nose can be affected by the surgeon. It is not unusual that, apart from correcting individual characteristics, members of individual races or ethnic groups want to re-shape the basic characteristics of their nose; for example, in Asia, people tend to strive to "westernize" by changing the East Asian elements of their physiognomy.

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Surgery requires four fundamental criteria – three objective and one subjective: balanced form, good function, correct proportions, and desired appearance. The common notion that the nose changes the profile is only partially correct because rhinoplasty affects the shape of all projections. If the surgery meets the objective requirements, the surgeon may be satisfied, but for complete success, the patient must also be satisfied. Therefore, it is necessary that the surgeon, prior to performing the surgery, has an interview with the patient to find out which anatomical specifics the patient is not satisfied with and what the patient's particular aesthetic expectations are regarding the appearance of the nose. This is important because patients sometimes have unrealistic expectations of surgery or motivations that are not in fact related to the appearance of the nose, but are caused by other social and psychological circumstances that they project on their external appearance (9).

Complications of rhinoplasty are relatively rare (10). Possible complications include: nosebleeds, swelling of the nose and the surrounding soft tissue of the eyes and cheeks (especially in "open" rhinoplasty, lasting up to one year), bleeding, infections, hypertrophic scars, re-deformation of the nose (due to scars and poor surgical techniques). Some patients can develop difficulty breathing through the nose following rhinoplasty, despite a successful aesthetic outcome of the operation. Even though the inside of the nose generally allows for good passage of air, rhinometric measurement of the airflow should measure the nasal discharge insufficiency. This is damage to the fine mechanism responsible for normal airflow in the throat and normal discharge, and it may be congenital or acquired. Treatment of this condition is very difficult and unpredictable, so it is best if it is prevented by proper surgical technique. Decisions regarding nose surgery should be preceded by detailed discussion and review of the situation. On that occasion, the doctor explains the nature of the problem to the patient and the realistic possibility of its correction. After rhinoplasty, a patch, plaster splint or plastic material is used to keep the

shape and position of the nose for the first 7-10 days until it is healed. Nose and face swelling is individual, depending on the severity of the surgery itself and the response of the patient's tissue. A return to daily activities is possible after approximately two weeks, depending on the individual situation. Strenuous physical activity should be avoided over the next two months. It is important to understand that the recovery process after rhinoplasty takes from six months to a year, until the nose reaches its final appearance. The final judgment on the appearance and function of the nose is made by the patient and the surgeon only after five years of patient monitoring, which is particularly the case in the West (10). Bleeding after the removal of the tampon is the most commonly observed complication; it is usually weak and stops after a few minutes. In some cases, the tampon is replaced until the next day. Sweating is not a common complication. The nose has very good blood supply, which provides a strong immune defence against pathogens, and today's medical institutions also follow stringent protocols regarding sterilization and instrument handling. Unsatisfactory aesthetic effect of the surgery is considered to be one of the late-stage complications of rhinoplasty (11). In some cases, the result of the surgery differs from what the patient expected, and this usually occurs when the desired look does not match the result achieved. To prevent this, realistically expected results are discussed prior to surgery, as well as after surgery. When images before and after the surgery are compared to help patients see the improvement in their appearance, most patients are satisfied.

Repetitive rhinoplasty, also known as secondary rhinoplasty (12), is rhinoplasty performed to correct inadequate results of the previous rhinoplasty. There are two reasons for performing secondary rhinoplasty. Patients often seek secondary rhinoplasty to correct a cosmetic nasal deformity. Nose fracture may not have been sufficiently reduced or was done too low (13). The overprojected nose may not be adequately resolved, or it may have been overly resolved. It may look squashed; it may look like a bell pepper or like a boxer's nose. There are

many ways in which the results of the previous rhinoplasty can be aesthetically unattractive to the patient. Another reason is the functionality. In the first case, rhinoplasty may be done to alleviate breathing difficulties, and the result may be unsatisfactory. In the second case, the first rhinoplasty may be performed for cosmetic reasons, but may also endanger the normal physiological mechanism that involves inhaling or exhaling, making it difficult to breathe. Secondary rhinoplasty is technically challenging

References

1. Rohrich R, Ahmad J. Rhinoplasty. *Plast Reconstr Surg* 2011; 128(2):49-73.
2. Vilar-Sancho B. Rhinoseptoplasty. *Aesthetic Plast Surg* 1984; 8(2):61-65.
3. Greco M, Ciriaco AG, Vonella M, Vitagliano T. The primacy of the Vianeo family in the invention of nasal reconstruction technique. *Ann Plast Surg* 2010; 64:702-5.
4. Bhattacharya S. Jacques Joseph: Father of modern aesthetic surgery. *Indian J Plast Surg.* 2008;41(suppl): S3-S8.
5. Šercer A. *Otorinolaringologija* 2, Klinika. Zagreb: JLZ, 1965, 356-357.
6. Gunter JP, Rohrich RJ, Adams, WP (Eds.). *Dallas Rhinoplasty – Nasal Surgery by the Masters*, 2nd edn., St. Louis: Quality Medical Publishing Inc; 2007
7. Sercer A, Mundich K. *Plastische Operationen an der nase und an der Ohrmuschel*, Stuttgart: Georg thieme verlag, 1962
8. Leong S, Eccles R. A systematic review of the nasal index and the significance of the shape and numerous procedures have to be done by open rhinoplasty.
9. Naraghi M, Atari M. Development and Validation of the Expectations of Aesthetic Rhinoplasty Scale. *Arch Plastic Surgery* 2016; 43(4):365-370.
10. Cochran CS, Landecker A. Prevention and management of rhinoplasty complications. *Plast Reconstr Surg* 2008; 122:60-67.
11. Rettinger G. Risks and complications in rhinoplasty. *GMS Curr Top Otorhinolaryngol Head Neck Surg.* 2007;6:Doc08.
12. Gruber RP, Noland S, Belek KA. Discussion: what motivates secondary rhinoplasty? A study of 150 consecutive patients. *Plast Reconstr Surg* 2012; 130:679-80.
13. Philpott CM, Clark A, McKiernan DC. Function or cosmesis--what is the predominant concern in patients with nasal trauma presenting for rhinoplasty? *Eplasty* 2009;9:e11.

Daniel R. Secondary Rhinoplasty Following Open Rhinoplasty. *Plast Reconstr Surg* 1995; 96(7):1539-1546.

Review article

Optical Coherence Tomography Angiography – A New Insight Into Macular Vasculature

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Abstract

Optical coherence tomography angiography (OCT-A) is a new non-invasive technology for imaging of retinal and choroidal vasculature of the macular area with resolution comparable to histological sections. OCT-A does not require usage of intravenous dye, contrary to fluorescein angiography, the current gold standard for imaging of retinal vessels, and indocyanine-green angiography, which is important for imaging of choroidal vessels. With the advancements in optical coherence tomography (OCT) scanning speeds and creation of powerful algorithms for improvement of image quality in recent years, OCT-A imaging of macular vasculature, superficial, deep and avascular retinal complex, as well as choriocapillaris and deep choroid has become available in everyday clinical practice. This review covers aspects important for understanding choroidal and retinal blood supply, as well as the development, mechanisms and clinical application of OCT and OCT-A technology.

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Introduction

Optical coherence tomography angiography (OCT-A) is a novel non-invasive technology for detailed imaging of retinal and choroidal vasculature of the macular area. It utilizes laser light reflectance off moving erythrocytes, generating information about volumetric blood flow in all retinal layers and the choroid (1). The resolution of OCT-A is comparable to the resolution of histological sections (2). Unlike fluorescein angiography (FA) or indocyanine-green angiography (ICG), OCT-A does not require the use of dye (1).

Dye-based angiography has been the gold standard for imaging macular and choroidal vasculature for decades. Because of the risk of adverse reactions, particularly vomiting, nausea, allergic reaction and anaphylaxis, coupled with the time-consuming nature of the examination (10 to 30 minutes), dye-based angiography is not frequently used for monitoring the course of retinal vascular diseases. While FA can only delineate superficial retinal vasculature, ICG imaging is restricted to visualization of the choroidal circulation. Moreover, FA is not capable of imaging the radial peripapillary capillary network (RPC), which is very important for monitoring of glaucoma (3).

FA is still the gold standard for detecting choroidal (CNV), retinal (NVE, neovascularization elsewhere), disc (NVD), neovascularization of the disc) and irideal (NVI, neovascularization of the iris) neovascularization (4).

