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Assessment of T2 Hyperintens Focies in Case of Occurrence of Arterial Hypertension and Type 2 Diabetes Mellitus Together and Separately

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Abstract Arterial Hypertension (AH) and type 2 Diabetes Mellitus(DM) have already become an epidemic in the last decades. Both of them are risk factors for formation of T2 hyperintense foci. MRI is the most convenient non-invasive method for detecting T2 hyperintense foci. Total of 275 patients between 35 and 70 years were included in this study. 77 of the patients were with only AH, 51 with only type 2 DM, 61 with AH + type 2 DM and 86 of them were healthy individuals. The purpose of the study is to note, compare (with each other and with control group) and check the statistical validity of the size and numbers of white matter hyperintensities (T2 hyperintense foci) detected in the brain in the presence of only AH or only type 2 DM and both pathologies together. The principles of randomization between age, gender (male, female) were followed. In patients with both AH and type 2 DM, the number of T2 hyperintense foci in the brain increases dramatically. When both diseases are present concurrently, the maximum and average size, number of foci are greater than those with AH or type 2 DM alone and control group. The cut-off for the average size of foci in patients with both AH and type 2 DM was 2.9 mm (sensitivity 73.2%±5.9%, specificity 92.2±3.8%), with only AH it was 1.9 mm (sensitivity 83.8%±4 .5%, specificity 52.9±7.0%), with only type 2 DM it was 2.9 mm for average size (sensitivity 45.7%±7 .3%, specificity 92.2±3.8%). The cut-off point for the number of foci in patients with both AH and type 2 DM is 23 (sensitivity 96.4±2.5%, specificity 98.0±1.9%), with only AH it was 14 (sensitivity 77.9±5.0%, specificity 94.1±3.3%), with only type 2 DM it was 14 (sensitivity 71.7±6.6%, specificity 94.1±3.3%).

Keywords: *MRI, brain, T2 hyperintens foci, arterial hypertension, type 2 diabetes mellitus, diagnostic value, healthy*

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1. Introduction

Cerebral small vessel disease (SVD) is one of the major known causes of stroke and dementia. The clinical presentation of SVD may be asymptomatic and can vary in severity. Usually MRI examination of the brain reveals T2 hyperintense foci, lacuna, microhemorrhages and atrophy [1,2].

T2 hyperintense foci, i.e., white matter lesions (especially when it tends to merge) reduces cognitive abilities such as memory, executive function, and response speed [3]. MRI is the most convenient non-invasive method for detecting T2 hyperintense foci, and it is also possible to repeat this examination periodically to monitor how T2 hyperintense foci change with time. In addition to the number of T2 hyperintense foci, the relationship was also revealed between the rate of progression and development of dementia [4,5]. Age-related white matter changes in the brain increase the risk of both ischemic and hemorrhagic stroke, as well as vascular death [6].

According to studies by Wartolowska and co-authors, a strong relationship was found between the increase in systolic blood pressure and the increase in T2 hyperintense foci (in those above 50 years of age) [7,8]. During hypertension, the microstructural white matter lesions are formed and do not disappear despite adequate treatment [9]. It has been found that the changes caused by arterial hypertension (AH) do not disappear even when hypertension is under control, and hence the disease prevention is more vital and efficient than treatment of consequences [10].

The number of patients with type 2 diabetes mellitus (DM) continues to rise, and this is the health issue that concerns the whole world. The risk of microvascular

complications is also closely related to type 2 DM. There is a strong evidence that type 2 DM causes cerebral structural abnormalities such as T2 hyperintense foci, lacunar stroke, and the brain atrophy. Although hypertension is a risk factor for T2 hyperintense foci, the studies show that diabetes produces more and larger T2 hyperintense foci [11,12].

AH and type 2 DM have already become an epidemic in the last decades [13]. Prevention of T2 hyperintense foci during active treatment of type 2 DM has important clinical significance [11].

The number of patients with type 2 diabetes is expected to reach 552 million by 2030 which is interlinked with the increased incidence rate in each country [14]. This is a serious reason to enhance the fight against complications of these diseases. When the type 2 DM and HTN present together they act synergistically to increase the risk of micro- and macrovascular complications [15,16].

