International Journal of Scientific Engineering and Applied Science (IJSEAS) – Volume-8, Issue-1, January 2022
ISSN: 2395-3470
www.ijseas.com

Atherogenic dyslipidemia and cardiometabolic risk. Epidemiological evaluation in Romania.

Lavinia Maris[1†], Lavinia Rațț[2†], Mircea Ioachim Popescu[3], Timea Claudia Ghitea[2†,*]

[1] Faculty of Medicine and Pharmacy, Department of General Medicine, "Vasile Goldiș" University, Arad, Romania
[2] Faculty of Medicine and Pharmacy, Pharmacy Department, University of Oradea, Oradea, Romania
[3] Faculty of Medicine and Pharmacy, Cardiology Department, University of Oradea, Oradea, Romania
† Equal contributions
* Correspondence: timea.ghitea@csud.uoradea.ro; Tel.: +40723546427

Abstract: The development of metabolic diseases such as diabetes is increasing. The prevalence increases with increasing sedentarism and with the adaptation of an inappropriate lifestyle. Dyslipidemia is an imbalance of lipids such as cholesterol, low-density lipoprotein (LDL-cholesterol), triglycerides, and high-density lipoprotein (HDL-cholesterol). Cardiometabolic complications in both type 2 diabetes mellitus (DM2) and dyslipidemia have reached alarming levels in the last decade. Starting from the idea that 80% of cardiometabolic diseases can be prevented if they are recognized over time, this paper aimed at clinical, paraclinical and stress factors to outline the group of patients at cardiometabolic risk. The study group, which included 462 patients diagnosed with non-insulin-dependent diabetes mellitus and metabolic syndrome (MS), was followed up and divided into 4 years of study. The assessment of the risk of atherogenic dyslipidemia was indirect by tracking diseases that are associated with both increased cardiovascular risk and atherogenic dyslipidemia. The quality of life assessment was carried out by completing the questionnaires. It has been observed that the highest risk is hypertension and obesity, but also hypercholesterolemia and sedentary lifestyle are a high risk factor. It was also reported that patients with higher levels of stress had a higher incidence of cardiovascular disease.

Keywords: Diabetes, Cardiometabolic disease, Hypertension, Stress

1. Introduction

Atherogenic dyslipidemia in diabetes consists of elevated serum concentrations of triglyceride-rich lipoproteins, a high prevalence of dense low-density lipoproteins (LDL-cholesterol) and low concentrations of high-density lipoproteins rich in high-density lipoprotein (HDL-cholesterol) [1]. This dyslipidemia is based on a lipoprotein abnormality, characterized by an increase in very low density lipoprotein (VLDL-cholesterol), and other lipoprotein abnormalities are metabolically related to elevated triglycerides. Insulin regulates serum VLDL-cholesterol levels by suppressing liver production and stimulating VLDL-cholesterol removal by activating lipoprotein lipase [2].

Many patients do not receive adequate treatment for the type of dyslipidemia that is common in these disorders of the "atherogenic lipid triad" of high serum triglyceride levels, low serum cholesterol, high density lipoprotein (HDL-cholesterol), and a predominance of small particles. low-density lipoprotein cholesterol (LDL-cholesterol) [3].

Hypertriglyceridemia is a strong predictor of coronary heart disease. There is also an inverse relationship between serum HDL-cholesterol and triglyceride levels in diabetic patients, with low serum HDL-cholesterol levels possibly representing an independent risk factor for cardiovascular disease. Small, dense, LDL-cholesterol particles are also very atherogenic because they are more likely to form oxidized LDL and are less easy to clean. Insulin resistance, which is essential for metabolic syndrome and type 2 diabetes, leads to high levels of very low density lipoprotein (VLDL), which contain a high concentration of triglycerides, resulting in high serum triglyceride levels and low serum triglyceride levels. HDL-C [3].

The increase in LDL-cholesterol resulting from the replacement of dietary saturated fats with carbohydrates or unsaturated fats is primarily due to the increase in high LDL-enriched cholesterol, with minimal changes in small, dense LDL particles and apolipoprotein B [4].

It is estimated that 20% -30% of the world's adults have metabolic syndrome. Metabolic syndrome is associated with an increased risk of type 2 diabetes, non-alcoholic fatty liver disease, myocardial infarction, and stroke. Thus, it is a major cause of worldwide morbidity and mortality. However, the molecular pathogenesis of metabolic syndrome is unknown. Recently, there has been interest in the role of mitochondria in the pathogenesis of metabolic problems, such as obesity, metabolic syndrome, and type 2 diabetes [5]. Mitochondrial dysfunction contributes to oxidative stress and systemic inflammation seen in metabolic syndrome. The role of mitochondria in the pathogenesis of metabolic syndrome is intriguing, but far from completely understood [6].

An important component of atherogenic dyslipidemia is central obesity, which is defined as increased waist circumference and has recently been identified as a major predictor of metabolic syndrome in some patients. Another recent study found that both body mass index and waist circumference were very predictive of a possible development of the metabolic syndrome. Because atherogenic dyslipidemia usually precedes the clinical manifestation of the metabolic syndrome, strategies for its treatment are at the heart of pharmacological intervention [7].

Obesity, glucose intolerance, diabetes and metabolic syndrome are becoming more common and are often associated with atherogenic dyslipidemia, affecting the long-term risk of CVD. Recognition at the office is best done by testing the ratio of non-HDL or total HDL cholesterol. The success of the treatment consists in optimizing the diet and physical exercises. Of the available drugs, statins produce the most benefits and can be titrated to patient tolerance, rather than target LDL levels, which have a weak evidence base. The addition of fenofibrate may be considered in patients with elevated triglycerides and low HDL levels who have responded poorly or have not tolerated statins.