Optical coherence tomography angiography- creating an image

Optical coherence tomography

Optical coherence tomography (OCT) is a diagnostic technique that enables in vivo cross-sectional visualization of the tissue in focus. It is currently used for imaging in cardiology, ophthalmology, oncology and dermatology (5). In ophthalmology, it was first introduced in 1991 by Huang et al. (6). OCT uses interferometry to measure the amplitude and delay of reflected or backscattered near-infrared light from ocular

structures. The depth of structure measured in this fashion is known as axial scan (A-scan). By sequential arranging of multiple A-scans in the transverse direction, a B-scan or cross-sectional image is generated (7).

OCT is based on two techniques: time-domain (TD-OCT), introduced in 1996 (8), and frequency-domain (FD-OCT), devised as spectral-domain (SD-OCT) and swept-source (SS-OCT). The importance of the advent of FD-OCT technology is the acceleration of slow scan so that artefacts caused by motion in earlier TD-OCT devices are no longer an impediment for better imaging of small vessels (9).

Doppler OCT (DOCT) was first introduced concurrently by Izatt et al. (10) and Chen et al. (11) in 1997. DOCT provides quantitative volumetric information about blood flow, together with vascular and structural anatomy. However, it is limited to larger vessels (12). In clinical practice, DOCT is not widely used (12, 13).

Optical coherence tomography angiography (OCT-A)

OCT-A is a three-dimensional functional extension of OCT which uses repeated B-scans of the same retinal location to detect blood flow. In 2012, OCT-A was introduced as a method for imaging the retinal microvasculature (14). OCT-A signals are primarily used to detect the presence or absence of vessels, rather than to provide information about blood flow speed, enabling three-dimensional en face imaging (15). If retinal location is stationary (i.e. if there is no blood flow), the repeated B-scans will be identical. However, if the tissue's optical scattering is time-dependent because of the blood flow through the region, the repeated B-scans will vary. The most important vascular component that can induce backscattering of light is red blood cells. Areas of faster blood flow will show greater change over a unit of time. The exact relationship of this change in regard to flow speed depends on many parameters, such as OCT beam size and blood vessel size, and is not necessarily linear (16).

By using different algorithms, OCT-A can monitor flow even in transverse motion, while the other form of monitoring the motion of RBCs, Doppler shift (used in DOCT), can monitor flow only in axial motion. This enables OCT-A to monitor flow in microvasculature, while DOCT can monitor flow only in larger vessels (17). Optical resolution of commercially available OCT-A systems ranges between 5-10 μ m in the axial, and averages $\sim$ 20 μ m in the transverse direction (16). Smaller resolution improves the differentiation of retinal vasculature but increases sensitivity to eye motion. If the signal is below a threshold, a mask is generated. Errors in imaging caused by bulk tissue motion are reduced by using different eye tracking modalities (15). OCT-A quantification of blood flow, namely flow index and vessel density, has great clinical importance. Flow index is the average flow signal in the area of interest. Vascular density is the percentage of the area occupied by vessels (18).

Image artefact is an anomaly in the visual presentation of information derived from an object. Projection artefact, one of the most important types of artefacts, represents the appearance of the object at a deeper location than where it exists in reality due to disturbance of the signal. Shadowing is the attenuation of a signal behind a scattering opacity or obstruction that absorbs the signal. Displacement artefact is caused by eye motion where one part of the image is from one retinal location, while the remaining part of the image is from a different retinal location. Stretch artefact is related to software correction of eye motion in which part of the image appears to be stretched. White line artefact is a white line seen due to eye movement (19).

One of the most important limitations of OCT-A is a fixed area of the central field of view measuring 3 × 3, 6 × 6 and 12 × 12 mm. Visualization of the peripheral retina is thus not possible (19). OCT-A can detect blood flow above the minimum threshold only. Areas with flow under the threshold remain invisible (20, 21).

For example, in case of branch retinal vascular occlusion, slow-flow areas may be perceived as areas of non-perfusion (21). Moreover, OCT-A is incapable of accurately determining vascular leakage, which is especially important in neovascular age-related macular degeneration (nAMD), diabetic macular oedema, and retinal vein occlusion (22). Because of the need for steady fixation, it is difficult to obtain images of children's retina.

Clinical use of OCT-A

In OCT-A, vascular abnormalities manifest as abnormal vessel density (dry age-related macular degeneration, AMD), anomalous vessel geometry (dilated vessels, aneurysms in diabetic retinopathy, DR), abnormal flow (CNV) and absent flow (nonperfusion/capillary dropout in retinal artery or vein occlusion). Therefore, OCT-A is currently extensively useful for patients with variable retinal diseases (15). OCT-A concurrently obtains images of both retinal and choroidal macular vasculature divided into different layers based on their depth. Moreover, OCT-A enables the imaging of RPC, originating from choroidal vessels, which is particularly vulnerable to glaucoma and retinal vascular occlusion (23). Retinal capillary plexuses are divided into (a) superficial vascular plexus (SVP), located in the retinal nerve fibre layer (RNFL) and ganglion cell layer (GCL), and (b) deep vascular plexus (DVP) that extends down to the inner nuclear layer (24). DVP is subdivided into intermediate (ICP) and deep capillary plexus (DCP) (25). Additionally, OCT-A is the only method capable of visualizing CC separately from the deeper choroid (15).

Foveal avascular zone (FAZ)

The capability of OCT-A to image capillaries with high resolution has enabled researchers to study the foveolar avascular zone (FAZ) in greater detail than it had been possible in the past with FA. On an OCT-A scan, FAZ is presented as a discoid zone within the macula that is devoid of capillaries (Figure 1).

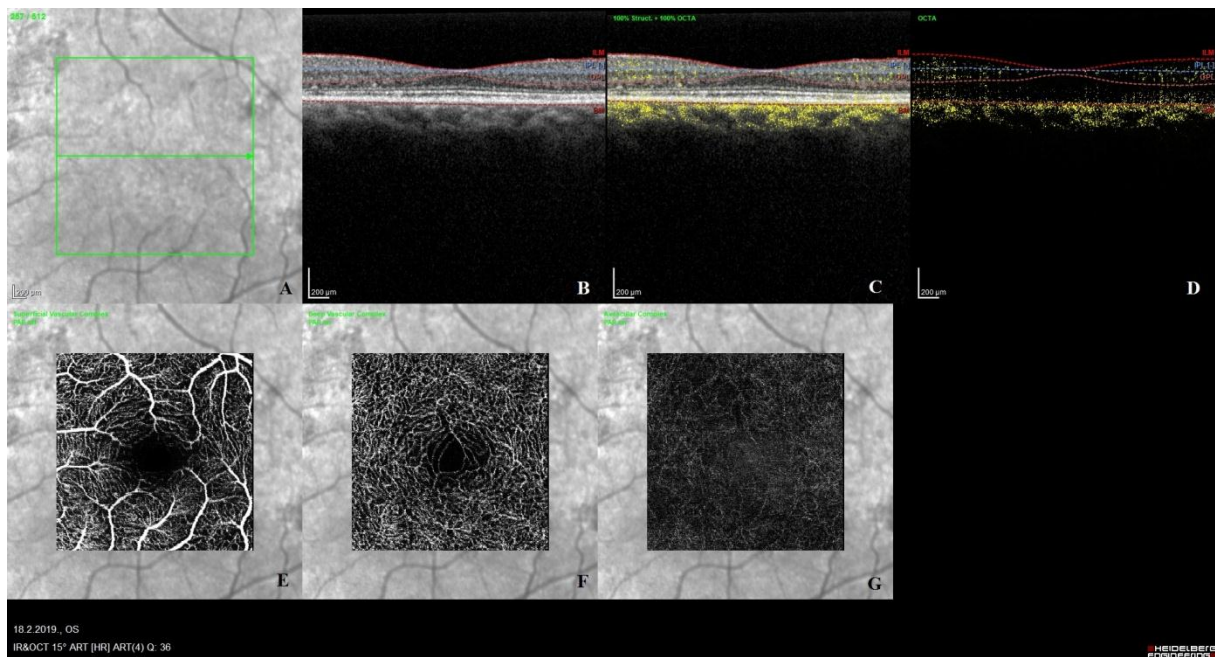


Figure 1. OCT-A image of the left eye of a healthy 60-year-old female patient. (A) Photography of the macula. (B) Foveal anatomy. (C) Foveal layers with depicted red blood cells (yellow). (D) Red blood cells (yellow) in the foveal area. Clear distinction is visible between (E) SVP, (F) DVP and (G) avascular complex of the retina. Images obtained from Spectralis® OCT (Heidelberg Engineering, Heidelberg, Germany). OCT-A-optical coherence angiography, OCT-optical coherence tomography, SVP-superficial vascular plexus, DVP-deep vascular plexus