2. Materials and Methods

Total of 275 patients between 35 and 70 years were included in this study. People over the age of 70 were not included in the study because they had age-related WMH. Patients with oncological diseases, trauma, history of surgery, demyelinating disease, migraine were not included in the study, as the white matter hyperintensities developed secondary to these reasons too. Ethics committee approval was received for this study from the Azerbaijan Medical University Ethics Committee (protocol number 22). Informed consent form was received from all participants after a detailed explanation of the examination.

The purpose of the study is to note, compare and check the statistical validity of the size and numbers of white matter hyperintensities (T2 hyperintense foci) detected in the brain in the presence of only AH or only type 2 DM and both pathologies together. At the same time, the parameters of patients with AH + type 2 DM were compared with the corresponding parameters of healthy individuals. The smallest (minimum) and largest (maximum) lengths of the detected foci were measured (at the same time, the average size was calculated). Thus, a comparison was done between the sexes.

Among 77 patients with only AH, 33 (42.9%) were males, 44 (57.1%) were females; among 51 patients with only type 2 DM, 24 (47.1%) were males, 27 (52.9%) were females; among 61 patients with AH + type 2 DM, 25 (42.6%) were males and 35 (57.4%) were females. In the control group, 47 (54.7%) of 86 patients were males and 39 (45.3%) were females.

The age range of patients with arterial hypertension (AH) was 35-70, with type 2 DM were 39-68, with both AH and type 2 DM were 39-70, and healthy individuals in the control group were between 35-69 years old. The duration of the disease in patients with AH was between 10-15 years. The duration of the disease in patients with type 2 DM was between 5-10 years. Patients diagnosed with type 2 diabetes with blood glucose levels above 7 mmol/l were included in the study.

We used 1.5-Tesla Magnetom Aera MRI equipment and images obtained with T2 turbo inversion recovery magnitude (TIRM) sequences (TR-9200, TI-2450, TE-84 and 3.5 mm slice thickness, and 10% interslice gap). In the T2 turbo inversion recovery magnitude (TIRM) mode WMH (T2 hyperintens foci) visualization and differentiation are clearer, because both the signal from the cerebrospinal fluid is reset, and the cortical hyperintensity is relatively reduced. WMH and T2 hyperintense foci terms are used interchangeably throughout the article. Due to the thinness of slices, small gap between slices and high image quality, it was easier to differentiate white matter hyperintensities. Statistical analysis was performed using SPSS-26 package program. Descriptive data were expressed as mean ± Standard Error of Mean, minimum, maximum, median, quartile 1 and quartile 3. The distribution of variables was checked with the t-Student-Bonferroni and U Mann-Whitney test. Frequencies between the groups of patients were compared on the basis of the OR (odds ratio) test. The influence of the factor was evaluated by the Fisher-Snedecor criterion. The relationship between the parameters was studied by Rho-Spearman correlation analysis. The null hypothesis was rejected at $p < 0.05$ [17,18].

The integral value (ROC-curve) for the sensitivity and specificity parameters was constructed in the entire variation range of the studied parameters in the In the ROC-analysis binary classification model. At this time, the area of the ROC-curve (S) was calculated and the result was evaluated statistically. The discovery of the cut of point, which is the farthest point of the ROC-curve from the reference line, made it possible to use the test as a selection criteria in subsequent studies.

3. Results

The average age of patients with arterial hypertension (AH) was 56.5±0.9, those with type 2 DM were 55.5±1.2, and with both hypertension and type 2 diabetes were 58.0±1.0. Average age of healthy individuals in the control group was 56.4± 1.0 years ($p_u>0.05$). At the same time, the principles of randomization between gender (male, female) were followed ($p_u>0.05$).

T2-hyperintense foci was detected in 56 (91.8%) patients in the AH + type 2 DM group, 68 (88.3%) in the group with AH only, and 46 (90.2%) patients in the group with DM only ($p>0.05$). Compared to the control group (51-59.3%), in patients with both AH and type 2 DM, there is a higher incidence of cerebral foci detection during MRI examination ($p_{\chi 2}<0.001$, $p_u<0.001$).

The number of detected WMH during brain MRI examination in patients with both AH and T2DM were 56, ranging from minimum 15 to maximum 150 (80±5.2). The number of foci in the patients of control group was minimum 1, and maximum 40 (6.1 ± 0.9). In patients with both AH and type 2 DM, the number of T2 hyperintense foci in the brain increases dramatically ($p_t<0.001$, $p_u <0.001$) (Figure 1, Figure 2). Each disease also separately leads to increase in the number of foci compared to healthy individuals ($p_u<0.001$).

