ASPECTS OF NASAL COLONIZATION OF THE MEDICAL STAFF IN SURGICAL UNITS

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REZUMAT

Scop. *În acest studiu am urmărit transmiterea exogenă a tulpinilor nazale de S. aureus de la personalul medical la pacienți într-un institut clinic universitar cu profil cardiovascular.* ***Material şi metodă.*** *Identificarea germenilor s-a bazat pe caracterele culturale şi pe cele biochimice. Identificarea finală şi antibiograma au fost efectuate utilizând analizorul automat Vitek2 (Bio Merieux France).* ***Rezultate.*** *Din cele 62 exudate nazale recoltate doar 29 au fost pozitive, izolîndu-se 14 tulpini S.aureus (48,29%), 7 tulpini E.coli (24,13%) şi 8 tulpini de Stafilococi coagulazo-negativi (27,58%). După efectuarea testării la chimioterapice antiinfecţioase utilizând carduri AST pentru gram pozitivi s-a constatat că toate tulpinile de Staphylococcus aureus au fost tulpini MRSA (Staphylococcus aureus meticilino-rezistent), cu sensibilitatea păstrată la vancomicină.* ***Concluzii.*** *Depistarea personalului medical colonizat nazal cu Staphylococcus aureus şi decolonizarea acestuia, întrerup calea de transmitere exogenă a acestui germene responsabil de etiologia numeroaselor infecţii nosocomiale.*
Cuvinte cheie: *colonizare nazală, personal medical, MRSA*

ABSTRACT

Objective. *The main objective of this study was to point out the exogenous route of nasal strains of S.aureus from the medical staff to the patients in a clinical university institute for cardiovascular diseases.* ***Material and method.*** *The germ identification relied on the cultural and biochemical characters. Final identification and antibiogram were performed using the Vitek 2 automatic analyser (Biomerieux France).* ***Results.*** *From the 62 nasal exudates collected only 29 were positive, with 14 strains of S.aureus (48.29%), 7 strains of E.coli (24.13%) and 8 strains of coagulase-negative staphylococci (27.58%). After performing the antimicrobial agents test using AST cards for the gram-positive, we noticed that all the Staphylococcus aureus strains were MRSA strains (meticiline-resistant Staphylococcus aureus), only with vancomicin sensitivity.* ***Conclusions.*** *The identification of medical staff nasally colonised with Staphylococcus aureus with consecutive decolonization*

interrupted the exogenous transmission of this germ responsible for the etiology of many nosocomial infections.

   Keywords: *nasal colonization, medical staff, MRSA*

INTRODUCTION

Staphylococcus aureus is both a commensal germ and a frequent cause of infections which are clinically significant. Staphylococcus aureus colonizes the skin and human mucous membranes but most frequently it is isolated in the nasal mucosa. Many S. aureus strains from those isolated are meticiline-resistant (MRSA). Nasal carriers may play an important role in Staphylococcus transmission. The medical staff can be contaminated from patients and, in their turn, they can pass it on to other patients [1].

MATERIAL AND METHOD

During 2007-2011, nasal exudates were collected from the medical staff in the surgical departments of the clinical university cardiovascular institute – ICU and the 2 surgical units (Table 1).

Table 1. Annual distribution of the medical staff microbiologically examined

Year	Microbiological exam	Number	Rate
2007	Nasal exudate	5	8.06%
2008	Nasal exudate	4	6.45%
2009	Nasal exudate	16	25.80%
2010	Nasal exudate	15	24.19%
2011	Nasal exudate	22	35.48%
Total		**62**	**100%**

The nasal exudates were inoculated on 5 % sheep blood agar, solid Chapman plate for the isolation of staphylococci as well as on Mac Conkey agar for the isolation of enterobacteria and of other gram-negative bacilli. After incubation at 37°C for 24 hours, the germ identification was made according to their cultural characters and with the help of the Vitek 2 automatic system using specific gram-positive and gram-negative cards. The Vitek 2 system was also used to test the sensitivity to antimicrobial agents.

RESULTS

Table 2. Distribution of medical staff nasal exudates according to pathogenity

Year	Non-pathologic samples	Pathologic samples
2007	0	5
2008	4	0
2009	7	9
2010	7	8
2011	15	7
Total	**33**	**29**

Table 3. The bacterial species isolated from the medical staff

Year	Bacterial species	Number	Rate
2007	*S.aureus*	**1**	**3.44%**
	CNS	3	10.34%
	E.coli	1	3.44%
2008	-	-	-
2009	*S.aureus*	**4**	**13.79%**
	CNS	2	6.89%
	E.coli	3	10.34%
2010	*S.aureus*	**6**	**20.68%**
	E.coli	2	6.89%
2011	*S.aureus*	**3**	**10.34%**
	CNS	2	6.89%
	E.coli	1	3.44%
	Group D streptococci	1	3.44%
Total		**29**	**100%**

Of the 62 nasal exudates collected only 29 were positive, 14 strains of S.aureus (48.29%), 7 strains of E.coli (24.13%) and 8 strains of coagulase-negative staphylococci (27.58%) being isolated (Tables 2, 3).

