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EFFECTS OF DIHYDROQUERCETIN (DHQ “P” DROPS) IN PATIENTS WITH PREVIOUS TRANSITORY ISCHEMIC ATTACKS ASSOCIATED WITH VISUAL DISORDERS

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Ключові слова: дигідрокверцетин, транзиторні порушення зору, артеріальна гіпертензія, гіпоксично-ішемічна енцефалопатія, транзиторні ішемічні атаки

Ключевые слова: дигидрокверцетин, преходящие нарушения зрения, артериальная гипертензия, гипоксическая ишемическая энцефалопатия, транзиторные ишемические атаки.

Abstract. Effects of dihydroquercetin (DHQ “P” drops) in patients with previous transitory ischemic attacks associated with visual disorders. Wang Zi Way, Pohorielov O.V., Bobokalo S.V., Baranenko O.M., Chun Liu. A study involved 48 patients aged 33 to 79 years (average age – 62.6 years) with transient ischaemic attacks (TIA) and visual disorders, caused by cerebrovascular diseases (CVD). 24 patients from this group underwent treatment by GCP criteria and medical care standards in acute brain blood supply disturbances, TIA and therapy with dihydroquercetin “DHQ” “P” drops in the dose of 7 drops, twice a day for 10 days. All the patients had arterial hypertension (AH) stage 1-2. Control group consisted of 26 men and 20 women of comparable age (n=46; average age - 65.9 years) without cerebral ischemic events and visual disorders, findings regarding neurophysiological parameters of visually evoked potentials (VEP) and microcirculatory system state (MCS) were compared. Exclusion criteria: acute heart diseases, type 1-2 diabetes mellitus, glaucoma, secondary types of arterial hypertension and AH stage 3, hemorrhages and hereditary cerebrovascular syndromes. Assessment of the “DHQ” “P” influence on such microcirculatory system parameters (retinopathy components) as perivascular edema, perivascular microhemorrhages, arterio-venular coefficient was carried out by results of the fundus oculi vessels computed photometry and biological microscopy of the bulbar conjunctival vessel layers. According to the data regarding distribution of TIA amount, retinopathy stage and age, correlation of TIA was conditioned by retinopathy stage and other factors except of patients’ age. Patients with TIA associated with visual disorders in presence of CVD suffered from arterial hypertension in 72.98%. Stage 1-3 of retinopathy and optic disc functional disorders were all detected. In case of therapy with “DHQ” “P” the positive changes in dynamic regarding capillary permeability restoration (in 71.43%±12,07, in retinopathy stage 1-2 in comparison with 38.46% without it) were established and less pronounced – in case of perivascular microhemorrhages. Such positive effects in the conducted study were characterized as tendency pattern (OR 2.87; p=0.08 for perivascular edema and OR 2.77; p=0.08 for microhemorrhages). The efficacy of therapy with “DHQ” “P” in restoration of impaired optic disk functions according to the data of VEP (for NO component of VEP; OR 2.87; p=0.041) in the dosage of 7 drops twice a day during 10 days in case of CVD was revealed; this determines the perspective of further investigation of “DHQ” “P” which contains dihydroquercetin.