FAZ borders are manually drawn on a certain capillary plexus level. Parameters defining FAZ are divided into two groups. Area (in mm²), perimeter (length of the FAZ borders, in mm) and Feret's diameter (maximum diameter of FAZ, in mm) assess the size, while circularity, axial ratio, roundness and solidity represent the shape of FAZ. FAZ circularity is the degree of resemblance to a perfect circle ($4\pi \times \text{area}/\text{perimeter}^2$). Axial ratio is obtained from a best-fit ellipse of the FAZ (length of major axis/length of minor axis of a best-fit ellipse). Roundness uses the best-fit ellipse and is similar to circularity, but is insensitive to irregular borders along the perimeter of the FAZ ($4\pi \times \text{area}/(\text{length of major axis})^2$). Solidity describes the extent to which a shape is convex or concave ($\text{area}/\text{convex area}$). These parameters are calculated using computer software (26). Most studies that investigated FAZ parameters in healthy individuals reported a larger deep area compared to the superficial area of FAZ (27, 28, 29, 30). Superficial and deep FAZ area are larger in females (26, 31, 32), and this is possibly related to thinner fovea (32). The FAZ area and foveal

thickness at both the SVP and DVP levels exhibited significant inverse correlation (26, 29, 30). This could be explained by an association between higher metabolic demand of a thicker retina and a reduction of the FAZ area (30).

Previous studies using FA observed an increase in the FAZ size with advancing age. However, FA as a diagnostic method is limited when it comes to SVP imaging and should not be correlated with OCT-A (32, 33). The studies that the examined changes that occur in FAZ with aging are inconclusive. Some studies reported significant (34, 35), while others observed insignificant changes in the FAZ area with aging (27, 28, 29, 36). Yu et al. found an increase in the FAZ size by 1.48% annually, with a decrease in vascular density by 0.4% (35). In studies using FA, it was proposed that in patients aged 40 or older, age was positively correlated with the FAZ area (32); however, studies using OCT-A did not support this conclusion (36). Coscas et al. divided their participants by age into three groups: 20–39 years old, 40–59 years old, and 60 years old or older (37). The FAZ size was smaller in the

oldest group compared to the two younger groups at the level of SVP. No statistically significant difference was found for the level of DVP among the groups (37).

A single study evaluated the FAZ shape in healthy eyes and demonstrated that none of these parameters was significantly correlated with age, sex and refractive error (26). There are no homogenous studies about FAZ parameters in children (Figure 2).

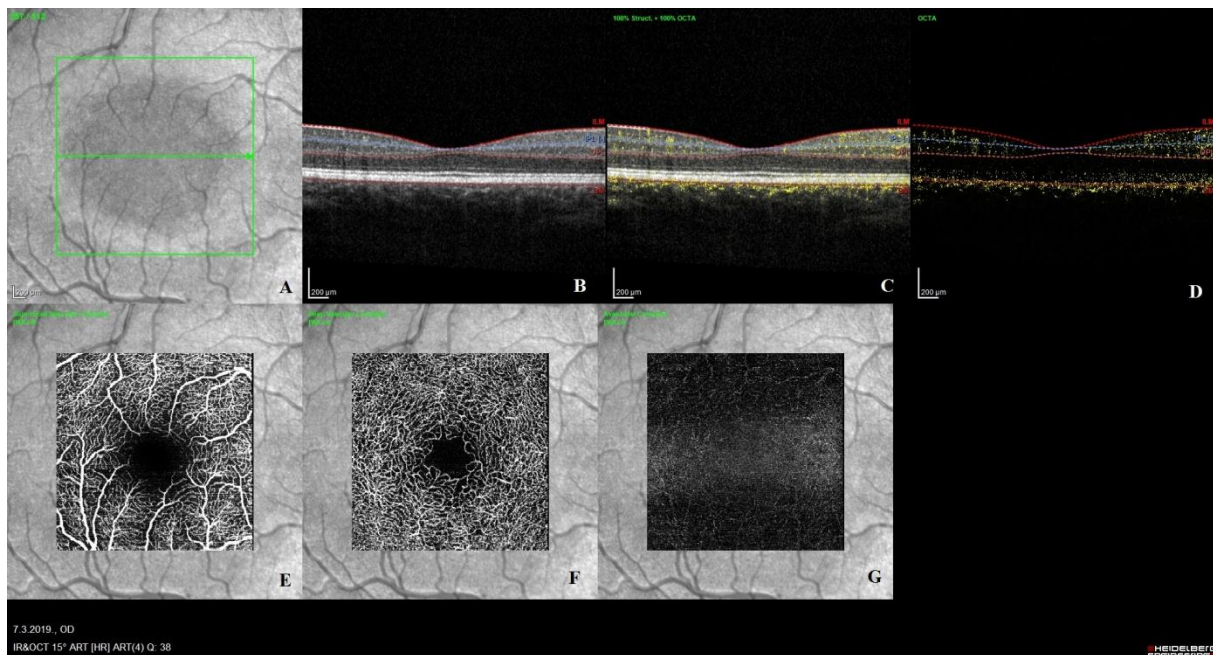


Figure 2. OCT-A image of the right eye of a healthy 4-year-old female patient. (A) Photography of the macula. (B) Foveal anatomy. (C) Foveal layers with depicted red blood cells (yellow). (D) Red blood cells (yellow) in the foveal area. Clear distinction is visible between (E) SVP, (F) DVP and (G) avascular complex of the retina. Images obtained from Spectralis® OCT (Heidelberg Engineering, Heidelberg, Germany). OCT-A-optical coherence angiography, OCT-optical coherence tomography, SVP-superficial vascular plexus, DVP-deep vascular plexus

Choroidal neovascularization (CNV)

The advent of OCT has enabled new classification of CNV: type 1 (beneath the RPE), which is the most common type, type 2 (above the RPE) (Figure 3) and type 3 (intra-retinal).

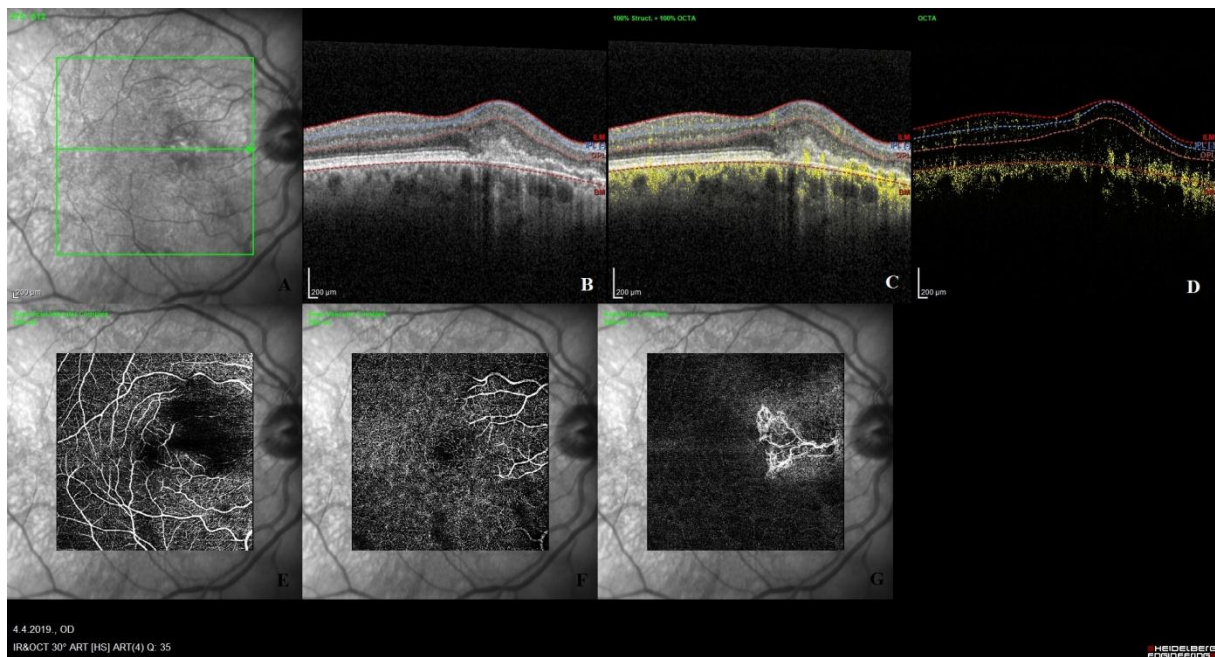


Figure 3. OCT-A image of the right eye of a 71-year-old male patient with type 2 CNV. (A) Photography of the macula with oedema of the papillomacular area. (B) Foveal anatomy. (C) Foveal layers with depicted red blood cells (yellow). (D) Red blood cells (yellow) in the foveal area. OCT images demonstrate mild oedema of retinal layers and Bruch's membrane rupture with NV emerging from the choroid. (E) SVP devoid of vessels in the area of the pathologic process. (F) DVP with NV. (G) NV emerging from the choroid. Images obtained from Spectralis® OCT (Heidelberg Engineering, Heidelberg, Germany). OCT-A-optical coherence angiography, CNV-choroidal neovascularization, OCT-optical coherence tomography, SVP-superficial vascular plexus, DVP-deep vascular plexus, NV-neovascularization

Type 1 is the most common type of CNV in AMD. FA is incapable of determining whether CNV is above or beneath the RPE and thus of defining the type of CNV or of detecting a polyp in polypoidal choroidal vasculopathy, a subtype of type 1 CNV. CNV therefore requires multimodal imaging (OCT, FA, ICG) (38). OCT-A can vastly improve the definition of exact CNV dimensions compared to FA (39, 40, 41, 42). This is of high importance as larger CNVs have poorer visual outcome (39).