After performing the antimicrobial agents test using AST cards for the gram-positive, we noticed that all the Staphylococcus aureus strains were MRSA strains (meticiline-resistant Staphylococcus aureus), only with vancomicin sensitivity.

DISCUSSION

Nosocomial infection is an infection which occurs as a result of patients staying in the hospital (or of the therapy received while in hospital) and which was not incubating upon hospital admission. This infection can be achieved during therapeutic or diagnostic procedures, either through plain exposure of the patient to the hospital environment or as a consequence of the patient's contact with the healthcare personnel.

The staphylococcus transmission from the nasally colonized medical staff can occur as follows:
  ➢ Directly through Flugge drops,
  ➢ Indirectly through air, objects, food.

S. aureus found in nasal carriers is considered to be a well defined risk factor for the subsequent infection in different groups of patients, especially in those undergoing dialysis, surgery, having hepatic cirrhosis, intravascular devices or under intensive care [2].

As for the medical staff, the colonization with MRSA strains, unlike the patients, is rarely followed by infections, but represents a serious source of infection for the persons that they have under care [3].

A strategic control plan must be established in every hospital, in order to prevent, detect and control the infections and the colonization with multi-antibiotic resistant strains. The plan must include the observation and control measures of the antibiotic use and to state that vancomycin, antibiotic of election for the treatment of MRSA infections, should be strictly used only with that purpose. Medical staff hand washing is a capital measure [4].

Special prevention consists in the use of antibiotics for the treatment of colonized persons in order to reduce the number of pathogenic agent sources. Microbial cultures from the medical staff nasal exudate will be performed whenever the epidemic situation will require it. Decolonization is performed to those persons considered to be permanent carriers through intranasal mupirocin [5].

CONCLUSIONS

The identification of medical staff nasally colonised with Staphylococcus aureus and its decolonization interrupt the exogenous transmission route of this germ responsible for many nosocomial infection cases. These prevention and control measures reduce auxiliary costs necessary for the treatment of nosocomial infections as well as the mortality and morbidity rates.

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THE EXOGENOUS TRANSMISSION VERSUS ENDOGENOUS SELECTION IN CARDIOVASCULAR SURGERY

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REZUMAT

Scop. Detectarea şi evaluarea transmiterii exogene într-o unitate medicală terţiară necesită tehnici pentru determinarea clonalităţii germenilor (PFGE sau AFLP-PCR). În lipsa acestora, studiul şi-a propus investigarea prin metode statistice a posibilităţilor de transmitere nosocomială, într-un institut universitar cu profil cardiovascular, în perioada 2008–2011. Material şi metodă. S-a utilizat un studiu prospectiv, de supraveghere a probelor pentru controlul microbiologic al mediului din secţiile chirurgicale, corelat cu supravegherea investigaţiilor bacteriene efectuate pacienţilor spitalizaţi aici. Analiza statistică a fost efectuată utilizând programul EPI-INFO 2002. Compararea variabilelor nominale caracterizate prin procentaj s-a efectuat prin calcularea testului hi² şi utilizarea la nevoie a corecţiei Fisher. Corelaţia bivariată s-a realizat prin aplicarea coeficientului de corelare Pearson. Rezultate. S-au corelat ratele de frecvenţă a speciilor bacteriene din 367 probe recoltate de pe suprafeţele secţiilor chirurgicale, 97, 154 de la personal, cu cele din 248 probe provenite de la pacienţii chirurgicali. Ratele E.coli de pe suprafeţele secţiilor chirurgicale s-au corelat invers, puternic, semnificativ statistic cu cele de la pacienţi (r= -0,997 cu p=0,05), dar nefiind o corelaţie directă, nu pledează pentru implicarea suprafeţelor în transmiterea agentului patogen nosocomial. Aceeaşi situaţie apare şi în cazul S. aureus din aeromicroflora secţiilor chirurgicale (r= -0,992, p=0,008). Ratele de frecvenţă ale speciilor izolate de la personal nu s-au corelat cu cele din probele pacienţilor. Concluzii. Rezultatele nu au obiectivat transmiterea exogenă în secţiile chirurgicale, principala cauză de apariţie a infecţiilor nosocomiale rămânând selecţia endogenă a unor tulpini condiţionat patogene, ce-şi modifică virulenţa sub acţiunea conjugată a unei multitudini de factori.