Реферат. Эффекты дигидрокверцетина (ДГК "Р" капли) у пациентов после перенесенных транзиторных ишемических атак с нарушениями зрения. Ван Цзы Вэй, Погорелов А.В., Бобокало С.В., Бараненко А.Н., Чунь Лю. Проведено исследование 48 больных в возрасте от 33 до 79 лет (средний возраст – 62,6 года) с преходящими ишемическими атаками (ТИА) и нарушениями зрения, обусловленные цереброваскулярными заболеваниями (ЦВЗ). 24 пациента из этой группы прошли лечение по критериям GCP и стандартам помощи при острых нарушениях мозгового кровообращения, ТИА и приемом дигидрокверцетина «ДГК «Р» в каплях в дозировке 7 капель 2 раза в сутки 10 дней подряд. Все пациенты имели артериальную гипертензию (АГ) 1-2 ст. Контрольная группа состояла из 26 мужчин и 20 женщин сопоставимого возраста (n=46, средний возраст – 65,9 года), без церебральных ишемических событий и нарушений зрения, с данными этой группы были сравнены нейрофизиологические показатели зрительных вызванных потенциалов (ЗВП) и состояние микроциркуляторного русла (МЦР). Критерии исключения: острые сердечные заболевания, аритмии, диабет 1-2 типа, глаукома, вторичные типы АГ и АГ 3 ст., геморрагии и наследственные цереброваскулярные синдромы. Оценка влияния «ДГК «Р» на такие показатели МЦР (составляющие ретинопатии), как периваскулярный отек, периваскулярные микрогеморрагии, артериоловеноулярный коэффициент, проведена по результатам компьютерной фотометрии морфологических особенностей сосудов глазного дна и биомикроскопии сосудистых слоев бульбарной конъюнктивы. По данным распределения количества ТИА, стадии ретинопатии и возраста, связь ТИА была со стадией РП или другими факторами, но не возрастом больных. Пациенты с ТИА с нарушениями зрения при ЦВЗ в 72,98% имели артериальную гипертензию, ретинопатию 1-3 ст. и нарушения функций зрительного нерва определялись без исключения. При применении ДГК "Р" установлена положительная динамика восстановления капиллярной проницаемости (в 71,43%±12,07 при ретинопатиях 1-2 ст. по сравнению с 38,46% без) и менее выраженная при периваскулярных микрогеморрагиях. Такие положительные эффекты в проведенном исследовании имели характер тенденции (OR 2,87; p=0,08 для периваскулярного отека и OR 2,77; p=0,08 для микрогеморрагий). Выявлена эффективность «ДГК «Р» в ДГК восстановлении нарушенных функций зрительного нерва по данным зрительных вызванных потенциалов (для N0 компонента ЗВП; OR 2,87; p=0,041) при применении дозы 7 капель 2 раза в сутки 10 дней подряд, что определяет перспективу дальнейшего исследования препарата «ДГК «Р», содержащего дигидрокверцетин, при ЦВЗ.

Cerebrovascular diseases (CVD), which also include acute cerebrovascular disorders (ACVD), rank first in mortality and disability factors, being significant medical, economic, social problems [5, 6, 8, 9, 13]. Transient ischemic attacks (TIAs) (including TIAs with visual disorders which are revealed in 20-25% of all TIAs [6, 9]), partly due to cardiovascular disease, in CVD not accidental ischemic events but a natural stage of degenerative-dystrophic disorders of vessels of different types: muscular, microvasculature (MV). Such processes lead to the so-called "small vessels disease" ("small vascular disease"), "hypoxic-ischemic encephalopathy" (hypoxic-ischemic encephalopathy according to the ICD-11 classification) [5, 6, 8, 13]. One of the factors of such vascular and related cerebral disorders is oxidative stress, dysfunction of cell membranes, the ratio of blood lipoproteins, protein metabolism and neurotransmitters [7, 11, 12]. Pharmacological protection, prevention of development and treatment of such conditions is an urgent task of modern angioneurology, pharmacology. One of the promising drugs of plant origin from the group of bioflavonoids which are likely to be effective in the described conditions is dihydroquercetin [7, 11, 12], the evaluation of the clinical effectiveness of which was the purpose of the study.

The aim of the study was to determine the effectiveness of dihydroquercetin (DHQ "P" in drops) in patients with CVD who previously suffered from

TIA with visual disorder in restoring the functions of the microcirculatory tract and optic nerve.

MATERIALS AND METHODS OF RESEARCH

A survey of 48 patients aged 33 to 79 years (mean age – 62.6 years, 22 women and 26 men) with transient visual disorders not caused by other proven factors than cerebral circulatory disorders was carried out. 24 patients were treated according to GCP criteria and standards of care for ACVD, TIA [6, 8, 9, 13], 24 patients additionally received DHQ "P" in a dosage of 7 drops 2 times a day for 10 consecutive days. The research was considered at a meeting of the commission on bioethics of the State Establishment "Dnipropetrovsk Medical Academy of Health Ministry of Ukraine" and recognized as meeting the generally accepted moral standards, requirements for the rights, interests and personal dignity of study participants. There was no risk for the subjects of the study during carrying out of the work (protocol number N 6 dated October 4, 2019). All patients in the study group had hypertension (AH) of 1-2 stage. The control group consisted of 26 men and 20 women of comparable age (n=46; mean age – 65.9 years) without cerebral ischemic events and visual disorders, neurophysiological parameters (data of visual evoked potentials – VEP) and the state of the microvasculature (MV) were compared with the data of this group. Exclusion criteria: acute heart disease, arrhythmias, type 1-2 diabetes, glaucoma, secondary types of hypertension and stage 3