Increasing the prevalence of obesity creates a risk of CVD that could be prevented not only by testing LDL cholesterol, but also by following the parameters associated with CVD [8]. Simple calculations from the results of a non-post lipid panel produce non-HDL levels and the total HDL-cholesterol ratio, both of which are superior for estimating risk in all patients [9].

The aim of this study is to establish a pattern of several risk factors for diseases associated with atherogenic dyslipidemia, which allows for a faster diagnosis of this complication, thus reducing mortality, and assess the importance of stress management in reducing of cardiovascular risk.

2. Materials and Methods

2.1. Body Analysis of Patients with MS

The clinical and paraclinical analyzes were performed in a private medical office of nutrition in Oradea, Romania Echo laboratories.

2.1.1. Anthropometric Tests

The clinical evaluation was performed with the Tanita MC780MA bioelectric impedance body analyzer (Tokyo, Japan) [10], and the results were evaluated using GMON 3.4.1 medical software (Chemnitz, Germany). BIA-type body analyzers are devices accepted by the WPHNA (World Public Health Nutrition Association) and were used to determine body composition with high accuracy. The margin of error was 0.1 kg. We followed the evaluation of the affinity for diet therapy with the non-invasive medical device Cnoga MTX (Or-Akiva, Israel), which helped to follow the changes of the clinical parameters as a whole, checking the oxygen saturation, the blood pressure, and the blood pH. Patients were evaluated on an empty stomach in the morning.

The diagnosis of the metabolic syndrome was made following the visceral fat, BMI mixed dyslipidemia (cholesterol and triglycerides, hypertension, myocardial infarction, congestive heart failure, ischemic heart disease, and the quality of life by completing the ISMA stress questionnaire and quality of life - diabetic neuropathy version. The criterion for including patients in the current study was a diagnosis of diabetes mellitus type 2. Diabetes mellitus type 1 and other independent diseases besides diseases associated with diabetes were the exclusion criteria. This study looked at the risk of cardiometabolic diseases, which have the most obvious changes due to stress, representing the highest risk for the unfavorable evolution of atherogenic dyslipidemia.

We followed the variations in the four independent groups, depending on sex, age, rural/urban environment, clinical parameters such as BMI, visceral fat, cholesterol and triglycerides, hypertension, myocardial infarction, congestive heart failure, ischemic heart disease, and the quality of life by completing the ISMA stress questionnaire and quality of life - diabetic neuropathy version.

The completion of the evaluation sheets of the patients included in the research study took place at the beginning of the study period by the participants.

2.1.2. Tracking Metabolic Parameters

Patients were evaluated at the beginning of the treatment with this device. With bare feet, they climbed on the base of the scale and held two electrodes in their hands. The measurements lasted up to 10 s after which the results were evaluated.

2.1.3. Paraclinical Analyses

Automated analyzer for clinical chemistry-SPOTCHEM EZ SP-4430-ARKRAY Inc. Koka-Shi, Japan. Whole blood samples can be measured easily and promptly with a built-in centrifuge for pretreatment. Continuous measurement, up to 9 items, is available.

By reading the “magnetic card” attached to each test strip, variations among lots and changes with the timing of test strips are automatically calibrated. The users are totally free from complicated operations.

Improvement of the sampling mechanism almost doubled the measurement speed at its maximum compared to the current model.

Measurement principle: Optical measurement of reflection intensity-five different types of optical filters (five wavelengths), and the optimal wavelength is selected for each parameter measured (tested).

240 microliters of whole blood are collected. It is placed in a special tank with heparin and placed in the device. The analyzer has a built-in centrifuge, processes the sample, and in 10 min the result is printed by the built-in printer.

Reagent type: dry chemistry

2.1.4. Statistical analyses

The descriptive and analytical analysis was performed with the statistical program SPSS 20 (New York, NY, USA), we could follow both the final result compared to the initial values and the possible correlations between health.

2.1.5. Quality of life questionnaires

The quality of life was assessed by completing the questionnaires on:

- stress through Stress Questionnaire © International Stress Management Association UK-2013

- quality of life through the Quality of Life Questionnaire (QOL-DN) - Diabetic neuropathy version

Interventionary studies involving animals or humans, and other studies that require ethical approval, must list the authority that provided approval and the corresponding ethical approval code.

3. Results

3.1.1. Demographic description

The research study included 462 patients, divided into 4 years, presented graphically in Figure 1 (A).

The distribution of patients according to sex, described in figure 1 (B), without significant differences, is as follows: in 2017 65 (14.1%) men and 96 (20.8%) women, in 2018 31 (6.7%) of men and 47 (10.2%) of women, in 2019 the number of men included 43 (9.3%), and 66 (14.3%) of women, and in the last year of study (2020) 52 (11.3%) men and 62 (13.4%) women were included. In the cohort, 17.4% more women were present than men, a percentage that is reflected in each year of study.

In terms of the environment of origin, it can be seen that most patients come from urban areas with 52.4% compared to rural areas, also shown in Figure 1 (C). In 2017 122 (26.4%) of patients from urban areas and 39 (8.4%) of people from rural areas were registered, in 2018 from urban areas 57 (12.3%) from people and from the environment rural (21%) of people included, in 2019 17.3% (80 patients) came from urban areas and 29 (6.3%) from rural areas, and in 2020 out of a total of 114 93 patients (20.1%) came from urban areas and only 21 (4.5%) from rural areas.

Following the age, we can see in 2017 the average age being 38.65 years (SD ± 14.33), in 2018 it was 43.28 (SD ± 14.04), in 2019 the average age was 39.68 (SD ± 14.28), and in 2020 the average age is 39.59 years (SD ± 16.23), per cohort being presented in figure 1 (D).