Cuvinte cheie: căi exogene, căi endogene, chirurgie cardiacă, suprafeţe de mediu, aeromicrofloră

ABSTRACT

Objective. Identification and assessment of exogenous transmission of germs in a tertiary medical unit require several techniques in order to determine the clonality of germs (PEGE or AFLP-PCR). In the absence of such techniques, the study aimed to investigate the

possibilities of nosocomial transmission using statistic methods in a clinical university institute for cardiovascular diseases, during the period 2008-2011. **Material and method.** *A prospective study was conducted, supervising the environmental microbiological samples collected in surgical units and also the bacterial investigations in patients treated in these units. The statistic analysis was performed by the EPI-INFO 2002 programme. The comparison between nominal variables characterized by percentage was made by the hi^2 test and by using the Fisher correction whenever needed. The bivariate correlation was made by applying the Pearson correlation coefficient/factor.* **Results.** *A correlation was made between the frequency rates of bacterial species from 367 samples, 97 collected from surfaces in surgical units, 154 from the staff and 248 samples from surgery patients. The E.coli rates from surgical surfaces were strongly reversely correlated statistically significant with those taken from patients (r= -0,997 with p=0,05), but since it was not a direct correlation, this does not support the involvement of contaminated surfaces in the nosocomial transmission pathogenic agents. The same situation also occurs in the case of S. aureus in the air samples collected from surgical units (r= -0,992, p=0,008). The frequency rates for the isolated species taken from the personnel did not correlate with those taken from patients.* **Conclusions.** *The results did not demonstrate the exogenous transmission within the surgical units, the main cause of nosocomial infection occurrence being the endogenous selection of some conditionally pathogenic strains which alter their virulence under the conjugated action of multiple factors.*

Keywords: exogenous routes, endogenous routes, cardiac surgery, enviromental surfaces, microbial airflora

INTRODUCTION

The role of the environment in nosocomial infections has been studied and debated for a long time. In 1981, McGowan [1] suggested that the interest in the role of the environemental factors in nosocomial infections appeared due to the fact that these are much easier to compare than other aspects related to this topic. Rhame [2] conducted researches in the role played by the environement in nosocomial infections and established the differences between the types of proofs supporting its involvement. In the end, he concluded that most of the reports barely indicated that a microorganism was isolated from a wound, with or without proliferation, and that the environment could have been infected by patients and not viceversa.

Although the specific literature abound in information about microbial contamination especially in hospitals, most of these articles describe the levels of contamination, not the levels of infection and the prescriptions for the reduction of these contamination levels

do not necessarily result in reduced incidence of nosocmial infections. Even when there is an evident correlation with the rate of infection frequency, the evidence are rare and the direct association with a rare environmental source is hard to prove.

Depending on the infection source and transmission mechanisms, one can identify:
- Endogenous infections – when an endogenous pathogen which colonizes the host organism or is present in a localised infectious process becomes innoculated/ vehiculated/ transmitted in another site (usually through invasive exploratory procedures) resulting in an secondary infectious process.
- Exogenous infections – when the infection is produced by pathogens which come from another patient, from the health care personnel or from the hospital environment.

OBJECTIVE

Identification and assessment of exogenous transmission within a tertiary medical unit require molecular typing techniques in order to determine germ cloning. As the PFGE technique and amplified fragment length polymorphism–PCR were not available for the present study, a direct assessment of the role played by exogenous transmission in the epidemiologic process of nosocomial infections was not possible. Nevertheless, willing to point out the exogenous transmission role versus endogenous selection of nosocomial infectious agents, indirect statistic methods were used corellating the frequency rate of species identified in control samples collected from hospital environment with that of the pathogenic flora isolated in hospitalised patients.

MATERIAL AND METHOD

From November 2007 to November 2011, a study regarding the role of the exogenous transmission versus endogenous selection of nosocomial infectious agents in surgery units of a clinical university institute for cardiovascular diseases was conducted.

In order to collect the microbial air flora we used the Koch sedimentation method. For each room we used 2 groups of 9 cm diameter Petri plates containing simple agar and blood agar, respectively. A group of plates was exposed on a table in the middle of the research room while the second group was placed on a table in a corner of the room. The exposure time was 10 minutes. All plates were incubated at 37ºC with incubation times of 24 hours for blood agar and 48 hours for simple agar plates. The number of germs/m³ air was reported according to the Omelianski formula :

No. of germs/m³ air = N x 10.000 / S x K

N = number of collonies on petri plate
S = the surface of Petri plate in cm² (for a diameter of 9 cm, S = 3.14 x R2 = 63.5 cm²)
K = the exposure time coefficient (factor) (5 min = 1; 10 min = 2; 15 min = 3)

The air microbial charge is acceptable if the total number of germs/m³ <500–1500 - according to the type of activity in the room and to the moment (beginning or end) of the working day.

No coagulase-positive hemolytic staphylo-cocci and β-hemolytic streptococci collonies are admissible.

Sampling from various surfaces was made with a non-hydrophilic cotton pad moistened in 1‰ sterile peptone saline which was used on a square surface with 10 cm on the inner side. In order to prevent the collection pad to dry, it will be discharged in 10 ml of 1‰ sterile peptone saline, left as such for 10-15 minutes and then strongly homogenised (gross dilution- DB). To count the germs in the gross dilution another 1/10 dilution in 1‰ peptone saline is made (decimal dilution-DZ). Both from the gross and from the decimal dilution we inoculated 1 ml on two simple agar Petri plates which were incubated for 48 hours at 37ºC.