OCT-A introduced new biomarkers for predicting disease activity and duration. Greater vessel calibres are fairly unresponsive to treatment due to excessive covering with pericytes (39). Encouraged by these insights, the greatest vascular calibre (GVC) was proposed as the marker of long-standing disease. The GVC could reveal the duration of CNV, which is important due to excessive damage caused by long-standing type 1 CNV, which remains

asymptomatic longer than type 2 (39). More mature vessels are found in type 1 CNV compared to type 2 (43). As a biomarker for active CNV, tiny branching vessels (TBV) can be used due to their presence in 82% of active lesions and only 30% of quiescent ones (44). The peripheral arcade is also present in 82% of active lesions compared to 40% of quiescent ones (44, 45). TBVs are important because they are more vulnerable to treatment due to their lack of pericytes compared to prominent vessels. In addition, pericytes appear later than angiogenesis, which means that TBVs could be related to the exudative status of the lesion; they could enable prompt treatment in order to preserve the macular architecture and thus, visual acuity (45). In light of these findings, it seems reasonable to include OCT-A imaging in the monitoring of all patients with CNV (45).

Nonexudative (subclinical) CNV was first described in post-mortem eyes by Green et al.

(46) and Sarks et al. (47) as abnormal choroidal vessels passing through breaks in Bruch's membrane in the absence of overlying haemorrhage or exudation. These lesions, which presented as plaques on ICG (48), can now be diagnosed more accurately using OCT-A (49). Compared with ICGA, the sensitivity and specificity of OCT-A in detecting subclinical CNV was reported as 81.8% and 100 %, respectively (50). It would be beneficial to determine the presence of subclinical CNV in fellow eyes of patients with unilateral exudative AMD, which ranges from 6.25% to 27%, respectively (49). The progression rate of subclinical CNV to exudative form is 20% and the existence of a possible protective effect of subclinical CNV against geographic atrophy progression has been suggested (51). Reduction in CC flow adjacent to CNV could be a marker of imminent exudation in subclinical CNV, as new evidence demonstrates (49, 51). Exudation may be triggered by the underlying progression of CC nonperfusion. Hypoxia of the retinal pigment epithelium causes the release of abnormal vascular endothelial growth factor (VEGF) signalling with growth and eventual exudations of a CNV (49).

Glaucoma

Pathophysiology of glaucoma and the onset of changes in macular vasculature are yet to be elucidated. Recent studies have suggested that macular vascular changes in glaucoma may be related to mechanisms other than intraocular pressure (IOP) (52, 53). In early glaucoma, OCT-A revealed focal loss of RPC (54) and decreased parafoveal vascular density (52). In eyes with central visual field defects, FAZ perimeter could be used as a biomarker for detecting glaucoma (55). In a recent study, eyes with open-angle glaucoma demonstrating central visual field defects (CVFDs) confined to a single hemifield exhibited a larger FAZ area and a less circular FAZ than those with peripheral visual field defects (55). Loss of FAZ circularity and increased size of the FAZ area were significantly correlated with the presence and severity of CVFD at initial presentation (55).

Parafoveal and peripapillary vascular density decrease in primary open-angle glaucoma compared to normal tension glaucoma (52, 53) is inconsistent with the earlier described mechanism of normal tension glaucoma development through its association with vascular compromise as a contrast to primary open-angle glaucoma, where the pathophysiology is mostly correlated with intraocular pressure (56). It is unclear whether vascular density changes in glaucoma antedate ganglion cell loss or are a direct result of loss of neural tissue and thus a marker for both primary open-angle glaucoma and normal tension glaucoma (53).

Diabetic retinopathy

Optical coherence tomography angiography offers a non-invasive alternative in the investigation of diabetic retinopathy. FAZ has been one of the most extensively investigated areas in diabetic retinopathy (57). In eyes with diabetic retinopathy, the circularity and axial ratio of the FAZ are significantly different from normal eyes. These metrics could be predictors of disease progression and response to therapy (58). However, even without retinopathy, OCT-A demonstrated significantly enlarged FAZ areas compared to controls – in both the SCP and DCP (57).

In eyes with diabetic retinopathy, OCT-A can identify microaneurysms (MA), microvascular abnormalities associated with diabetic macular oedema (DMO), and areas of capillary non-perfusion associated with neovascularization, allowing enhanced analysis compared to FA in that their intraretinal location beyond SVP can be identified (59). However, the sensitivity for MA detection and small field of view are currently the major limitations of OCT-A technology (57). A lower number of MA visible on OCT-A as compared to FA may be due to slower flow speeds in MA that are beyond the OCT-A detection threshold (60) or due to focal staining of vessel walls allowing superior identification by FA (61).

In eyes with proliferative diabetic retinopathy, OCT-A can visualize preretinal

neovascularization. Compared to FA, OCT-A has demonstrated moderate agreement for grading of diabetic macular ischemia (59).

By enabling three-dimensional visualization of the individual retinal vascular networks, OCT-A is enhancing our understanding of the role of deeper vasculature in the pathogenesis of diabetic retinopathy and maculopathy. OCT-A can differentiate between different subgroups of diabetic retinopathy severity by measuring perfusion indices in eyes with DR and branching complexity of vessels (57). The decrease in vascular density with the progression of the disease has already been established (62, 63). Reduction of vascular density in DVP occurs earlier in the course of the disease and this finding gives rise to possible new studies concerning vascular density in DVP as a marker of disease severity in earlier stages of diabetic retinopathy (60). FAZ enlargement and reduction of parafoveal deep and superficial vascular density can be beneficial as a marker of increased disease severity in diabetic retinopathy (60).

Central serous chorioretinopathy

Diagnosing CNV as a complication of chronic central serous chorioretinopathy (CSCR) using FA is difficult due to the confusing signs of the primary disease, such as choroidal hyperpermeability, retinal pigment epithelium leakage, or atrophy and cystic macular oedema (64). OCT-A has the advantage of identifying only the flow, without the exudative component, and it allows for depth-correlated visualization of flow with separation of the signal generated from the pathologic area between RPE and the Bruch membrane from the CC. These advantages of OCT-A are more prominent for type 1 CNV (65). CNV locations correspond to slightly irregular and hyperreflective RPE areas (66), which is consistent with earlier observations (67).

With OCT-A, a higher detection rate of CNV (mainly type 1) in chronic CSCR is achieved compared to ICG and FA (65). Thus, in case of CSCR, using OCT-A B-scan and en-face mode is always recommended in order to define the area of flat irregular pigment epithelial detachment, which is claimed to be imperative for the CNV diagnosis (65).

Ocular oncology

A significant enlargement of the deep FAZ and a decrease in the superficial and deep vascular density in eyes with choroidal melanoma were observed compared to healthy eyes (68). These changes are correlated with larger tumour size and presence of subretinal fluid, which could elucidate the pathogenesis of vision loss in patients with melanoma (68). One possible mechanism behind these changes is VEGF-induced microvascular compromise preceding macular oedema (68). These features are absent in eyes with choroidal nevi, giving rise to easier differentiation of small melanoma from choroidal nevi (68).

Early vascular changes in radiation retinopathy that can be detected by OCT-A as irregular widening of FAZ, discontinuity of retinal vasculature and retinal MA have been used as a part of a new grading scheme and treatment decisions for radiation retinopathy (69).

Conclusion

OCT-A is an important new non-invasive tool for imaging of the chorioretinal vasculature. It has provided new insights into the pathogenesis of multiple retinal and choroidal diseases, but its full contribution is yet to come. Regarding the paediatric population, the normal values have to be defined first in order for us to accurately elucidate the pathology.