hypertension, hemorrhage and hereditary cerebrovascular syndromes [5]. This work is part of the dissertation research, it presents the results of clinical, neurophysiological studies of VEP [1, 2, 3, 7, 12], (XAI-Medica, 21-channel EEG and EP). The condition of the fundus was examined by direct ophthalmoscopy, the perimeter – on automated spherometer Zeiss Humphrey 720. Classification of the degree of retinopathy (RP) was performed by Keith-Wagener [8, 13]. The initial processing of the obtained data was performed by descriptive statistics using Microsoft Office Excel-2003® software packages (N 74017-641-9475201-57075) (Microsoft Corporation, USA) and Statistica v6.1 (StatSoft Inc., USA) (ser. N AJAR909E415822FA) with the

presentation of results for quantitative features in the form of: the number of observations (n), the arithmetic mean (M), the standard error of the mean (m), for qualitative features in the form of relative indicators – intensive and extensive, expressed in%±m (standard error), visibility indicators. Estimation of the probability of differences between binary and average for all samples – according to the sample of Student's criteria (t) and odds ratio (OR) indicating the limits of CI (confidence interval) and values of p (significance level) [10].

RESULTS AND DISCUSSION

Descriptive statistics of the group, distribution by age, stage of retinopathy are shown in Table 1.

Table 1

Distribution of patients in the study group by age, sex, stage of retinopathy, n=48

Age of patients	People, n=26	Of them with RP 1-2 stage	Of them with RP 3 stage	Women, n=22	Of them with RP 1-2 stage	Of them with RP 3 stage	Total n=48
25-44	5	4	1	4	3	1	9
%	55.56	80.0	20.0	44.4	75.0	25.0	18.75
±m	16.56	17.89	17.89	16.56	21.65	21.65	5.63
45-59	10	5	5	8	4	4	18
%	55.56	50.0	50.0	44.4	50.0	50.0	37.5
±m	11.71	15.81	15.81	11.71	17.68	17.68	6.99
60-74	11	6	5	10	5	5	21
%	52.38	54.55	45.45	47.62	50.0	50.0	43.75
±m	10.9	15.01	15.01	10.9	15.81	15.81	7.16
Total (n=48)	26	15	11	22	12	10	48
%	54.17	57.69	47.31	45.83	54.55	45.5	
±m	7.19	9.69	9.69	7.19	10.62	10.62	

Note. RP – retinopathy. Distribution by age according to WHO classification.

At the age of 25-44 years there were 9 patients, all with hypertension, 2 – with retinopathy of the 3 stage, which in modern medical practice is not a frequent condition due to preventive methods of hypertension control. At the age of 45-59 years there were 18 patients, 9 of them (50%) with RP of the 3 stage. At the age of 60-75 years there were 21 patients, 10 (47.62%) of them with RP of the 3

stage. AH was diagnosed in 18 (69.23%) men and 17 (77.27%) women, in general in 72.98% in the group. In the study group there was a uniform distribution of RP by sex, so further analysis of the data obtained concerned men and women together. Evaluation of the effect of DHQ on such indicators of RP as perivascular edema (PVE), perivascular microhemorrhage (PVMH), arteriovenular coefficient

(AVC) was performed based on the results of computer photometry of morphological features of MV vessels (ophthalmoscopy of the fundus and biomicroscopy of the vascular layers of the bulbar conjunctiva) when taking DHQ and without this bioflavonoid complex. According to the distribution of the number of TIA cases, stage of RP and age

(Table 1) it is possible to assume (concerning data in the study group) that the relationship between TIA is associated with RP stage or other factors, but not with age (distribution from 20% to 50% without significant differences in age), so further analysis of the obtained data was performed taking into account the stages of RP.

Table 2

Distribution of patients depending on the stage of retinopathy and dynamics of PVE, PVMH, AVC indicators in DHQ and without DHQ, n=48

		PVE	PVMH	AVC	OR, p
1-2 st. RP n=27	DHQ, n=14	10	10	3	PVE = 4.0; p = 0.09 PVMH = 2.14; p = 0.34 AVC = 0.90; p = 0.91
	Without DHQ, n=13	5	7	3	
3 st. RP n=21	DHQ, n=10	3	5	1	PVE = 1.92; p = 0.52 PVMH = 4.5; p = 0.13 AVC = 3.63; p = 0.44
	Without DHQ, n=11	2	2	0	
1-3 st. RP n=48	DHQ, n=24	13	15	4	PVE = 2.87; p = 0.08 PVMH = 2.77; p = 0.08 AVC = 1.4; p = 0.68
	Without DHQ, n=24	7	9	3	

Notes. PVE – perivascular edema, PVMH – perivascular microhemorrhages, AVC – arteriolo-venular coefficient. The dynamics is evaluated as binary (yes/no) with the outlined changes in photometry. OR - odds ratio, p – significance level.