The number of germs on cm² of clean surface was calculated with the help of the following formula :

$$\text{No. of germs/cm}^2 = \frac{\text{(no. of colonies DB x 10) + (no. of colonies DZ x 100)}}{2 \text{ X pattern surface (100 cm}^2\text{)}}$$

A surface is considered to be clean if < 5 germs / cm² grow on it and those germs do not include coli bacilli, Proteus bacilli or coagulase-positive staphilococci.

The collection of samples from patients was performed by qualified staff, in sterile containers adequate for each type of sample, stricltly observing the general regulations

for the collection of samples for bacteriological examination. Special attention was given to the collection of these samples because an incorrect collection could damage from the beginning the bacteriological diagnosis.

Germ identification relied on cultural and biochemical characters. Final identification and antibiogram were performed using the Vitek 2 (Bio Merieux France) automatic analyzer.

The statistic analysis of the data resulting from this study was made with the program EPI-INFO version 6.04 (January 2001) and EPI-INFO 2002 (November 2002).

Continuous numerical variables charcterised through the average and standard deviation

were compared by the unpaired t test (Student's t test). The comparison between these nominal variables characterized by percentage was made by calculating the chi squared test and by using the Fisher correction whenever needed. All statistic tests were calculated with 2 extremes and the statistic significance was taken into account at $p \leq 0,05$. The bivariate correlation was made by applying the Pearson correlation coefficient/ factor. Its statistic significance was considered to be $\leq 0,05$ or $\leq 0,01$, according to the statistic indications of the calculating program.

RESULTS AND DISCUSSION

In the two surgical units 367 samples were collected for the microbiological control of surfaces according to Figure 1.
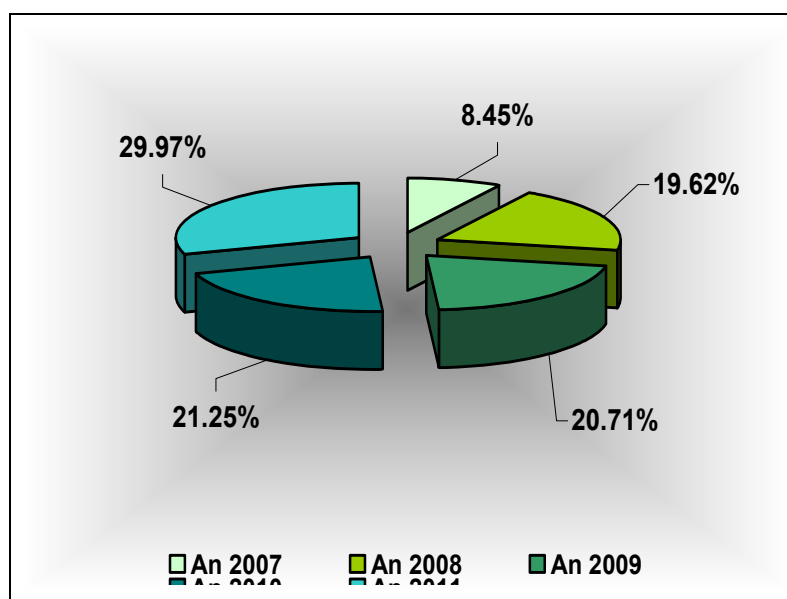

Figure 1. The annual distribution of samples collected from surfaces in surgical units

As shown in Table 1, most of the samples were collected from rooms (128-38.87%) and from the food office (101-27.52%),

followed by those collected from floors (66-17.98%).

Table 1. The distribution of samples collected from various surfaces in surgical units

Year	Surface type	n	%	IC 95%	
2007	Bed sheets	3	9.67%	2.00%	25.80%
	Bathroom surfaces	5	16.13%	5.50%	33.70%
	Food office surfaces	10	32.25%	16.70%	51.40%
	Medical staff office surfaces	3	9.67%	2.00%	25.80%
	Room surfaces	10	32.25%	16.70%	51.40%
	Total	31	100.00%		
2008	Bed sheets	3	4.16%	0.90%	11.70%
	Floor	10	13.88%	6.90%	24.10%
	Bathroom surfaces	12	16.67%	8.90%	27.30%
	Food office surfaces	22	30.55%	20.20%	42.50%
	Room surfaces	25	34.72%	23.90%	46.90%
	Total	72	100.00%		
2009	Bed sheets	1	1.31%	0.00%	7.10%
	Floor	12	15.78%	8.40%	26.00%
	Bathroom surfaces	11	14.47%	7.50%	24.40%
	Food office surfaces	25	32.89%	22.50%	44.60%
	Room surfaces	27	35.52%	24.90%	47.30%
	Total	76	100.00%		
2010	Oxygenator surface	2	2.56%	0.30%	9.00%
	Floor	17	21.79%	13.20%	32.60%
	Bathroom surfaces	14	17.94%	10.20%	28.30%
	Food office surfaces	19	24.35%	15.30%	35.40%
	Room surfaces	26	33.33%	23.10%	44.90%
	Total	78	100.00%		
2011	Bed sheets	2	1.81%	0.20%	6.40%
	Floor	27	24.54%	16.80%	33.70%
	Bathroom surfaces	16	14.54%	8.50%	22.50%
	Food office surfaces	25	22.72%	15.30%	31.70%
	Room surfaces	40	36.36%	27.40%	46.10%
	Total	110	100.00%		

The Student-test led to the conclusion that the total number of germs/cm2 remained constant during the entire period, as shown in Table 2.