3.1.2. Anthropometric results

Obesity is the main risk factor for cardiovascular disease. Thus, in order to follow obesity as a risk factor, the body mass index (BMI) and visceral fat, presented in table 1, were followed, both at the level of the cohort and in each year of study. The evaluation of the patients included in the study in terms of weight status, an average BMI of 30.3 (SD ± 4.74) was obtained, ie the patients were in the degree of grade I obesity. Following the evaluation of each year can be seen that only in 2020 they were in the overweight field (BMI = 29.61 kg / m2), in the other three years of study, the average value of BMI has always reached the threshold of grade I obesity.

3.1.3. Paraclinical results

To verify the effect of the type of intervention on cholesterol, we used the ANOVA statistical test for the 4 independent groups and obtained F=0.212, p=0.881, so compared to the research years cholesterol does not differ significantly. The results obtained with the BONFERRONI Post Hoc tests indicate insignificant differences between the groups as follows: between 2018 and 2020 (p>0.05), and between 2018-2017, 2018-2019, there were also statistically insignificant differences.

Regarding triglycerides, we used the ANOVA statistical test for 4 independent groups and obtained F=0.265, p=0.851, so compared to the study years the value of triglycerides does not

differ significantly in the 2 groups. With the help of the BONFERRONI Post Hoc tests, the data obtained do not indicate any significant differences between groups. These data explained as a percentage are presented in Figure 2 of cholesterol (A) and triglycerides (B) in the 4 years of research

3.1.4. Evaluation of cardiovascular diseases

Cardiovascular disease, shown in the third figure, was monitored by the following research parameters as hypertension, myocardial infarction, congestive heart failure and ischemic heart disease.
Therefore, the cohort patients being young (average age under 40 years), 45.23% of the cohort had female hypertension, 30.73% male.
The incidence of myocardial infarction is higher in women (3.03%) than in men (1.73%).
According to the cohort study, congestive heart failure is present in 75 women (16.23%) and 51 men (11.03%).
Ischemic heart disease was present in 78 women (16.88%), more than men (59 people 12.77%).
The average age in cardiovascular diseases, shown in Figure 3, shows the lowest average age in those with a history of myocardial infarction (38.41 years SD 15.36), and in the case of ischemic heart disease there was the highest average age (41.12 years SD 15.37).

3.1.5. Life quality questionnaire results

ISMA stress questionnaire

In the case of ISMA, it was marked with "1" patients without stress, with "2" patients prone to stress-induced diseases, and with "3" patients with stress-induced diseases.

Following the statistical processing of the obtained data, an average value of 2.38±0.81 was obtained, described in table 3 together with statistical significance, and in figure 4.

In the 4 years of study, ISMA reached the highest values in 2017, with can be seen in Table 3. At the same time can be seen the higher number of patients with stress-induced diseases in each year of study.
Table 4 shows the situation of patients with hypertension and stress. It can be seen that patients with hypertension present are either with stress-induced diseases or with a marked predisposition to stress-induced diseases. It can be seen that the most stressed have an increased incidence of hypertension.

QoL-DN Questionnaire - Norfolk (QOL-DN) - Quality of life questionnaire - Diabetic neuropathy version

Following the statistical processing of the QoL-DN acquirer, no problems were observed in 78 people, very weak problems in 163 people, weak problems in 165 participants, moderate problems in 40 patients, and severe problems in 16 of the 462 patients, presented as a percentage in Figure 6. There was also a statistically significant distribution of differences between the results for each year of study. Thus the quality of life is independent of the year of study, according to figure 5.

3.2. Figures, Tables and Schemes

Table 1. Statistical analysis of risk factors for obesity of participants in the research study

Parameters	N	Mean	SD	t	Sig.
BMI	462	30.3056	4.74973	137.143	0.001
Visceral fat		10.5823	4.35277	52.256	0.001

N=Number of patents
SD=Standard deviation

t=Coefficient t Student
Sig.=Statistical significance

Table 2. Analiza statistică a bolilor cardiovasculare ale participanților din studiu de cercetare

Parameters	N	Mean	SD	t	Sig.
Hypertension	462	0.7597	0.42770	38.181	0.001
Myocardial infarction		0.0476	0.21319	4.801	0.001
Congestive heart failure		0.2727	0.44584	13.148	0.001
Ischemic heart disease		0.2965	0.45723	13.940	0.001

N=Number of patents
SD=Standard deviation
t=Coefficient t Student
Sig.=Statistical significance

Table 3. Descriptive presentation of ISMA during the 4 years of the study

Variable				N	N %
Group	2017	ISMA	No stress	32	6.9%
			Predisposed to stress-induced diseases	31	6.7%
			With stress-induced diseases	98	21.2%
	2018	ISMA	No stress	19	4.1%
			Predisposed to stress-induced diseases	15	3.2%
			With stress-induced diseases	44	9.5%
	2019	ISMA	No stress	23	5.0%
			Predisposed to stress-induced diseases	14	3.0%
			With stress-induced diseases	72	15.6%
	2020	ISMA	No stress	24	5.2%
			Predisposed to stress-induced diseases	27	5.8%
			With stress-induced diseases	63	13.6%

N=Number of patients
ISMA=Stress questionnaire

Table 4. Descriptive presentation of ISMA in the 4 years of study depending on the presence or absence of hypertension

Parameters						N	N %
Group	2017	ISMA	No stress	Hypertension	absent	7	1.5%
					present	25	5.4%
			Predisposed to stress-induced diseases	Hypertension	absent	6	1.3%
					present	25	5.4%