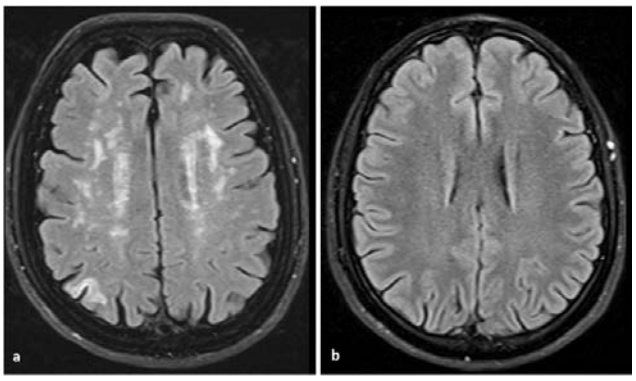


Figure 1. Brain MRI, axial T2 TIRM image. **a.)** In a patient with AH +Type 2 DM, T2 hyperintense foci are observed on both sides of the frontal and parietal lobes. **b.)** T2 hyperintense foci is not observed in a healthy patient

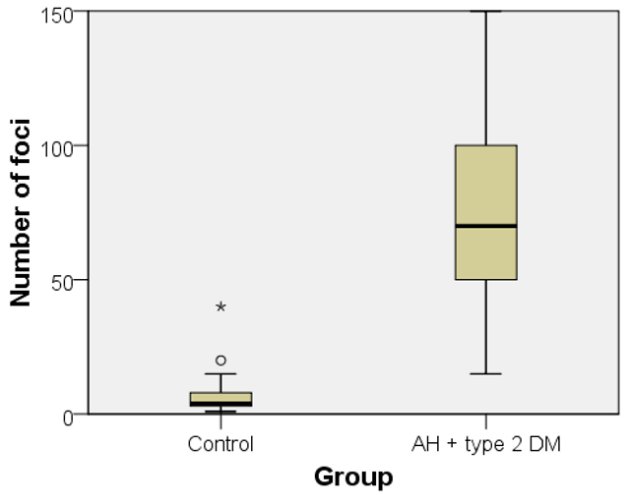


Figure 2. Comparison of the number of foci in patients with AH + type 2 DM with the control group

Number of detected T2 hyperintense foci in 68 patients only AH group ranged from minimum of 1 to the maximum of 150 (45.1 ± 4.6) during MRI examination. In 46 type 2 DM patients with T2 hyperintense foci, the minimum number of foci was 2 and the maximum was 150 (35.6 ± 4.4) during MRI examination. In patients with both AH and type 2 DM (80±5.2), there is higher number of T2 hyperintense foci in the brain than in patients with only either AH or DM (p_u <0.001).

In the AH + type 2 DM group, the average size of foci was 4.01 ± 0.19 mm (1.5-7.5 mm). In the group with both AH and type 2 DM, the minimum size of foci was 1.14±0.05 mm (1-2 mm). And the maximum size of the detected foci was 6.88 ± 0.37 mm (2-14 mm).

In the control group, the average size of foci was 1.90 ± 0.09 mm (1-4 mm), the minimum size was 1.16 ± 0.06 mm (1-2.5 mm), the maximum size was 2.65 ± 0,16 mm (1-6 mm).

In the group with both AH and type 2 DM patients, the average and maximum size of foci length was greater than in the control group (Figure 3). This means that AH + type 2 DM leads to development of foci with larger average and maximum size compared to the healthy individuals (p_u <0.001).