Table 2 .The variation of the average number of germs/cm^2 in surgical units

Year	Average number of germs/cm^2	Variation	p	p
2007	30.61	7240.04	0.707	
2008	36.76	5189.90		0.676
2009	43.68	14748.01	0.956	
2010	44.76	15250.8		0.109
2011	25.18	805.21		
Total	35.88	8138.36		

In 18.98% of the samples pathogenic germ collonies developed, thus supporting the nosocomial risk of environmental surfaces through cross contamination (Table 3).

Table 3. The distribution of samples from the surgical units according to the presence/ absence of pathogenic germs colonies

Year	N samples	N Conformity samples	% Conformity samples	IC 95%		N Non-conformity samples	% Non-conformity samples	IC 95%	
2007	31	23	74.19%	55.40%	88.10%	8	25.80%	11.90%	44.60%
2008	72	62	86.11%	75.90%	93.10%	10	13.89%	6.90%	24.10%
2009	76	58	76.31%	65.20%	85.30%	18	23.68%	14.70%	34.80%
2010	78	64	82.05%	71.70%	89.80%	14	17.94%	10.20%	28.30%
2011	110	94	85.45%	77.50%	91.50%	16	14.54%	8.50%	22.50%
Total	367	301	82.01%	77.70%	85.80%	66	18.98%	14.30%	22.40%

Apart from most of the samples which did not present bacterial growth or from which CNS strains were isolated, a larger amount of gram negative bacilli, especially Acinetobacter baumannii could be noticed in the food office.

Since there is a high nosocomial risk in surgical units, the survey of the hospital environment is much more careful, which can be seen also in the great number of samples collected. For the analysis of the air microbial charge, during the studied period, 97 samples were collected, with the following annual distribution (Table 4).

Table 4. The annual distribution of air microbial flora samples from surgical units

Year	N	%	IC 95%	
2007	6	6.18%	2.30%	13.00%
2008	17	17.52%	10.60%	26.60%
2009	17	17.52%	10.60%	26.60%
2010	23	23.71%	15.70%	33.40%
2011	34	35.05%	25.60%	45.40%
Total	97	100.00%		

After calculating the statistical significance value (p), we can confirm that a significant growth of the average number of germs /m3 was registered in 2010 as compared to 2009. For the other variable, the evolution was steady throughout the period. (Figure 2).
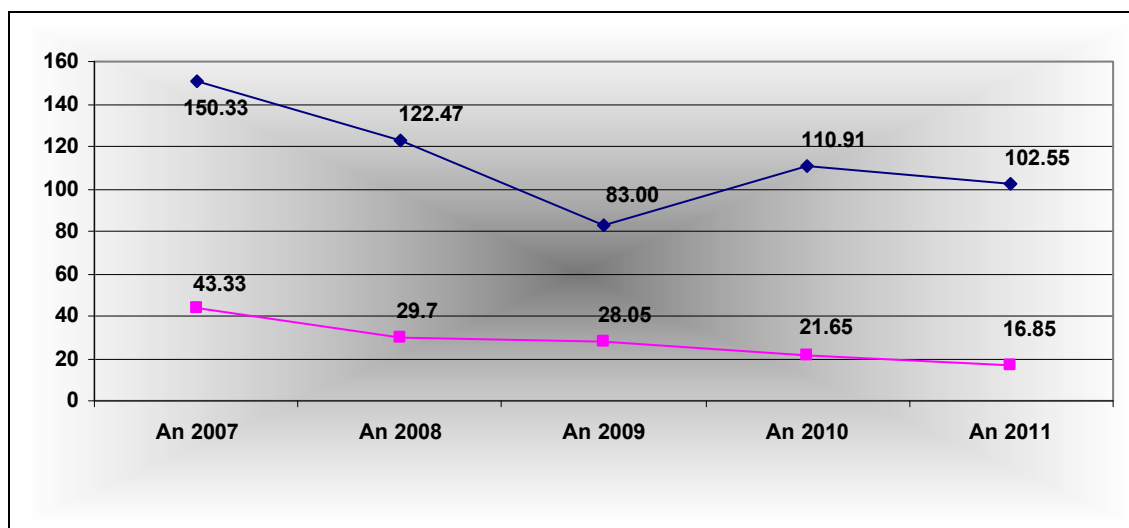
Figure 2. The evolution of air microbial charge in surgical units