			With stress-induced diseases	Hypertension	absent	16	3.5%
					present	82	17.7%
	2018	ISMA	No stress	Hypertension	absent	5	1.1%
					present	14	3.0%
			Predisposed to stress-induced diseases	Hypertension	absent	1	0.2%
					present	14	3.0%
			With stress-induced diseases	Hypertension	absent	17	3.7%
					present	27	5.8%
	2019	ISMA	No stress	Hypertension	absent	7	1.5%
					present	16	3.5%
			Predisposed to stress-induced diseases	Hypertension	absent	0	0.0%
					present	14	3.0%
			With stress-induced diseases	Hypertension	absent	17	3.7%
					present	55	11.9%
	2020	ISMA	No stress	Hypertension	absent	7	1.5%
					present	17	3.7%
			Predisposed to stress-induced diseases	Hypertension	absent	7	1.5%
					present	20	4.3%
			With stress-induced diseases	Hypertension	absent	21	4.5%
					present	42	9.1%

N=Number of patients
ISMA=Stress questionnaire

Table 4. The paired significance of stress with the parameters being followed

Correlations of pair parameters		N	Correlations	Sig.
Pair 1	ISMA & Myocardial infarction	462	0.156	0.001
Pair 2	ISMA & Congestive heart failure	462	0.461	0.001
Pair 3	ISMA & Ischemic heart disease	462	0.413	0.001

N=Number of patients
ISMA=Stress questionnaire
Sig.=Statistical significance

Table 5. Pearson correlation between the relationship between Qol-DN and research parameters

Pearson correlation		BMI	Visceral fat	Microvascular disease	Congestive heart failure	Peripheral vascular disease
QoL-DN	r	0.857**	0.435**	0.148**	0.096*	0.144**
	Sig.	0.001	0.001	0.001	0.040	0.002
	N	462				

N= Number of patients
r=coefficient Pearson
Sig.=Statistical significance
**=Correlation is significant at the 0.01 level (2-tailed).

*=Correlation is significant at the 0.05 level (2-tailed).

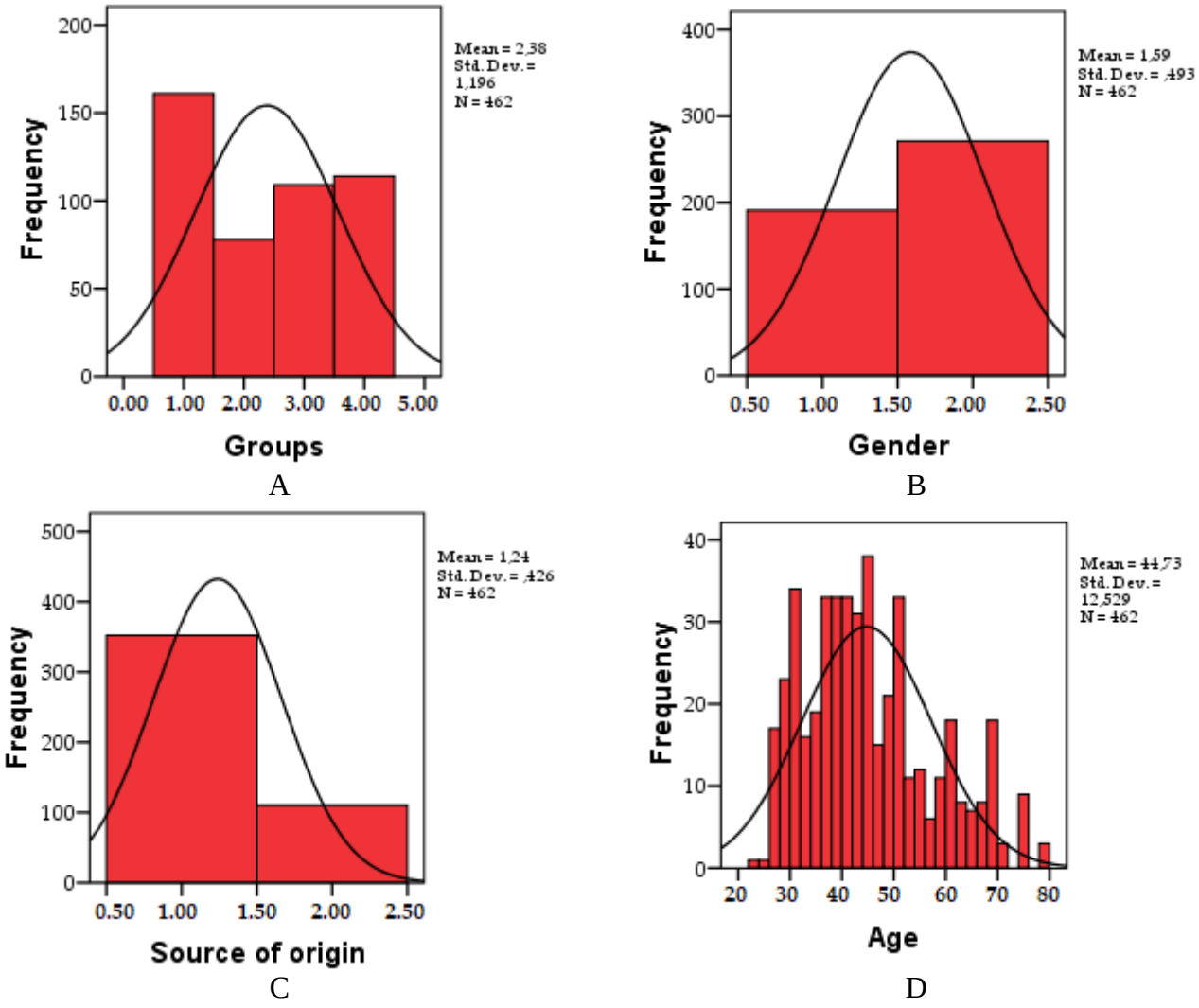
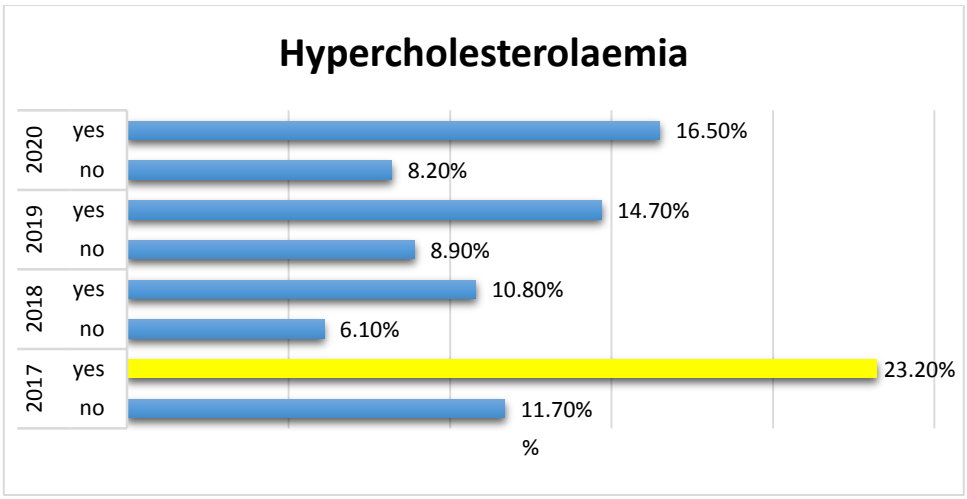
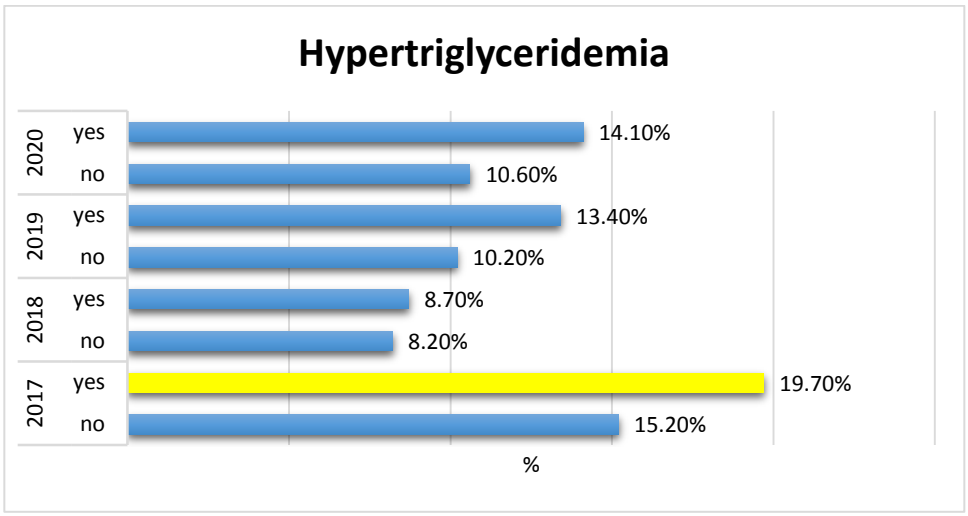