Patients with RP 1-2 stages who received DHQ "P" in 71.4% had a satisfactory result of the dynamics of PVE and PVMH by the principles of assessment of symptoms in the classification of Keith-Wegener [8], the proportion of subjectivity of such an assessment as a common fact also was taken into account. Patients with RP 1-2 stages who did not receive the drug had similar dynamics of symptoms (PVE) in 38,46% and 53,85% for PVMH with odds ratio (OR) 4.0 for PVE and 2,14 for PVMH in both cases $p > 0.05$. Taking into account the significant difference in the absolute indicators of positive dynamics in the application of DHQ "P" directs the line of further research in a more representative sample of patients. An objective assessment of the symptoms of RP was performed according to the AVC, which was changed in most patients and is calculated as a ratio of sizes but at all stages of RP neither significant dynamics nor tendency in its changes was revealed. In patients with RP 3 stage positive dynamics of PVE and PVMH was detected only in 18 to 30% of cases, regardless of DHQ taking with odds ratio (OR) below the confidence level (PVE – 2.87; $p = 0.08$;

PVMH=2.77; $p = 0.08$; AVC=1.4; $p = 0.68$). The distribution of patients depending on the degree of retinopathy and dynamics of VEP on day 10 of DHQ taking is shown in Table 3. The feasibility of such analysis is based on known data on the relationship between VEP and oxidative stress in different models of hypertension [12].

The study of VEP was performed on a flash of red light, taking into account the LP of the initial components of the response (N0, in the control group in 95% was up to 20 ms) and the final N 3 (in the control group in 95% was up to 280 ms). Components N0 are responsible for the response of the optic nerve, N3 is the final component mainly of the cortico-limbicoreticular complex, which is responsible for the activity of these structures of the visual analyzer [1, 2, 3]. According to the data obtained, it is impossible to identify preferences in the restoration of response for N0 or N3 separately in each stage of RP, but in the end there were significant differences in the number of patients with better recovery results when taking DHQ for N0 compared to N3 component (N0=2.87; 0.87-9.44; $p = 0.041$; N3=1.73; $p = 0.18$).

Table 3

**Distribution of patients depending on the degree of retinopathy
and the dynamics of VEP on day 10 of DHQ taking, n=48**

		N0	N3	OR; (95% CI), p
1-2 st. RP n=27	DHQ, n=14	10	8	N0=2.91; 0.59-14.32; p=0.093 N3=2.13; 0.45-9.94; p=0.16
	Without DHQ, n=13	6	5	
3 st. RP n=21	DHQ, n=10	3	2	N0= 4.28; 0.36-50.19; p=0.12 N3=1.12; 0.18+; p=0.45
	Without DHQ, n=11	1	2	
1-3 st. RP n=48	DHQ, n=24	13	10	N0= 2.87; 0.87-9.44; p=0.041* N3=1.73; 0.65+ p=0.18
	Without DHQ, n=24	7	7	

Notes: OR – odds ratio; p – significance level. N0 - negative zero component, LP – latency period, A – value of N0 or N3 in μV ; all values – on day 10 of treatment. VEP indicators are taken into account as binary variables on the basis of: returned to the reference values of the control group – yes/no. Classification of retinopathy by Keith-Wagener, no stage 4 in the study.

RESULTS AND DISCUSSION

According to the data obtained, the study group was homogeneous in etiology (CVD) of TIA origin, which affects the reliability of the assessment of DHQ effect. In the group of patients with TIA and transient visual disorders, 72.98% had hypertension (18 (69.23%) men and 17 (77.27%) women), which was considered as a factor influencing the development of RP detected without exception, as well as optic nerve dysfunction, assessed by the results of VEP. When using DHQ "P" and assessing symptoms of capillary permeability and perivascular microhemorrhages, positive results were achieved in 71.43%±12.07 in retinopathies of 1-2 stage compared with 38.46% without DHQ taking. A significant variation in the number of patients taking DHQ and without the drug raises considerable interest in continuing the study in larger samples of patients with CVD. Unfortunately, such positive effects in the study were only a trend (OR 2.87; p=0.08 for perivascular edema and OR 2.77; p=0.08 for the parameter of microhemorrhage), which does not deny the possibility of proof detection of the capillary-stabilizing effect of DHQ in larger study groups. Microcirculation disorders in patients with this type of TIA revealed a disturbed LP response of the optic nerve and cortical, limbico-reticular-related structures of the brain. In the process of restoring these functional parameters, the effectiveness of DHQ "P" was statistically significant when using a