From the 97 samples, 96 (98.96%) presented hemolytic colonies, as for the distribution of identified species, a better representation of gram negative germs can be noticed. Among the species of fungi we identified Aspergillus niger, Microsporum spp. şi Penicillinum spp. During the investigated period, 72 persons belonging to the medical staff were examined- ICU; surgical wards (Figure 3).
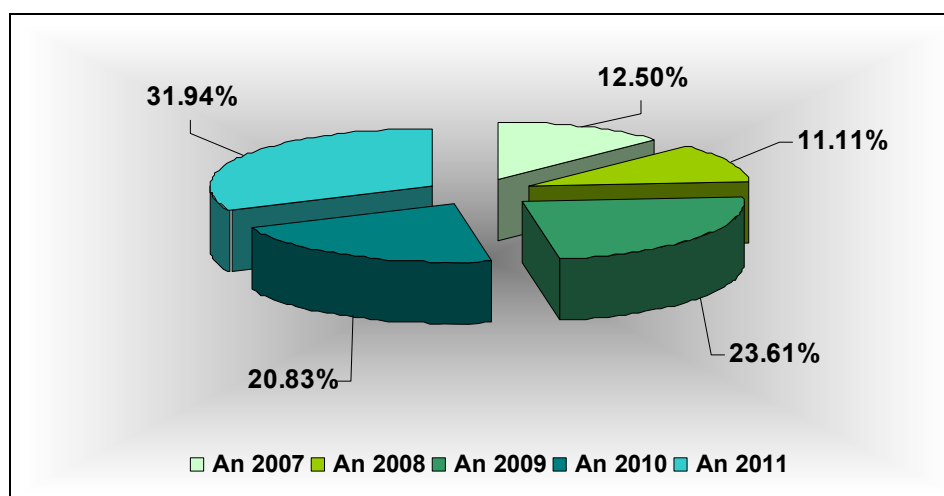

Figure 3. The annual distribution of surgical staff microbiologically investigated

Forty nine persons were females (68.05%) the remaining 23 (31.94%) being males. 154 microbiological examinations were performed. Almost half of the investigations revealed a pathogenic germs, which can generate nosocomial risk for the assisted patients (Table5).

Table 5. The distribution of samples collected from surgical staff according to the pathogenity

Year	Non-pathologic samples				Pathologic samples			
	n	%	IC 95%		n	%	IC 95%	
2007	5	45.45%	16.70%	76.60%	6	54.54%	23.40%	83.30%
2008	9	69.23%	38.60%	90.90%	4	30.77%	9.10%	61.40%
2009	16	47.05%	29.80%	64.90%	18	52.94%	35.10%	70.20%
2010	19	47.50%	31.50%	63.90%	21	52.50%	36.10%	68.50%
2011	35	62.50%	48.50%	75.10%	21	37.50%	24.90%	51.50%
Total	84	54.54%	46.30%	62.60%	70	45.45%	37.40%	53.70%

Most of the samples contained pathogenic microbial flora (41.14%) or S. aureus strains (31.01%), with the rest revealing the growth of gram negative strains or micrococci.

During 2008-2011, 161 patients admitted in cardiovascular surgery units required microbiological investigations, the frequency going higher in 2010 (Figure 4).
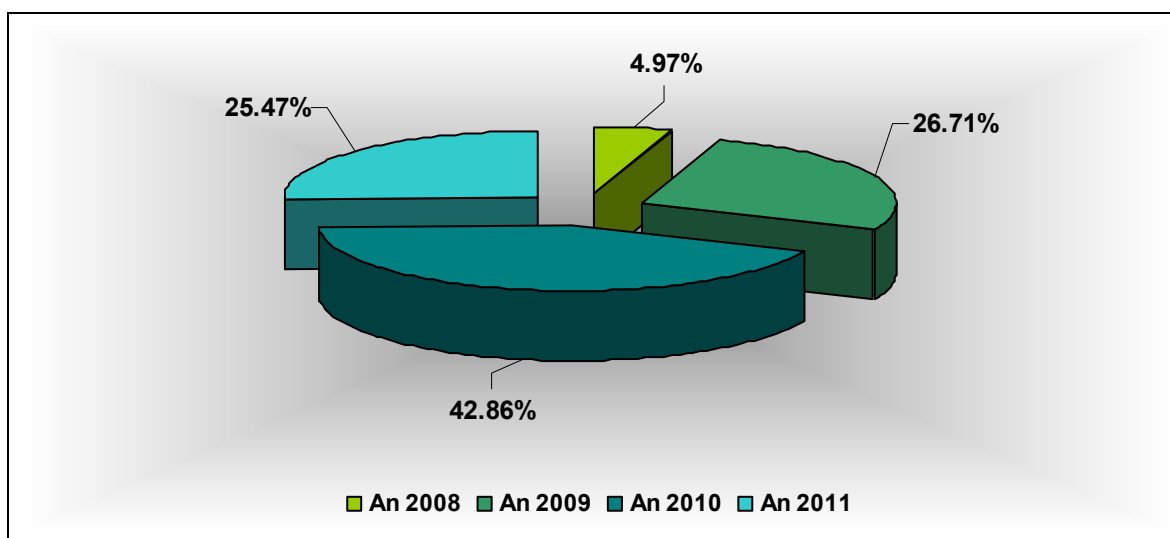
Figure 4. The annual distribution of patients in surgical units

From these patients, 248 samples were collected, most of them secretions of postoperative wounds (160-64.51%) but also other pathological products. In 12 samples no pathogenic flora was cultivated and from the rest, 242 strains were isolated (3 Candida spp., 239 bacterial strains). According to the microbial types identified, the first 3 places were represented, in

descending order, by S.aureus (in 58 pathological products – 23.38%), E.coli and CNS (in 16 samples – 6.45%).