Figure 1. Graphic presentation of demographic characteristics in study cohort, distribution by lot (A), division by sex (B), background (C) and age (D).



A



B

Figure 2. Graphical presentation of cholesterol (A) and triglycerides (B) during the 4 years of research

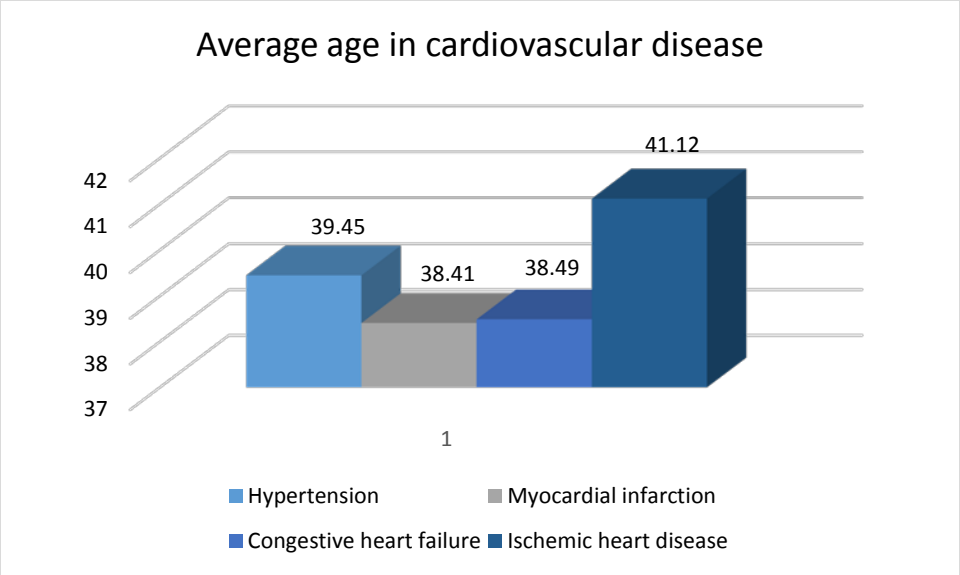


Figure 3. Graphical representation of the average age in the cardiovascular diseases present