References

1. Koustenis A, Harris A, Gross J, Januleviciene I, Shah A, Siesky B. Optical coherence tomography angiography: an overview of the technology and an assessment of applications for clinical research. *Br J Ophthalmol* 2017; 101(1):16-20.
2. Grover S, Murthy RK, Brar VS, Chalam KV. Normative data for macular thickness by high definition spectral domain optical coherence tomography (Spectralis). *Am J Ophthalmol* 2009; 148:266-71.
3. Spaide RF, Klancnik JM, Cooney MJ. Retinal vascular layers imaged by fluorescein angiography and optical coherence tomography angiography. *JAMA Ophthalmol* 2015; 133(1):45-50.
4. Sambhav K, Grover S, Chalam VK. The application of optical coherence tomography angiography in retinal diseases. *Surv Ophthalmol*. 2017; 62:838-66.
5. Wojtkowski M, Bajrazewski T, Gorczyńska I, Targowski P, Kowalczyk A, Wasilewski W, Radzewicz C. Ophthalmic imaging by spectral optical coherence tomography. *Am J Ophthalmol* 2004; 138(3):412-9.
6. Huang D, Swanson EA, Lin CP, Schuman JS, Stinson WG, Chang W, Hee MR, Flotte T, Gregory K, Puliafito CA, Fujimoto JG. Optical coherence tomography. *Science* 1991; 254(5035):1178-81.
7. Spaide RF, Fujimoto JG, Waheed NK, Sadda SR, Staurengi G. Optical coherence tomography angiography. *Prog Retin Eye Res* 2018; 64:1-55.
8. Puliafito CA, Hee MR, Schuman JS, Fujimoto JG. Optical coherence tomography of ocular diseases. 1st Ed. New York: Slack Inc; 1996.
9. Budenz DL, Anderson DR, Varma R, Schuman J, Cantor L, Savell J, Greenfield DS, Patella VM, Quigley HA, Tielsch J. Determinants of normal retinal nerve fibre layer retinal thickness measured by Stratus OCT. *Ophthalmol* 2007; 114(6):1046-52.
10. Izatt JA, Kulkarni MD, Yazdanfar S, Barton JK, Welch AJ. In vivo bidirectional color Doppler flow imaging of picoliter blood volumes using optical coherence tomography. *Opt Lett* 1997; 22:1439-41.
11. Chen ZP, Milner TE, Dave D, Nelson JS. Optical doppler tomographic imaging of fluid flow velocity in highly scattering media. *Opt Lett* 1997; 22:64-66.
12. Dai C, Liu X, Zhang HF, Puliafito CA, Jiao S. Absolute retinal blood flow measurement with a dual-beam doppler optical coherence tomography. *Invest Ophthalmol Vis Sci* 2013; 54:7998-8003.
13. Leitgeb RA, Werkmeister RM, Blatter C, Schmetterer L. Doppler optical coherence tomography. *Prog Retin Eye Res* 2014; 41(100):26-43.
14. Motaghiannezam R, Fraser S. Logarithmic intensity and speckle-based motion contrast methods for human retinal vasculature visualization using swept source optical coherence tomography. *Biomed Opt Express* 2012; 3:503-21.
15. Gao SS, Yia Y, Zhang M, Su JP, Liu G, Hwang TS, Bailey ST, Huang D. Optical coherence tomography angiography. *Invest Ophthalmol Vis Sci* 2016; 57:27-36.
16. Gorczynska I, Migacz JV, Zawadzki RJ, Capps AG, Werner JS. Comparison of amplitude-decorrelation, speckle-variance and phase-variance OCT angiography methods for imaging the human retina and choroid. *Biomed Opt Express* 2016; 7(3):911-42.
17. Pircher M. Development and application of optical coherence tomography (OCT) [Internet]. Basel: MDPI google books; 2018 (cited 2019 June 12). Available from: <https://www.mdpi.com/books/pdfview/book/537>
18. Jia Y, Morrison JC, Tokayer J, Tan O, Lombardi L, Baumann B, Lu CD, Choi WJ, Fujimoto JG, Huang D. Quantitative OCT

angiography of optic nerve head blood flow. *Biomed Opt Express* 2012; 3:3127-37.

19. Spaide RF, Fujimoto JG, Waheed NK. Image artifacts in optical coherence angiography. *Retina* 2015; 35(11):2163-80.

20. Zhang Q, Rezaei KA, Saraf SS, Chu Z, Wang F, Wang RK. Ultra-wide optical coherence tomography angiography in diabetic retinopathy. *Quant Imaging Med Surg* 2018; 8(8):743-53.

21. Bonnin S, Krivosic V, Cognat E, Tadayoni R. Visibility of blood flow on optical coherence tomography angiography in a case of branch retinal artery occlusion. *J Ophthalmic Vis Res* 2018; 13(1):75-7.

22. Agrawal S, Chawla R, Sundar D, Azad SV, Kumar S, Vohra R. OCT Angiography-A perspective based on 3 years of clinical application. *Digit J Ophthalmol* 2019; 29:67-71.

23. Mase T, Ishibazawa A, Nagaoka T, Yokota H, Yoshida A. Radial peripapillary capillary network visualized using wide-field montage optical coherence tomography angiography. *Invest Ophthalmol Vis Sci* 2016; 57:504-10.

24. Pournaras CJ, Rungger-Brändle E, Riva CE, Hardarson SH, Stefansson E. Regulation of retinal blood flow in health and disease. *Prog Retin Eye Res* 2008; 27(3):284-330.

25. Hirano T, Chanwimol T, Weichsel J, Tepelus T, Sadda S. Distinct retinal capillary plexuses in normal eyes as observed in optical coherence tomography angiography axial profile analysis. *Sci Rep* 8:9380. [Online]. 2018 June 20
<https://www.nature.com/articles/s41598-018-27536-5> (cited 2019 June 26)

26. Shiihara H, Terasaki H, Sonoda S, Kakiuchi N, Shinohara Y, Tomita M, Sakamoto T. Objective evaluation of size and shape of superficial foveal avascular zone in normal subjects by optical coherence tomography angiography. *Sci Rep* 8:10143. [Online]. 2018 July 4
<https://www.nature.com/articles/s41598-018-28530-7> (cited 2019 October 11)

27. Tan CS, Lim LW, Chow VS, Chay IW, Tan S, Cheong KX, Tan GT, Sadda SR. Optical coherence tomography angiography evaluation of the parafoveal vasculature and its relationship with ocular factors. *Invest Ophthalmol Vis Sci* 2016; 57:224-34.

28. Shahlaee A, Pefkianaki M, Hsu J, Ho AC. Measurement of foveal avascular zone dimensions and its reliability in healthy eyes using optical coherence tomography angiography. *Am J Ophthalmol* 2016; 161:50-5.

29. Samara WA, Say EA, Khoo CT. Correlation of foveal avascular zone size with foveal morphology in normal eyes using optical coherence tomography angiography. *Retina* 2015; 35:2188-95.

30. Falavarjani KG, Shenazandi H, Naseri D, Anvari P, Kazemi P, Aghamohammadi F, Alismail F, Alemzadeh SA. Foveal avascular zone and vessel density in healthy subjects: an optical coherence tomography angiography study. *J Ophthalmic Vis Res* 2018; 13(3):260-5.

31. Ghassemi F, Mirshahi R, Bazvand F, Fadakar K, Faghihi F, Sabour S. The quantitative measurements of foveal avascular zone using optical coherence tomography angiography in normal volunteers. *J Curr Ophthalmol* 2017; 29(4):293-9.

32. Laatikainen L. The fluorescein angiography revolution: a breakthrough with sustained impact. *Acta Ophthalmol Scand* 2004; 82:381-92.

33. Wu LZ, Huang ZS, Wu DZ, Chan E. Characteristics of the capillary-free zone in the normal human macula. *Jpn J Ophthalmol* 1985; 29:406-11.

34. Iafe NA, Phasukkijwatana N, Chen X, Sarraf D. Retinal capillary density and foveal avascular zone area are age-dependent: quantitative analysis using optical coherence tomography angiography. *Invest Ophthalmol Vis Sci* 2016; 57:5780-7.

35. Yu J, Jiang C, Wang X. Macular perfusion in healthy Chinese: an optical coherence

tomography angiogram study. *Invest Ophthalmol Vis Sci* 2015; 56:3212-7.