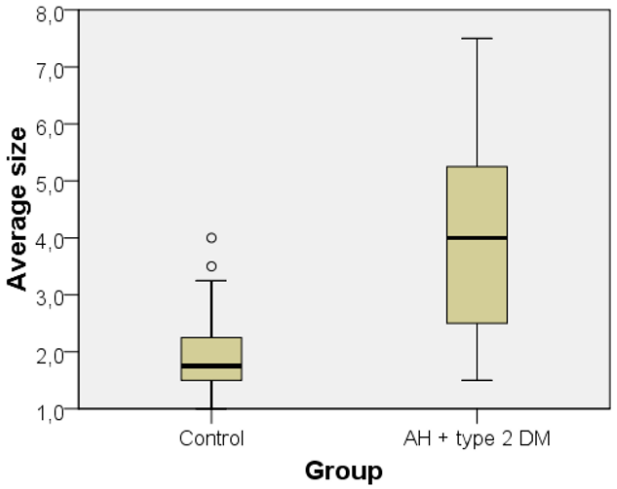


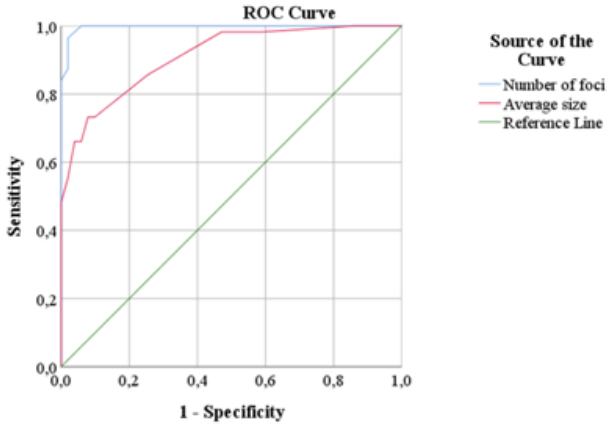
Figure 3. Comparison of the average size of foci in patients with AH + type 2 DM and the control group

Table 1. The number and size of T2 hyperintense foci in our patients

	Group						
Factor's	Statistical paramcters	Control	AH	Type 2 DM	AH+ Type 2 DM	Pt	Pu
Number of foci	Valid N	51	68	46	56	<0.001	<0.001
	Mcan	6.1	45.1	35.6	80.0		
	St.error	0.9	4.6	4.4	5.2		
	Minimum	1	1	2	15		
	Maximum	40	150	150	150		
	Median	4.0	35.0	30.0	70.0		
	Quartile 1	3.0	15.0	10.0	50.0		
	Quartile 3	8.0	68.5	50.0	100.0		
Average size	Valid N	51	68	46	56	<0.001	<0.001
	Mean	1.90	2.97	2.83	4.01		
	St.error	0.09	0.16	0.16	0.19		
	Minimum	1.0	1.5	1.5	1.5		
	Maximum	4.0	5.5	5.5	7.5		
	Median	1.75	2.50	2.50	4.00		
	Quartile 1	1.50	2.00	2.00	2.50		
	Quartile 3	2.50	3.75	3.50	5.25		

Note: Statistical integrity of the difference between the parameters of the groups: P_t – with the Student-Bonferoni criterion, P_u – with the Mann-Whitney criterion.

In patients with only type 2 DM, the average size of foci was 2.83 ± 0.16 mm (1.5-5.5 mm), the minimum size was 1.09 ± 0.04 mm (1-2 mm), the maximum size was 4.57±0.31 mm (2-10 mm). In the AH(only) group, the average size of foci was 2.97± 0.16 mm (1.5-5.5 mm), the minimum size was 1.21± 0.08 mm (1.0-4.0 mm), the maximum size was 4.74± 0.30 mm (2-10 mm). When both diseases are present concurrently, the maximum and average size of foci are greater than those with AH or type 2 DM alone (p_u <0.001). In patients with only type 2 DM average size of foci was 35,6 ± 4,4 (2-150), with only AH this parameters was 45,1± 4,6 (1-150), with both of them it was 80± 5,2 (15-150). In control group this parameter was 6,1 ± 0,9 (1-40). When both diseases are present concurrently, the number of foci are more than those with AH or type 2 DM alone and control group (p_u <0.001). (Table 1)



Area Under the Curve

Test Result Variable(s)	Area	Std. Error	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
Number of foci	0,996	0,003	0,000	0,990	1,000
Average size	0,911	0,026	0,000	0,859	0,963

Figure 4. The results of ROC analysis for the number of foci and the average size in the AH + type 2 DM group

The area of the ROC curve, which is an integral parameter of sensitivity and specificity in the diagnosis of type AH + type 2 DM, is 0.996±0.003. For the average size of the foci this indicator is 0.911±0.026 (p<0.001). (Figure 4).

The cut-off point for the number of foci in patients with both AH and type 2 DM is 23 (sensitivity 96.4±2.5%, specificity 98.0±1.9%).