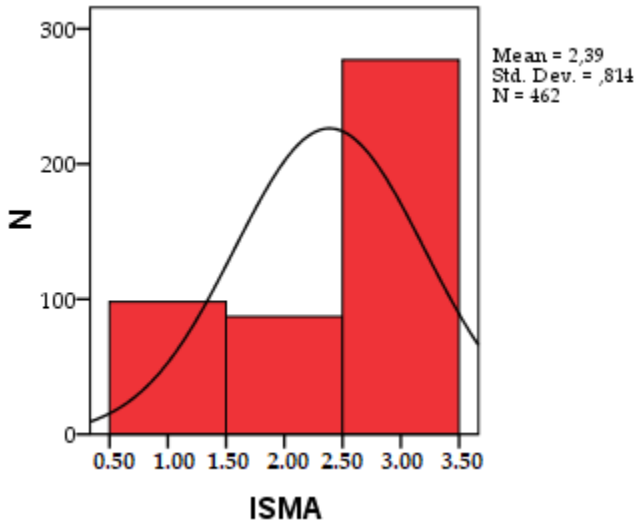


Figure 4. Graphical representation of the average ISMA per cohort, where N represents the number of patients

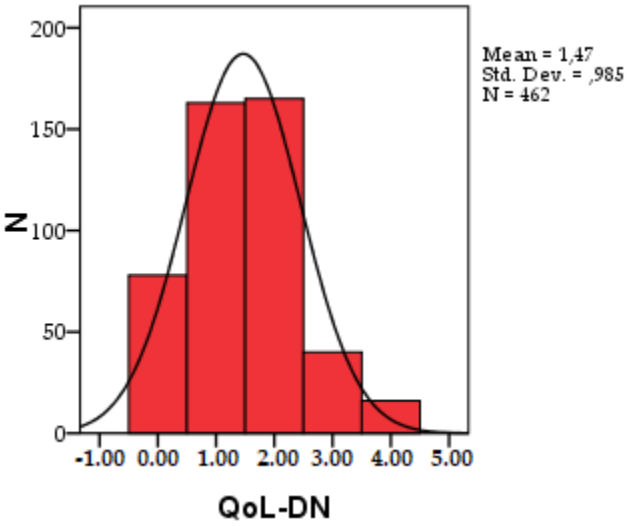


Figure 5. Graphical representation of the QoL-DN mean per cohort, where N represents the number of patients

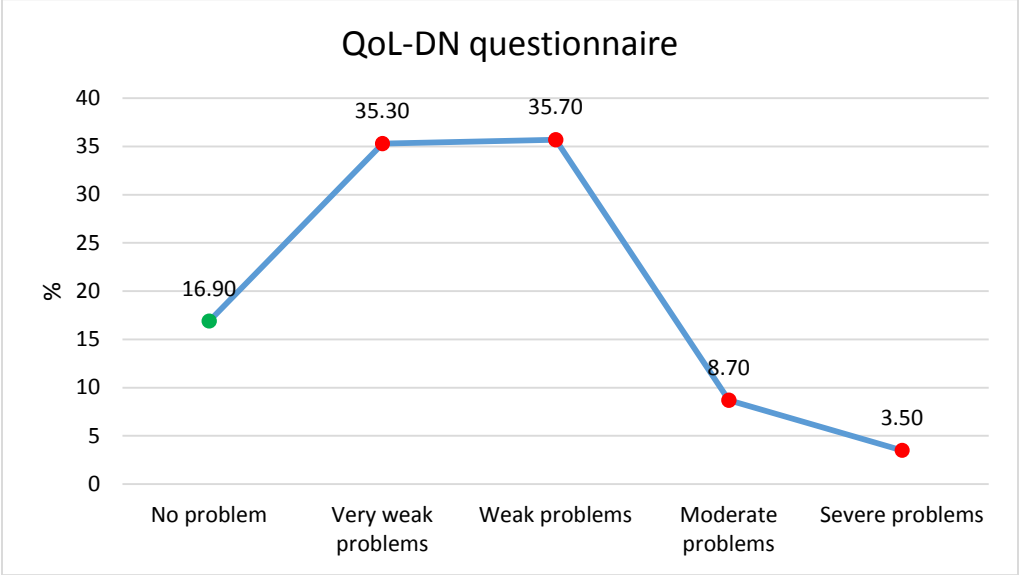


Figure 6. Graphic representation of the quality of life according to the QoL-DN questionnaire

4. Discussion

The risk factor is being studied very intensively in atherogenic dyslipidemia. The main value and role is to recognize over time all the diseases and all the factors that can pose a health risk, to treat, avoid or manage them. In Europe, the risk factor for atherogenic dyslipidemia is 55% [11], and in the presented study it is very close (54.27%). In Europe, different areas with higher risk and lower risk have been observed, depending on the socio-economic development of the country [12-14]. Many studies, but especially in the last decade, have been intensely involved in the evaluation of daily stress [15], of oxidative stress [16], which has been shown to be involved

in the development and aggravation of many chronic diseases [17,18]. A high risk of stress contributes to hypertension, according to a 2017 study [19], or dyslipidemia after Jabarpour [20]. But a sedentary lifestyle not only affects a stress factor, but also promotes the development of psycho-emotional imbalances, according to several studies [21-24]. Stress in adults has an important role in triggering atherosclerotic plaque diseases and it works as a determinant of prognosis and outcome in those with pre-existing cardiovascular or cerebrovascular disease, according to a 2018 study [25].

In 2016, a study of the sympathetic nervous system drew a parallel between mental stress and cardiovascular disease, but more so with atherosclerosis and hypertension [26]. Our study using the ISMA stress questionnaire is in line with the results and the field studied.

Quality of life is greatly affected in metabolic diseases related to obesity and sedentary lifestyle [27]. The role of this assessment is to identify and change a sedentary, inactive to active lifestyle, and to encourage weight loss to increase quality of life [28].