The analysis of the flora residing on surfaces in surgical units and isolated from patients is synthesised in the following table (Table 5).

Table 5. The correlation between pathogenic agents identified on surfaces in surgical units and those isolated in patients

Year	Result	N samples=367 % surfaces	N samples=248 % patients	p
2008	CNS	61.11%	11.11%	<0.001
	S.aureus	4.16%	44.44%	0.002
2009	CNS	42.10%	7.35%	<0.001
	S.aureus	10.52%	29.41%	0.008
	E.coli	3.94%	5.88%	0.707
2010	CNS	51.28%	4.58%	<0.001
	S.aureus	2.56	16.51%	0.002
	E.coli	1.28%	7.34%	0.082
	Enterobacter aerogenes	5.12%	0.92%	0.162
	Acinetobacter baumannii	3.84%	0.92%	0.309
	Klebsiella spp.	3.84%	0.92%	0.309
	Serratia marcescens	1.28%	1.83%	1
2011	CNS	60.90%	9.67%	<0.001
	S.aureus	6.36%	25.80%	<0.001
	E.coli	2.72%	6.45%	0.253
	Klebsiella spp.	2.72%	4.83%	0.668
	Pseudomonas spp.	1.81%	4.83%	0.352

Apparently, the highest number of correspondent species can be found in 2010, which is the year with the greatest frequency of nosocomial infections in surgical units. Also, two main patterns can be noticed:

- the two types of samples show statistically significant differences regarding the frequency of gram positive germs (CNS more frequent on surfaces, but rarely found in bacterial agents isolated from patients, while the case of S.aureus is exactly opposite), which indirectly supports the low involvement of surfaces in the transmission of these germs. Actually, the correlation index for CNS was -0.218 with p=0.782 and for S.aureus r=0,127 with p =0.873

- the gram negative – especially E.coli was found in statistically similar proportions from both on surfaces and in patients in 3 of the 4 years of study. The correlation index r = - 0.997 with p=0.05 show a strong, statistically significant, inversed correlation, this reducing the possibility of surface involvement in nosocomial pathogenic agent transmission.

The same analysis was applied to air microbial flora from surgical units and to germs isolated in samples collected in medical staff, the results being synthesised in the following tables. (Tables 6, 7).

Table 6. The correlation of pathogenic agents identified in the air microbial flora collected in surgical units and in patients

Year	Result	N samples=97	N samples=248	p
		% air microbial flora	% patients	
2008	CNS	82.35%	11.11%	<0.001
	S.aureus	5.88%	44.44%	0.034
2009	CNS	88.23%	7.35%	<0.001
	S.aureus	17.64%	29.41%	0.542
2010	CNS	100%	4.58%	<0.001
	S.aureus	26.08%	16.51%	0.370
	Serratia marcescens	13.04%	1.83%	0.037
	Klebsiella spp.	4.34%	0.92%	0.319
2011	CNS	64.70%	9.67%	<0.001
	S.aureus	17.64%	25.80%	0.362
	Klebsiella spp.	5.88%	4.83%	1
	Pseudomonas spp.	2.94%	4.83%	1

The coagulase-negative staphylococci, widely spread in the air microbial flora but rarely identified in patient samples, aspect pointed out by the steady statistically significant differences observed during the study period, cannont be transmited through contaminated air (r = -0.752, p=0.248). As for S.aureus, in 3 from the 4 years, the percents were similar, they inversely correlated, with statistic significance (r = -0.992, p = 0.008), but the inverse correlation reduces the suspicion of air transmission. The constant presence of fungi in the air microbial flora was not accompanied by similar identification frequency in patients. Also, Acinetobacter baumannii was more frequent in air samples, while constantly absent in bialogical samples collected from patients.

Table 7. The correlation between pathogenic agents identified in samples collected from the staff of surgical units and those isolated in patients

Year	Result	N samples=154	N samples=248	p
		% staff	% patients	
2008	*S.aureus*	23.10%	44.44%	0.376
	Non-pathogenic flora	46.20%	11.11%	0.164
2009	*S.aureus*	31.40%	29.41%	0.922
	Non-pathogenic flora	34.30%	2.94%	<0.001
	CNS	8.60%	7.35%	1
	E.coli	11.40%	5.88%	0.435
	Candida albicans	2.90%	1.47%	1
2010	*S.aureus*	39.00%	16.51%	0.002