The positive predictive value (pPV) of having the number of foci more than 23 was 98.2±1.8%. In order to identify its practical importance (value), the accuracy ratio of the positive results was calculated. As a result, the clinical application of this value with the help of a special scale was considered as excellent. The negative predictive value (nPV) of having the number of foci exceeding 23 was 96.2±2.7, and the practical value of this result was also concluded to be excellent.

In patients with AH + type 2 DM, the odds ratio (OR) for the number of foci parameter was 1350.0 (118.7-15351.1). And it shows that this parameter (number of foci) has high statistical validity when occurs in patients with both AH and type 2 DM (p<0.05).

Having the number of foci greater than 23 had a strong impact of 818.8 (791.9-845.8) on the diagnosis of AH + type 2 DM, which was statistically significant according to the Fisher-Snedecor criterion (p<0.001).

The cut-off for the average size of foci in patients with both AH and type 2 DM was 2.9 mm (sensitivity 73.2%±5.9%, specificity 92.2±3.8%). The positive predictive value (pPV) for average size of foci greater than 2.9 mm is 91.1±4.2. In order to find out the practical significance of this, the accuracy ratio of the positive results was calculated, and as a result, with the help of a special scale, this value was found to be practically `good`. The negative predictive value (nPV) of the average size of foci greater than 2.9 mm was 75.8±5.4, and the practical value of this result was considered `sufficient`.

In patients with AH + type 2 DM, the odds ratio (OR) for the average size of the foci was 32.1 (9.9-104.5), which corresponds to the greater statistical significance in incidence of this parameter in patients with both AH and type 2 DM (p<0.05).

The influence of the average size of foci greater than 2.9 mm in the diagnosis of AH + type 2 DM was 77.8 (76.9-78.6) and considered statistically reliable according to the Fisher-Snedecor criterion (p<0.001).

In addition, the cut-off point for the number of foci in AH(only) patients was 14 (sensitivity 77.9±5.0%, specificity 94.1±3.3%), and for the average size it was 1.9 mm (sensitivity 83.8%±4.5%, specificity 52.9±7.0%). The cut-off point was 14 (sensitivity 71.7±6.6%, specificity 94.1±3.3%) for foci number in patients with type 2 DM, and 2.9 mm for average size (sensitivity 45.7%±7 .3%, specificity 92.2±3.8%).

In patients with AH + type 2 DM, a statistically significant positive correlation was found between the number of foci and the maximum and average size of foci (Rho = +0.359; p = 0.007). That is, in patients with AH + type 2 DM, the size of foci increases with the rise in the number of foci, and this is accompanied with more damage to the brain parenchyma. The maximum and average size of foci in females and males in AH + type 2 DM group were not statistically significant between sexes (p_u >0.05).

If patients with AH +type 2 DM are compared based on sex, the number of foci found in males (99.0±7.7) was higher than in females (64.6±5.7) (p_u =0.001). Males (97%) with AH had more T2 hyperintense foci in their brains than females (81.8%) (p_u =0.042).

4. Discussion

Type 2 DM and HTH have a synergistic effect on increase in the risk of micro- and macrovascular complications when present together [15]. The results obtained during our research also confirm this. In the study conducted by Havenon and co-authors, an increase in T2 hyperintense foci was found in type 2 DM patients with high systolic arterial pressure who underwent brain MRI with interval of 40 months. However, unlike other authors, they did not observe a difference in the increase of T2 hyperintense foci during glycemic or blood pressure control. Like the previous studies, they reported that the

presence of T2 hyperintense foci on baseline images is related to hypertension and age [15]. During our study, it was determined that T2 hyperintense foci detected in AH +DM patients did not show statistically significant differences between age groups (p>0.05).

According to global estimates, more than 50% of people with diabetes have a diagnosis of arterial hypertension. Epidemiological data show that the risk of dementia in diabetic patients without hypertension is 19%, and in those with both diabetes and hypertension, it is 23% [19]. For this reason, the changes in the brain has been studied.

A study of patients between the ages of 40 and 69 found that patients with both AH and type 2 DM had worse brain and cognitive health than patients with either of these diseases alone [19,20]. On neuroimaging, patients with only hypertension have greater brain volume preservation and smaller T2 hyperintense foci than patients with AH and type 2 DM present together. Also, patients with diabetes alone had fewer T2 hyperintense foci [19]. During our study, there was a statistically significant difference between the number and size (average, maximum) of T2 hyperintense foci in patients with AH alone compared with control group (p<0.05). When divided by sex, the statistically significant larger and more foci were detected in both males and females with AH + DM in comparison to their counterparts with AH or type 2 DM alone (p<0.05). However, it was proven once again that more lesions are found in the brain when both diseases present. From a clinical perspective, simultaneous treatment of both disorders will lead to better outcomes for brain and cognitive health [19].