Physical activity has a positive effect not only on weight loss diets but also on reducing cardiovascular disease [29]. The quality of life can be improved with the decrease of visceral fat, which in addition to reducing the risk of direct metabolic diseases and indirect cardiovascular diseases, helps to improve health, thus increasing the quality of life.

Another factor that has been statistically significantly correlated with quality of life in our study is congestive heart failure. The pathophysiology of this disease, which greatly limits both movement and many daily activities, negatively influences the quality of life, leading to its decline. Studies in the literature show that many of the cardiovascular factors may either alone [30,31] or correlate with the degradation of the quality of life of people with metabolic diseases, respectively atherogenic dyslipidemia [32,33].

5. Conclusions

The risk factor for the development of atherogenic dyslipidemia is 54.27%, slightly lower than in European studies, where this percentage is 55%.

The most stressed patients were in 2017, a year in which both the number of people with non-stress-induced diseases was the highest (21% of the total cohort) and the number of those prone to stress-induced diseases (6.7% of the total cohort). The highest risk is high blood pressure and obesity, but also hypercholesterolemia and sedentary lifestyle are high risk factors.

Following the correlation between ISMA and study parameters, it was significantly correlated only with the parameters of cardiovascular disease, namely ischemic heart disease, congestive heart failure and myocardial infarction. Therefore, it can be concluded that patients with high levels of stress have a higher incidence of cardiovascular disease. Thus, stress management is very important to reduce the cardiovascular risk.

The quality of life was most affected in 2018, and the least in 2020. The quality of life was influenced by several factors. This was concluded from Pearson's correlation with the research parameter. It has been shown that increased BMI, visceral fat, microvascular incidence, incidence of congestive heart failure or peripheral vascular disease decrease quality of life.

Funding: This research received no external funding

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of ECHO LABORATOARE (protocol code 98/2018), Romania.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: All the epidemiological dates regarding the cardiovascular, renal and vascular diseases are archived in the clinical hospital of Arad, Romania, and the data obtained from the questionnaire of quality of life are in the doctoral studies archives.

Acknowledgments: Nothing to acknowledge.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Aday, A.W.; Everett, B.M. Dyslipidemia Profiles in Patients with Peripheral Artery Disease. *Curr Cardiol Rep* **2019**, *21*, 42, doi:10.1007/s11886-019-1129-5.
2. Hirano, T. Pathophysiology of Diabetic Dyslipidemia. *J Atheroscler Thromb* **2018**, *25*, 771-782, doi:10.5551/jat.RV17023.
3. Nesto, R.W. Beyond low-density lipoprotein: addressing the atherogenic lipid triad in type 2 diabetes mellitus and the metabolic syndrome. *Am J Cardiovasc Drugs* **2005**, *5*, 379-387, doi:10.2165/00129784-200505060-00005.
4. Chiu, S.; Williams, P.T.; Krauss, R.M. Effects of a very high saturated fat diet on LDL particles in adults with atherogenic dyslipidemia: A randomized controlled trial. *PLoS One* **2017**, *12*, e0170664, doi:10.1371/journal.pone.0170664.
5. De Pauw, A.; Tejerina, S.; Raes, M.; Keijer, J.; Arnould, T. Mitochondrial (dys)function in adipocyte (de)differentiation and systemic metabolic alterations. *Am J Pathol* **2009**, *175*, 927-939, doi:10.2353/ajpath.2009.081155.
6. Prasun, P. Mitochondrial dysfunction in metabolic syndrome. *Biochim Biophys Acta Mol Basis Dis* **2020**, *1866*, 165838, doi:10.1016/j.bbadis.2020.165838.
7. Vinik, A.I. The metabolic basis of atherogenic dyslipidemia. *Clin Cornerstone* **2005**, *7*, 27-35, doi:10.1016/s1098-3597(05)80065-1.
8. au, A.P.C.S.C.a.g.o. Cholesterol, diabetes and major cardiovascular diseases in the Asia-Pacific region. *Diabetologia* **2007**, *50*, 2289-2297.
9. Bosomworth, N.J. Approach to identifying and managing atherogenic dyslipidemia: a metabolic consequence of obesity and diabetes. *Can Fam Physician* **2013**, *59*, 1169-1180.
10. Tanita.eu. medical-approved-body-composition-monitors/mc-780-portable-instruction-manual.pdf. Available online: (accessed on
11. Chew, G.T.; Gan, S.K.; Watts, G.F. Revisiting the metabolic syndrome. *Medical journal of Australia* **2006**, *185*, 445-449.
12. Møller, N.; Gormsen, L.; Fuglsang, J.; Gjedsted, J. Effects of ageing on insulin secretion and action. *Hormone Research in Paediatrics* **2003**, *60*, 102-104.
13. Kumar, S.; Behl, T.; Sachdeva, M.; Sehgal, A.; Kumari, S.; Kumar, A.; Kaur, G.; Yadav, H.N.; Bungau, S. Implicating the effect of ketogenic diet as a preventive measure to obesity and diabetes mellitus. *Life Sci* **2021**, *264*, 118661, doi:10.1016/j.lfs.2020.118661.
14. Artham, S.M.; Lavie, C.J.; Schutter, A.D.; Ventura, H.O.; Milani, R.V. Obesity, Age, and Cardiac Risk. *Current Cardiovascular Risk Reports* **2011**, *5*, 128-137, doi:doi:10.1007/s12170-011-0155-7.