dose of 7 drops 3 times a day for 10 consecutive days (for N0 component of VEP; OR was 2.87; CI=0.87-9.44; p=0.041).

CONCLUSIONS

1. Patients with TIA with visual disorders in CVD in 72.98% had hypertension, retinopathy 1-3 stage and optic nerve dysfunction were found without exception.

2. In DHQ "P" taking a positive dynamics of restoration of capillary permeability (in 71.43%±12.07 in retinopathies of 1-2 stage in comparison with 38.46% without DHQ) is established, being less expressed in perivascular microhemorrhages. Such positive effects in the study were of a tendency nature (OR 2.87; p=0.08 for perivascular edema and OR 2.77; p=0.08 for microhemorrhages), which determines the prospect of additional, larger samples of the effects of DHQ on microcirculation state.

3. The effectiveness of DHQ "P" in the restoration of impaired functions of the optic nerve according to the data of visual evoked potentials (for N0 component of VEP; OR 2.87; CI=0.87-9.44; p=0.041) at a dose of 7 drops 2 times a day for 10 consecutive days was proved.

Conflict of interest. The authors declare no conflict of interest.

REFERENCES

- Pohorielov OV. [Diagnostic significance of visual stimulated potentials in cerebral ischemic disorders due to cerebral atherosclerosis]. *Medical perspectives*. 2010;15(2):1-4. Ukrainian.
- Pohorielov OV. [Dynamics and stability in time of the visual brain activity at patients with cerebral atherosclerosis]. *Ukrainian Herald of Psychoneurology*. 2009;17(4):18-22. Ukrainian
- Cerri E. Visual Evoked Potentials in Glaucoma and Alzheimer's Disease. *Methods Mol. Biol.* 2018;1695:69-80.
doi: https://doi.org/10.1007/978-1-4939-7407-8_7
- Saraf-Bank S, Ahmadi A, Paknahad Z, Maracy M, Nourian M. Effects of curcumin on cardiovascular risk factors in obese and overweight adolescent girls: a randomized clinical trial. *Sao Paulo Med J.* 2019;4. doi: <https://doi.org/10.1590/1516-3180.2018.0454120419>
- ICD-11 for Mortality and Morbidity Statistics. [Internet]. Available from: <https://icd.who.int/browse11/l-m/en>.
- Kobayashi A. European Academy of Neurology - European Stroke Organisation consensus statement and practical guidance for pre-hospital management of stroke. *Eur. J. Neurol.* 2018;25(3):425-33.
doi: <https://doi.org/10.1111/ene.13539>
- Nakagawa T, Ohta K. Quercetin Regulates the Integrated Stress Response to Improve Memory. *Int. J. Mol. Sci.* 2019;20(11).
doi: <https://doi.org/10.3390/ijms20112761>
- Takayama K, Kaneko H, Ito Y, Kataoka K, Iwase T, Yasuma T, et al. Novel Classification of Early-stage Systemic Hypertensive Changes in Human Retina Based on OCTA Measurement of Choriocapillaris. *Sci Rep.* 2018;8(1):15163.
doi: <https://doi.org/10.1038/s41598-018-33580-y>
- Lavallée PC, Cabrejo L, Labreuche J, Mazighi M, Meseguer E, Guidoux C, Abboud H, Lapergue B, Klein IF, Olivot Jean-Marc, Sirimarco G, Gonzales-Valcarcel J, Touboul Pierre-Jean, Amarenco P. Spectrum of Transient Visual Symptoms in a Transient Ischemic Attack Cohort. *Stroke.* 2013;44:3312-7.
doi: <https://doi.org/10.1161/STROKEAHA.113.002420>
- Stirling WD. Textbooks for Learning Statistics: Public CAST e-books. 2013. [Internet]. Available from: http://cast.massey.ac.nz/collection_public.html
- Ditano-Vázquez P, Torres-Peña JD, Galeano-Valle F, Pérez-Caballero AI, Demelo-Rodríguez P, Lopez-Miranda J, Katsiki N, Delgado-Lista J, Alvarez-Sala-Walther LA. The Fluid Aspect of the Mediterranean Diet in the Prevention and Management of Cardiovascular Disease and Diabetes: The Role of Polyphenol Content in Moderate Consumption of Wine and Olive Oil. *Nutrients.* 2019;11:11. doi: <https://doi.org/10.3390/nu11112833>
- Göçmen AY, Celikbilek A, Hacıoğlu G, Tanık N, Açar A, Yargıçoğlu P, Gümüşlü S. The relationship between oxidative stress markers and visual evoked potentials in different hypertension models. *Anadolu Kardiyol. Derg.* 2014;14(6):498-504.
doi: <https://doi.org/10.5152/akd.2014.4923>
- Whelton PK. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/Apha/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension.* 2018;71:1269-324.
doi: <https://doi.org/10.1161/HYP.000000000000066>