36. Fujiwara A, Morizane Y, Hosokawa M, Kimura S, Shiode Y, Hirano M, Doi S, Toshima S, Takahashi K, Hosogi M, Shiraga F. Factors affecting foveal avascular zone in healthy eyes: An examination using swept-source optical coherence tomography angiography. *PLoS ONE* [Online]. 2017. <https://doi.org/10.1371/journal.pone.0188572> (cited 2019 June 20)

37. Coscas F, Sellam A, Glacet-Bernard A. Normative data for vascular density in superficial and deep capillary plexuses of healthy adults assessed by optical coherence tomography angiography. *Invest Ophthalmol Vis Sci* 2016; 57:211-23.

38. Yeo JH, Chung H, Kim JT. Swept-source optical coherence tomography angiography according to the type of choroidal neovascularization. *J Clin Med* 2019; 8:1272.

39. Zhao Z, Yang F, Gong Y, Yu S, Liu H, Wang H, Wang F, Sun X. The comparison of morphologic characteristics of type 1 and type 2 choroidal neovascularization in eyes with neovascular age-related macular degeneration using optical coherence tomography angiography. *Ophthalmologica* 2019; 242(3):178-86.

40. Boyer DS, Antoszyk AN, Awh CC, Bhisitkul RB, Shapiro H, Acharya NR. MARINA Study Group. Subgroup analysis of the MARINA study of ranibizumab in neovascular age-related macular degeneration. *Ophthalmology* 2007; 114(2): 246-52.

41. Ying GS, Huang J, Maguire MG, Jaffe GJ, Grunwald JE, Toth C, Daniel E, Klein M, Pieramici D, Wells J, Martin DF. Comparison of Age-related Macular Degeneration Treatments Trials Research Group. Baseline predictors for one-year visual outcomes with ranibizumab or bevacizumab for neovascular age-related macular degeneration. *Ophthalmology* 2013; 120(1):122-9.

42. Schneider EW, Fowler SC. Optical coherence tomography angiography in the

management of age-related macular degeneration. *Curr Opin Ophthalmol* 2018; 29(3):217-25.

43. Nakano Y, Kataoka K, Takeuchi J, Fujita A, Kaneko H, Shimizu H, Ito Y, Terasaki H. Vascular maturity of type 1 and type 2 choroidal neovascularization evaluated by optical coherence tomography angiography. *PLoS One*. 2019;14(4):e0216304. [Online] 2019 Apr 29 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6488195/> (cited 2019 Oct 17)

44. Coscas F, Lupidi M, Boulet JF, Sellam A, Cabral D, Serra R, Francais C, Souied EH, Coscas G. Optical coherence tomography angiography in exudative age-related macular degeneration: a predictive model for treatment decisions. *Br J Ophthalmol* 2019; 103:1342-6.

45. Al-Sheikh M, Iafe NA, Phasukkijwatana N, Sadda SR, Sarraf D. Biomarkers of neovascular activity in age-related macular degeneration using optical coherence tomography angiography. *Retina* 2018; 38:220-30.

46. Green WR, Key S III. Senile macular degeneration: a histopathologic study. *Trans Am Ophthalmol Soc* 1977; 75:180.

47. Sarks S. New vessel formation beneath the retinal pigment epithelium in senile eyes. *Br J Ophthalmol* 1973; 57:951.

48. Yannuzzi LA, Slakter JS, Sorenson JA, Guyer DR, Orlock DA. Digital indocyanine green videoangiography and choroidal neovascularization. *Retina* 1992; 12:191-223.

49. Treister AD, Nesper PL, Fayed AE, Gill MK, Mirza RG, Fawzi AA. Prevalence of subclinical CNV and choriocapillaris nonperfusion in fellow eyes of unilateral exudative AMD on OCT angiography. *Transl Vis Sci Technol* 2018; 7(5):19.

50. Carnevali A, Cicinelli MV, Capuano V, Corvi F, Mazzafero A, Querques L, Scordia V, Souied EH, Bandello F, Querques G. Optical coherence tomography angiography: a useful tool for diagnosis of treatment-naïve quiescent choroidal neovascularization. *Am J Ophthalmol* 2016; 169:189-98.

51. Heiferman MJ, Fawzi AA. Progression of subclinical choroidal neovascularization in age-related macular degeneration. *PLoS One* 2019;14(6):e0217805. [Online] 2019 Jun 4. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6548359/> (cited 2019 Oct 19)
52. Onishi AC, Treister AD, Nesper PL, Fawzi AA, Anchala AR. Parafoveal vessel changes in primary open-angle glaucoma using optical coherence tomography angiography. *Clin Ophthalmol* 2019; 13:1935-45.
53. Bojikian KD, Chen CL, Wen JC, Zhang Q, Xin C, Gupta D, Mudumbai RC, Johnstone MA, Wang RK, Chen PP. Optic disc perfusion in primary open angle and normal tension glaucoma eyes using optical coherence tomography-based microangiography. *PLoS One*. 2016; 11(5):e0154691.
54. Mansoori T, Sivaswamy J, Galampati J, Balakrishna N. Radial peripapillary capillary density measurement using optical coherence tomography angiography in early glaucoma. *J Glaucoma* 2017; 26(5):438-43.
55. Kwon J, Choi J, Shin JW, Lee J, Kook MS. Alterations of the foveal avascular zone measured by optical coherence tomography angiography in glaucoma patients with central visual field defects. *Invest Ophthalmol Vis Sci* 2017; 58:1637-45.
56. Shields MB. Normal-tension glaucoma: is it different from primary open-angle glaucoma? *Curr Opin Ophthalmol* 2008; 19:85-8.
57. Gildea D. The diagnostic value of optical coherence tomography angiography in diabetic retinopathy: a systematic review. *Int Ophthalmol* 2019; 39(10):2413-33.
58. Krawitz BD, Mo S, Geyman LS, Agemy SA, Sripsema NK, Garcia PM, Chui TYP, Rosen RB. Acircularity index and axis ratio of the foveal avascular zone in diabetic eyes and healthy controls measured by optical coherence tomography angiography. *Vis Res* 2017; 139:177-86.
59. Ishibazawa A, Nagaoka T, Takahashi A, Omae T, Tani T, Sogawa K, Yokota H, Yoshida A. Optical coherence tomography angiography in diabetic retinopathy: A prospective pilot study. *Am J Ophthalmol* 2015; 160:35-44.
60. Mastropasqua R, Toto L, Mastropasqua A, Aloia R, De Nicola C, Mattei PA, Di Mazio G, Di Nicola M, Di Antonio L. Foveal avascular zone area and parafoveal vessel density measurements in different stages of diabetic retinopathy by optical coherence tomography angiography. *Int J Ophthalmol* 2017; 10(10):1545-51.
61. Matsunaga DR, Yi JJ, De Koo LO, Ameri H, Puliafito CA, Kashani AH. Optical coherence tomography angiography of diabetic retinopathy in human subjects. *Ophthalmic Surg Lasers Imaging Retina* 2015; 46:796-805.
62. Agemy SA, Sripsema NK, Shah CM, Chui T, Garcia PM, Lee JG, Gentile RC, Hsiao YS, Zhou Q, KO T, Rosen RB. Retinal vascular perfusion density mapping using optical coherence tomography angiography in normals and diabetic retinopathy patients. *Retina* 2015; 35(11):2353-63.
63. Samara WA, Shahlaee A, Adam MK, Khan MA, Chiang A, Maguire JI, Hsu J, Ho AC. Quantification of diabetic macular ischemia using optical coherence tomography angiography and its relationship with visual acuity. *Ophthalmology* 2017; 124(2):235-244.
64. Spaide RF, Campeas L, Haas A, Yanuzzi LA, Fisher YL, Guyer DR, Slakter JS, Sorenson JA, Orlock DA. Central serous chorioretinopathy in younger and older adults. *Ophthalmology* 1996; 103: 2070-79.
65. Romdhane K, Mantel I. Choroidal neovascularization complicating central serous chorioretinopathy: The discovery rate on multimodal imaging. *Klin Monatsbl Augenheilkd* 2019; 236(04): 536-41.
66. Sulzbacher F, Schutze C, Bergmuller M, Vecsei-Marlowitz PV, Weingessel P. Clinical evaluation of neovascular and non-neovascular chronic central serous chorioretinopathy (CSC) diagnosed by swept source optical coherence tomography angiography (SS OCTA). *Graefes Arch Clin Exp Ophthalmol* 2019; 257:1581.