15. Guerra, J.V.S.; Dias, M.M.G.; Brilhante, A.J.V.C.; Terra, M.F.; García-Arévalo, M.; Figueira, A.C.M. Multifactorial Basis and Therapeutic Strategies in Metabolism-Related Diseases. *Nutrients* **2021**, *13*, 2830.
16. Alberti, K.G.; Eckel, R.H.; Grundy, S.M.; Zimmet, P.Z.; Cleeman, J.I.; Donato, K.A.; Fruchart, J.-C.; James, W.P.T.; Loria, C.M.; Smith Jr, S.C. Harmonizing the metabolic syndrome: a joint interim statement of the international diabetes federation task force on epidemiology and prevention; national heart, lung, and blood institute; American heart association; world heart federation; international atherosclerosis society; and international association for the study of obesity. *Circulation* **2009**, *120*, 1640-1645.
17. Huda, M.N.; Kim, M.; Bennett, B.J. Modulating the Microbiota as a Therapeutic Intervention for Type 2 Diabetes. *Frontiers in Endocrinology* **2021**, *12*, 153.
18. Corb Aron, R.A.; Abid, A.; Vesa, C.M.; Nechifor, A.C.; Behl, T.; Ghitea, T.C.; Munteanu, M.A.; Fratila, O.; Andronie-Cioara, F.L.; Toma, M.M.; et al. Recognizing the Benefits of Pre-/Probiotics in Metabolic Syndrome and Type 2 Diabetes Mellitus Considering the Influence of Akkermansia muciniphila as a Key Gut Bacterium. *Microorganisms* **2021**, *9*, 618, doi:10.3390/microorganisms9030618.
19. Berg, G.; Rybakova, D.; Fischer, D.; Cernava, T.; Vergès, M.-C.C.; Charles, T.; Chen, X.; Cocolin, L.; Eversole, K.; Corral, G.H. Microbiome definition re-visited: old concepts and new challenges. *Microbiome* **2020**, *8*, 1-22.
20. Savage, D.C. Microbial ecology of the gastrointestinal tract. *Annual review of microbiology* **1977**, *31*, 107-133.
21. James, W.P.; Ferro-Luzzi, A.; Waterlow, J.C. Definition of chronic energy deficiency in adults. Report of a working party of the International Dietary Energy Consultative Group. *Eur J Clin Nutr* **1988**, *42*, 969-981.
22. Sekirov, I.; Russell, S.L.; Antunes, L.C.M.; Finlay, B.B. Gut microbiota in health and disease. *Physiological reviews* **2010**.
23. Ley, R.E.; Turnbaugh, P.J.; Klein, S.; Gordon, J.I. Microbial ecology: human gut microbes associated with obesity. *Nature* **2006**, *444*, 1022-1023, doi:10.1038/4441022a.
24. Tilg, H.; Zmora, N.; Adolph, T.E.; Elinav, E. The intestinal microbiota fuelling metabolic inflammation. *Nature Reviews Immunology* **2020**, *20*, 40-54.
25. Otrisal, P.; Bungau, C.; Obsel, V.; Melicharik, Z.; Tont, G. Selected Respiratory Protective Devices: Respirators and Significance of Some Markings. *Sustainability* **2021**, *13*, 4988.
26. Gurung, M.; Li, Z.; You, H.; Rodrigues, R.; Jump, D.B.; Morgun, A.; Shulzhenko, N. Role of gut microbiota in type 2 diabetes pathophysiology. *EBioMedicine* **2020**, *51*, 102590.
27. Qin, J.; Li, Y.; Cai, Z.; Li, S.; Zhu, J.; Zhang, F.; Liang, S.; Zhang, W.; Guan, Y.; Shen, D.; et al. A metagenome-wide association study of gut microbiota in type 2 diabetes. *Nature* **2012**, *490*, 55-60, doi:10.1038/nature11450.
28. Turnbaugh, P.J.; Hamady, M.; Yatsunenko, T.; Cantarel, B.L.; Duncan, A.; Ley, R.E.; Sogin, M.L.; Jones, W.J.; Roe, B.A.; Affourtit, J.P.; et al. A core gut microbiome in obese and lean twins. *Nature* **2009**, *457*, 480-484, doi:10.1038/nature07540.
29. Ley, R.E.; Bäckhed, F.; Turnbaugh, P.; Lozupone, C.A.; Knight, R.D.; Gordon, J.I. Obesity alters gut microbial ecology. *Proc Natl Acad Sci U S A* **2005**, *102*, 11070-11075, doi:10.1073/pnas.0504978102.

30. Schwiertz, A.; Taras, D.; Schäfer, K.; Beijer, S.; Bos, N.A.; Donus, C.; Hardt, P.D. Microbiota and SCFA in lean and overweight healthy subjects. *Obesity* **2010**, *18*, 190-195.
31. Larsen, N.; Vogensen, F.K.; van den Berg, F.W.; Nielsen, D.S.; Andreasen, A.S.; Pedersen, B.K.; Al-Soud, W.A.; Sørensen, S.J.; Hansen, L.H.; Jakobsen, M. Gut microbiota in human adults with type 2 diabetes differs from non-diabetic adults. *PLoS One* **2010**, *5*, e9085, doi:10.1371/journal.pone.0009085.
32. Dao, M.C.; Everard, A.; Aron-Wisnewsky, J.; Sokolovska, N.; Prifti, E.; Verger, E.O.; Kayser, B.D.; Levenez, F.; Chilloux, J.; Hoyles, L.; et al. Akkermansia muciniphila and improved metabolic health during a dietary intervention in obesity: relationship with gut microbiome richness and ecology. *Gut* **2016**, *65*, 426-436, doi:10.1136/gutjnl-2014-308778.
33. Reunanen, J.; Kainulainen, V.; Huuskonen, L.; Ottman, N.; Belzer, C.; Huhtinen, H.; de Vos, W.M.; Satokari, R. Akkermansia muciniphila Adheres to Enterocytes and Strengthens the Integrity of the Epithelial Cell Layer. *Appl Environ Microbiol* **2015**, *81*, 3655-3662, doi:10.1128/aem.04050-14.