СПИСОК ЛІТЕРАТУРИ

- Погорелов О. В. Діагностична значущість зорових викликаних потенціалів при церебральних ішемічних порушеннях внаслідок церебрального атеросклерозу. *Медичні перспективи*. 2010. Т. 15, № 2. С. 54-57.
- Погорелов О. В. Динаміка та стабільність в часі зорової викликанної активності головного мозку при церебральному атеросклерозі. 2009. *Укр. вісник психоневрології*. Т. 17, № 4. С. 18-22.
- Cerri E. Visual Evoked Potentials in Glaucoma and Alzheimer's Disease. *Methods Mol. Biol.* 2018. Vol. 1695. P. 69-80.
DOI: https://doi.org/10.1007/978-1-4939-7407-8_7
- Effects of curcumin on cardiovascular risk factors in obese and overweight adolescent girls: a randomized clinical trial / S. Saraf-Bank et al. *Sao Paulo Med J.* 2019. 4 Nov.
DOI: <https://doi.org/10.1590/1516-3180.2018.0454120419>
- ICD-11 for Mortality and Morbidity Statistics. Web: <https://icd.who.int/browse11/l-m/en>.
- Kobayashi A. European Academy of Neurology - European Stroke Organisation consensus statement and practical guidance for pre-hospital management of stroke. *Eur. J. Neurol.* 2018. Vol. 25, No. 3. P. 425-433.
DOI: <https://doi.org/10.1111/ene.13539>
- Nakagawa T., Ohta K. Quercetin Regulates the Integrated Stress Response to Improve Memory. *Int. J. Mol. Sci.* 2019. Vol. 20, No. 11.
DOI: <https://doi.org/10.3390/ijms20112761>
- Novel Classification of Early-stage Systemic Hypertensive Changes in Human Retina Based on OCTA Measurement of Choriocapillaris / K. Takayama et al. *Sci Rep.* 2018. Vol. 8, No. 1. P. 15163.
DOI: <https://doi.org/10.1038/s41598-018-33580-y>
- Spectrum of Transient Visual Symptoms in a Transient Ischemic Attack Cohort / P. C. Lavallée et al. *Stroke.* 2013. Vol. 44. P. 3312-3317.
DOI: <https://doi.org/10.1161/STROKEAHA.113.002420>

10. Stirling W. D. Textbooks for Learning Statistics: Public CAST e-books. 2013.

URL: http://cast.massey.ac.nz/collection_public.html.

11. The Fluid Aspect of the Mediterranean Diet in the Prevention and Management of Cardiovascular Disease and Diabetes: The Role of Polyphenol Content in Moderate Consumption of Wine and Olive Oil / P. Ditano-Vázquez et al. *Nutrients*. 2019. Vol. 11, No. 11. DOI: <https://doi.org/10.3390/nu11112833>

12. The relationship between oxidative stress markers and visual evoked potentials in different hypertension

models / A. Y. Göçmen et al. *Anadolu Kardiyol. Derg.* 2014. Vol. 14, No. 6. P. 498-504.

DOI: <https://doi.org/10.5152/akd.2014.4923>

13. Whelton P. K. 2017 ACC/AHA/AAPA/ABC/ACPM/ AGS/ APhA/ ASH/ ASPC/ NMA/ PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension*. 2018. Vol. 71. P. 1269-1324. DOI: <https://doi.org/10.1161/HYP.0000000000000066>

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