67. Quaranta-El Maftouhi M, El Maftouhi A, Eandi CM. Chronic central serous chorioretinopathy imaged by optical coherence tomographic angiography. *Am J Ophthalmol* 2015; 160:581–587

68. Davila JR, Mruthyunjaya P. Updates in imaging in ocular oncology [version 1; peer review: 3 approved]. *F1000Research* 2019,

8(F1000 Faculty Rev):1706 [Online]. 2019 Oct 1 <https://doi.org/10.12688/f1000research.19979.1> (cited 2019 Oct 14)

69. Veverka KK, AbouChehade JE, Iezzi R Jr, Pulido JS. Noninvasive grading of radiation retinopathy: The use of optical coherence tomography angiography. *Retina* 2015; 35(11): 2400-10.

Review article

Effect Of Iron Deficiency Anemia And Other Clinical Conditions On Hemoglobin A1c Levels

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Abstract

Iron deficiency anemia is the most common type of anemia in the world, the most common form of malnutrition deficit with a prevalence of 50% affecting the developed countries as well as developing countries with a strong influence on social and economic development. According to current guidelines of the American Diabetes Association (2019.) glycated hemoglobin (HbA1c) is a reflection of the patient's glycemic status in the last three months and is used for monitoring of therapeutic effect as well as for diagnostic purposes. Previous studies have proven that not only iron deficiency anemia but also a range of other clinical conditions can affect the level of HbA1c independent of glycemic status. The exact mechanism of the effect of iron deficiency on glycated hemoglobin levels remains unknown and is still at the hypothesis level. Studies have proven that treatment of iron deficiency anemia leads to better control of HbA1c level, regardless of whether the patient is diabetic or not. A small number of studies have noted a correlation between iron deficiency and levels of glycated hemoglobin, thus further research on larger number of patients is certainly necessary in order to improve the therapeutic possibilities for patients with diabetes, more accurately diagnose and understand the pathophysiology of formation and influence on glycated hemoglobin levels.

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Introduction

Iron deficiency anemia in today's modern world is the most common form of malnutrition and the most common form of anemia. Globally, iron deficiency is the cause of 50% of all anemias (1). Hemoglobin A1c (HbA1c) is a glycated hemoglobin, which is used to monitor average value of glycemic index of the patient in the last 3 months (2). HbA1c is produced by glycation of the terminal amino acid valine at the β chain of hemoglobin and, unlike other markers for monitoring glycemic status, is less susceptible to daily fluctuations depending on diet, physical activity or disease (3). According to the latest guidelines of the American Diabetes Association (2019), the level of HbA1c $\geq 6.5\%$ is the criteria for the diagnosis of diabetes (3). Various other factors can also affect glycated hemoglobin levels such as hemolytic anemia (4), hemoglobinopathies (5), acute blood loss (6), pregnancy (7) and uremia in chronic renal failure (8). What can be concluded is that the level of hemoglobin A1c is not only related to diabetes and glycemic index, but that different factors can affect the level of the same (Table 1).

Table 1. Diseases and clinical conditions affecting hemoglobin A1c level

HbA1c $\geq 6.5\%$
Diabetes Mellitus
Chronic renal failure
Uremia
Iron deficiency anemia
Hemoglobinopathies
Hemolytic anemia
Acute blood loss
Pregnancy

Note: Summarized findings from studies to date on the most common diseases and clinical conditions that affect the value of HbA1c levels.

Therefore, it is of the utmost importance to identify comorbidities that may affect the level of glycated hemoglobin before its level is taken into account for diagnostic and therapeutic purposes. New studies have provided data on alternative glycemic markers that are not as

susceptible to these comorbidities and that can be used to monitor glycemic status in particular patient populations, but their application has not yet become widely used.

From past to present

Previous studies which examined the correlation of sideropenic anemia and HbA1c levels (depending or independent of the patient's glycemic status) have shown conflicting results. Books and colleagues examined HbA1c values in 35 patients with iron deficiency anemia without proven diabetes, and found significantly elevated levels of HbA1c in patients with iron deficiency anemia and normalization of values after iron substitution therapy (9). Similar results were obtained in the studies of Sluiter et al. (10) and Mitchell et al. (11) who attempted to explain the correlation of HbA1c and sideropenic anemia by alternation of hemoglobin structure and HbA1c levels in old and newly synthesized erythrocytes. According to the conclusion of Sluiter et al., hemoglobin glycation is an irreversible process that is present in accordance with the erythrocyte lifetime.

A prospective study from 2010, on a small sample of patients with proven diabetes mellitus and chronic renal failure (stage IIIB-IV), examined the effect of intravenous iron supplementation and erythropoietin stimulating agents (ESA) on HbA1c values. Both therapeutic choices led to a statistically significant decrease in HbA1c (12). Similar results were obtained in patients with diabetes without developed renal insufficiency (13-16).

CLEVER was the first study to test the hypothesis that intravenous administration of iron carboximaltosis leads to a reduction in HbA1c levels in patients with type 2 diabetes and sideropenic anemia, thereby improving metabolic status and quality of life. Organized as a randomized, single-blind study, it was conducted on subjects divided into two groups; study group (treated with iron carboximaltosis) and control group (treated with placebo). The

findings show that iron deficiency is associated with an increased risk of developing insulin resistance and obesity, and iron excess with the development of diabetes (the effect of pancreatic beta-cell stimulation on enhanced insulin secretion) (17).

A 2016. cross-sectional study conducted on 150 patients (75 patients with iron deficiency anemia and 75 patients without anemia) examined HbA1c values relative to the degree of sideropenic anemia. Anemia severity was defined as mild anemia (Hb 120-129 g/L for men and 110-119 g/L for women), moderate anemia (Hb 90-119 g/L for men and 80-109 g/L for women) and severe anemia (Hb <90 g/L for men and <80 g/L for women). An elevated HbA1c was found in the patient with anemia in proportion to the degree of iron deficiency. Upon completion of the study, an increased HbA1c value was observed in a group of patients with iron deficiency anemia that correlated with the severity of the anemia (18). Similar results have been reported in other studies (19-20).

Increased glucose during pregnancy is now a well-known risk factor for the development of perinatal complications of mother and child, so strict control of the glycemic index during pregnancy is of particular importance. Pregnant women with known gestational diabetes have a significantly higher risk of developing type 2 diabetes at the end of pregnancy than pregnant women with normal glucose levels during pregnancy (21). Studies have shown that hemoglobin A1c during pregnancy (the gold standard of glycemic control) is not a true reflection of the glycemic status due to frequent iron deficiency anemia (22-23). Studies also noted that glycated albumin (GA) values were well maintained throughout pregnancy, suggesting that elevated glycated hemoglobin during gestation could be independent of glycemic index and that glycated serum albumin presents more accurate factor for glycemic control in pregnancy.

Furthermore, some studies found no correlation between HbA1c values in patients with iron deficiency anemia and control group (24-25),

other studies have reported lower values of HbA1c in diabetic patients with sideropenic anemia compared to diabetics without anemia (26), while other studies found elevated HbA1c values upon completion of substitution therapy in patients with iron deficiency anemia (unknown variables) (27).

Disclosure

In conclusion, HbA1c is widely used today as a diagnostic tool for diabetes and a means of controlling the patient's glycemic status. Different clinical conditions and diseases may affect the erythropoiesis process with an impact on HbA1c levels. Numerous clinical studies, mostly based on a small number of patients, have confirmed that in the presence of iron deficiency anemia, HbA1c levels are elevated even in non-diabetic patients with normal glycemic status (Table 2).

Table 2. Results of studies examining the association between hemoglobin A1c and sideropenic anemia

Author and year of the study	No. of subjects	Iron deficiency anemia	Diabetes mellitus	Serum iron ($\mu\text{mol/L}$) / Ferritin (ng/ml)	Hemoglobin (g/l)	HbA1c % (examined group)	HbA1c % (control group)
Shanti et al. 2013.	50	yes	no	no data / 3.68	106 $\pm$ 1.4	7.6 $\pm$ 0.5	5.5 $\pm$ 0.8
Alap L. Christy et al. 2014. *	120	yes	yes	no data / 11.41	95.4 (male) / 93.7 (female)	6.87 $\pm$ 1.4	5.65 $\pm$ 0.69
Bhardway et al. 2016.	50	yes	no	2.7 / 7.51	61.8	6.60 $\pm$ 0.1	5.48 $\pm$ 0.56
Rajagopal et al. 2016.	75	yes	no	2.12 / 120.9	114.6	6.84 $\pm$ 0.07	5.12 $\pm$ 0.04
Sinha et al. 2011.	50	yes	no	no data / 7.0	62	4.6 $\pm$ 0.6	5.5 $\pm$ 0.6
Solomon et al. 2019. *	174	yes	yes	no data / no data	99.7	6.18 $\pm$ 1.57	7.74 $\pm$ 1.81

* control group; diabetic patients without iron deficiency anemia
All numeric data expressed as mean values

The expected elevated values of glycated hemoglobin in patients with diabetes are well correlated with diabetes control, therefore, in patients with controlled blood glucose levels, HbA1c is expected to be less than 6.5% (3). The initial belief that the level of glycated hemoglobin is proportional exclusively to glycemic status, has been rejected. The mechanism by which iron deficiency anemia affects the level of HbA1c remains unknown, largely based on hypotheses. From the foregoing, it is suggested that the iron status of the patient be taken into account before interpretation of the HbA1c value, with or without proven diabetes. Early diagnosis and treatment of iron deficiency anemia in patients with diabetes may improve glycemic control and delay the onset of complications (28). As there is not enough studies on a large sample from this still-unexplained pathophysiological mechanism, further research is needed in the future to elucidate the correlation of hemoglobin glycation and iron deficiency.