The cut-off point for the number of foci in patients with both AH and type 2 DM is 23. However, for AH only and type 2 DM only, this value is 14, which indicates that there is more lesions in the brain when both diseases are present at the same time. Using the cut-off values obtained for all three groups (considering specificity and sensitivity), we can note that radiologically we suspect AH, type 2 DM, AH + type 2 DM in patients who come to our clinic with complaints like headache(thoose who do not know their disease).

The cut-off for the average size of foci in patients with both AH and type 2 DM was 2.9 mm. However, the cut-off point for average size of foci in AH alone was 1.9 mm, indicating larger size brain lesions when both diseases are present at the same time. But in patients with only type 2 DM, this value is 2.9 mm. This is an indication that when both diseases are present, the type 2 DM has stronger impact on the size of T2 hyperintense foci than does AH. However, during the study of Daniel and Victorina, it was reported that hypertension has a greater effect on the volume of T2 hyperintense foci in patients with AH + type 2 DM [19].

AH has a direct and indirect effect on the development of late vascular complications of type 2 DM (stroke, chronic heart disease, peripheral vascular disease, death). Hypertension is more harmful in patients with type 2 diabetes in developing countries than in high-income countries. The risk of complications (stroke, death, etc.) related to type 2 DM decreases when blood pressure is lowered. Patients with diabetes are 1.5-3 times more likely to have AH than patients without DM [14].

According to the study conducted by Tchistiakova and co-authors on 18 patients with AH + type 2 DM and 22 patients with AH only, the volume of T2 hyperintense foci was significantly different in both groups (p<0.2) [21]. This difference was also confirmed during our study. Thus, 56 (98.1%) of 61 AH + type 2 DM patients had a T2 hyperintense focus. 68 (88.3%) of 77 patients with AH only had a T2 hyperintense focus. For the number of T2 hyperintense foci, the Median-score in the group with AH + type 2 DM was 70, and it was 35 in patients with AH only. This difference was statistically significant (p<0.001). That is, the patients with AH + type 2 DM have more lesions in the brain than those with AH only. At the same time, this value for the average size of T2 hyperintense foci in the group with AH + type 2 DM was 4 mm, and in the group with AH only was 2.5 mm. In the maximum size of T2 hyperintense foci, this value was calculated as 7 mm and 4 mm, respectively. These differences were statistically significant (p<0.001). That is, the larger lesions are seen on brain MRIs of patients with AH + type 2 DM when compared to patients with AH only. The difference between the groups in terms of the size and the number of T2 hyperintensive foci in females and males is found to be statistically significant (p<0.05). However, there was no statistically significant difference in the number and the size of T2 hyperintense foci between sexes within the groups (p>0.05).

High blood pressure increases the risk of death. 46% of AH patients do not know about their disease. Only 21% of hypertensive patients have their blood pressure under control [22].

Cerebral increased periventricular white matter signals are risk factors for intracerebral hemorrhage and microbleeds increase the risk of intracerebral hemorrhage. The presence of microbleeds in patients with ischemic infarction was known to be a distinct risk factor for independent anticoagulant therapy. Cerebral hemosiderin foci have an influential relationship with white matter lesions. AH and DM are the most important causes of stroke and hemorrhage. Especially in middle-aged and older people, it is important to include T2W GRE and SWI sequences in conventional multiplanar imaging of cranial MRI to reveal microhemorrhagic foci [23].

5. Conclusion

Thus, when arterial hypertension and type 2 diabetes occur at the same time, the size and number of foci (WMH) in the brain are greater than both in healthy people and in patients who have one of these diseases. For this reason, it is necessary to intensively treat each disease separately. About half of patients with AH (46%) are unaware of their disease. In these patients, as well as in those with undiagnosed type 2 DM, radiologists can guide physicians by using cut-off points for the number and size of T2 hyperintense foci detected on brain MRI ordered for headache or other reasons. The results obtained do not require any sophisticated software to perform extensive calculations. All radiologists can easily use these cut-off points in their practice.

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