Precisely because the limitations of hemoglobin A1c are known today, there is great interest in the use of alternative glycemic markers. Among the alternative markers that can be used as a complement to hemoglobin A1c is glycated albumin. As the level of glycated hemoglobin is dependent on red blood cell turnover, albumins have a shorter half-life, therefore indicating a glycemic index of the last 2-3 weeks. Postprandial glucose values are also better in states with marked disease progression, such as in type 1 fulminant diabetes mellitus. Restrictions on the use of GA are pathological conditions related to blood albumin levels such as nephrotic syndrome, liver disease, obesity, glucocorticoid administration, Cushing's syndrome and hyperthyroidism. Regardless of the known, routine administration of glycated hemoglobin has not yet taken root in clinical practice, which will require long-term prospective studies (29-31).

References

1. John A. Iron Deficiency and Other Hypoproliferative Anemias. In: Longo D, Fauci A, Kasper D, Hauser S, Jameson J, Loscalzo J, editors. Principles of Internal Medicine by Harrisons. 20th ed. United States of America: McGraw-Hill; 2018. pp. 684–90.
2. Telen MJ, Kaufman RE (2004) The mature erythrocyte. In: Greer JP, Forester J (Eds). Wintrobe's clinical hematology. (11th edn). Lippincott: Williams and Wilkins 230.
3. American Diabetes Association Diabetes Care 2019 Jan; 42(Supplement 1): S13–S28.
4. Horton BF, Huisman TH (1965) Studies on the heterogeneity of hemoglobin. VII. Minor hemoglobin components in haematological diseases. Br J Haematol 11: 296–304.
5. Eberentz-Lhomme C, Ducrocq R, Intrator S, Elion J, Nunez E, et al. (1984) Haemoglobinopathies: a pitfall in the assessment of glycosylated haemoglobin by ion-exchange chromatography. Diabetologia 27: 596–598.
6. Starkman HS, Wacks M, Soeldner JS, Kim A (1983) Effect of acute blood loss on glycosylated hemoglobin determinations in normal subjects. Diabetes Care 6: 291–294.
7. Lind T, Cheyne GA (1979) Effect of normal pregnancy upon the glycosylated haemoglobins. Br J Obstet Gynaecol 86: 210–213.
8. Paisey R, Banks R, Holton R, Young K, Hopton M, et al. (1986) Glycosylated haemoglobin in uraemia. Diabet Med 3: 445–448.
9. Brooks AP, Metcalfe J, Day JL, Edwards MS. Iron deficiency and glycosylated haemoglobin A1. Lancet. 1980 Jul;316(8186)
10. Sluiter WJ, van Essen LH, Reitsma WD, Doorenbos H (1980) Glycosylated haemoglobin and iron deficiency. Lancet 2: 531–532.
11. Mitchell TR, Anderson D, Shepperd J (1980) Iron deficiency, haemochromatosis, and glycosylated haemoglobin. Lancet 2: 747.
12. Ng JM, Cooke M, Bhandari S, Atkin SL, Kilpatrick ES. The effect of iron and erythropoietin treatment on the A1C of patients with diabetes and chronic kidney disease. Diabetes Care. 2010 Nov;33(11):2310–3.
13. Alap L, Christy, Poornima A, Manjrekar, Ruby P, Babu, Anupama Hegde, Rukmini M.S. Influence of Iron Deficiency Anemia on Hemoglobin A1C Levels in Diabetic Individuals with Controlled Plasma Glucose Levels. Iran Biomed J. 2014 Apr; 18(2): 88–93.
14. Somiman A, De Sanctis, Yassin M, Soliman N. Iron deficiency anemia and glucose metabolism. Acta Biomed. 2017; 88(1): 112–118.
15. Urrechaga E. Influence of iron deficiency on Hb A1c levels in type 2 diabetic patients. Diabetes Metab Syndr. 2018 Nov;12(6):1051–1055.
16. Bhardwaj K, Sharma SK, Rajpal N, et al. Effect of Iron Deficiency Anaemia on Haemoglobin A1c Levels. Ann Clin Lab Res. 2016 October; 4: 4.
17. Schindler C, Birkenfeld AL, Hanefeld M, Schatz U, Köhler C, Grüneberg M, Tschöpe D, Blüher M, Hasslacher C, Bornstein SR. Intravenous Ferric Carboxymaltose in Patients with Type 2 Diabetes Mellitus and Iron Deficiency: CLEVER Trial Study Design and Protocol. Diabetes Ther. 2018 Feb;9(1):37–47. doi: 10.1007/s13300-017-0330-z. Epub 2017 Nov 13.
18. Lavanya Rajagopal, Shivashekar Ganapathy, Sundaram Arunachalam, Veena Raja, Balaji Ramraj. Does Iron Deficiency Anaemia and its Severity Influence HbA1C Level in Non Diabetics? An Analysis of 150 Cases. J Clin Diagn Res. 2017 Feb; 11(2): EC13–EC15.
19. Silva JF, Pimentel AL, Camargo JL. Effect of iron deficiency anaemia on HbA1C levels is dependent on the degree of anaemia. Clinical Biochemistry. 2016;49(1):117–20.
20. El-Agouza I, Abu Shahla A, Sirdah M. The effect of iron deficiency anaemia on the levels of haemoglobin subtypes: Possible consequences for clinical diagnosis. Clin Lab Haematol. 2002;24(5):285–89.

21. Bellamy L, Casas JP, Hingorani AD, Williams D. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. *Lancet*. 2009;373:1773–1779.
22. Hashimoto K, Noguchi S, Morimoto Y, Hamada S, Wasada K, Imai S, et al. A1C but not serum glycosylated albumin is elevated in late pregnancy owing to iron deficiency. *Diabetes Care*. 2008 Oct;31(10):1945–8.
23. Hashimoto K, Koga M. Indicators of glycemic control in patients with gestational diabetes mellitus and pregnant women with diabetes mellitus. *World J Diabetes*. 2015 Jul 25; 6(8): 1045–1056.
24. vanHeyningen C, Dalton RG (1985) Glycosylated haemoglobin in iron-deficiency anaemia. *Lancet* 1: 874.
25. Mitchell TR, Anderson D, Shepperd J (1980) Iron deficiency, haemochromatosis, and glycosylated haemoglobin. *Lancet* 2: 747.
26. Solomon A, Hussein M, Negash M, Ahmed A, Bekele F, Kahase D. Effect of iron deficiency anemia on HbA1c in diabetic patients at Tikur Anbessa specialized teaching hospital, Addis Ababa Ethiopia. *BMC Hematol*. 2019; 19: 2.
27. Nitin Sinha, M.D., T.K. Mishra, M.D., Tejinder Singh, M.D., Naresh Gupta. Effect of Iron Deficiency Anemia on Hemoglobin A1c Levels. *Ann Lab Med*. 2012 Jan; 32(1): 17–22.
28. Soliman A, De Sanctis V, Yassin M, Soliman N. Iron deficiency anemia and glucose metabolism. *Acta Biomed*. 2017; 88(1): 112–118.
29. Koga M, Murai J, Morita S, Saito H, Kasayama S. Comparison of annual variability in HbA1c and glycosylated albumin in patients with type 1 vs. type 2 diabetes mellitus. *J Diabetes Complications*. 2013;27:211–213.
30. Hirsch IB, Brownlee M. Beyond hemoglobin A1c--need for additional markers of risk for diabetic microvascular complications. *JAMA*. 2010;303:2291–2292.
31. Lee J. Alternative biomarkers for assessing glycemic control in diabetes: fructosamine, glycosylated albumin, and 1,5-anhydroglucitol. *Ann Pediatr Endocrinol Metab*. 2015 Jun; 20(2): 74–78.