	Non-pathogenic flora	36.60%	5.50%	<0.001
	CNS	2.40%	4.58%	1
	E.coli	9.80%	7.34%	0.734
	Klebsiella spp.	2.40%	0.92%	0.466
2011	*S.aureus*	24.10%	25.80%	0.919
	Non-pathogenic flora	55.20%	4.83%	<0.001
	CNS	3.40%	9.67%	0.277
	E.coli	1.70%	6.45%	0.367
	Klebsiella spp.	3.40%	4.83%	1
	Group F Streptococci	1.70%	3.22%	1

The samples with non-pathogenic flora were significantly more frequent in medical staff because the frequency of nasal exudates made for the control carrier status was higher in the total number of samples collected from the medical staff as compared to patients. S. aureus, although recording similar frequency rates both in patients and in the medical staff, did not statistcally correlate (r = -0.774, p=0.226). E.coli, and the species with similar statistic percents, did not correlate (r=-0.029, p=0.982). Proteus spp., Serratia spp., Enterobacter spp., Pseudomonas aeruginosa, Acinetobacter baumannii, Stenotrophomonas maltophilia were found only in patients and not in the medical staff, so we can neither support nor eliminate an exogenous transmission in these cases, given the ubiquitous character of nonfermentative germs in hospital environment, and the efficient transmission potential of medical staff hands.

Although the statistic analysis did not point out the frequency of exogenous transmission, the correlation between the resistance of the strains isolated from various elements of the nosocomial enviroment and between these and the strains collected from patients was performed, all these being components of the bacterial circulating population, knowing the bidirectional relationship – the patients contaminate the nosocmial

environment but this one also can determiune the colonisation/infection of patients.

In surgical units there were identified: direct, strong, significantly statistic correlation between the resistance of strains isolated from the medical staff and of those from the air microbial flora, and a direct but mild correlation with the resistance of the strains isolated from samples collected on surfaces (which support the colonisation of the medical staff by the internal hospita flora); between the resistance of the patient flora and that from the surfaces/air there are direct, medium, significant correlations; and between the resistance of strains from the air microbial flora versus those from the surfaces or between the sensitivity of the patients and that from the medical staff mediun and weaker correlations were identified.

Robert A. Weinstein et al claim that the role of surfaces in nosocomial infection transmission is controversial. The fact that pathogens were isolated from the hospital environment is not enough to prove that they play an important role in infection pathogenesis. Enterobacteria are unlikely to be transmitted to patients from surfaces, as they do not survive long enough in the air. Enterobacteria infections mainly occur due to the endogenous pathway or to cross-contamination among patients through the

hands of the medical staff. They also show that Pseudomonas aeruginosa infections mainly come from the endogenous flora in comparison with the exogenous flora. Although they survive very well in the environment, some Acinetobacter baumannii strains affect patients while others were not found in patients [3]. D'Agata EM et al identified Acinetobacter baumannii infection outbreaks in patients, without identifying these germs in the environment [4].

Robert A Weinstein and co-workers show that the major source of MRSA is represented by patients and occasionally by the medical staff and its transmission mechanism is through the hands of the medical staff. The role of the environment is controversial, the environment-patient transmission is not well documented and the contamination of the environment is variable. Boyce JM and co-workers reached the conclusion that there are few evidence supporting the fact that reducing the MRSA contamination of the environment actually leads to the decrease of the infection rate [5].

David J. Webber and his co-workers sustain the fact that the major source of nosocomial pathogens is the endogenous flora, while 20-40% of the nosocomial infections were assigned to cross-contamination through the hands of the medical staff. More rarely the patients are contaminated with pathogens through direct contact with the environmental surfaces. These researchers also proved that in many Acinetobacter baumanii outbreaks they could notice a high contamination of the environment with this germ, its frequency being of 3-50%. Markogiannakis and co-workers proved also the colonisation of the medical staff hands in proportion of 28.6% [7].

Bootsma MC and co-workers, relying on algorithm, proved that the endogenous pathway is much more important than the exogenous one [8].

Orgunsola FT and co-workers isolated from the surfaces the following germs: S. aureus (39.3%), Klebsiella pneumoniae (24.6%), CNS (13.7%), E. coli (8.3%), Pseudomonas aeruginosa (9%), Proteus mirabilis (1.8%), Enterobacter aerogenes (0.4%) and other germs [9].

Alireza A shows that the role of the microbial air flora in the pathology of nosocomial infections has been underestimated. The isolation rates were: P. aeruginosa (29%), Acinetobacter sp. (19%), Proteus sp. (12%), Stenotrophomonas maltophilia (11%), Enterobacter sp. (9%), other germs (20%) [10].

Quediesat K. and co-workers state that the main source of pathogenic agents in the air are actually the infected patients, finding the following rates: S. aureus (16.2%), Micrococcus luteus (13.3%) and CNS (13%), and fungi Aspergillus sp. (6%), Penicillum sp. (2%) [11].

Awosika SA and co-workers show that, although many of the isolated species are potentially pathogenic, a correlation between them and reported nosocomial infections was not found. That is why, the contribution of the microbial air flora to their occurrence was not pointed out. The most frequently isolated strains were S. aureus, B. cereus, Klebsiella sp, Serattia marcescens, B. subtilis, S. pyogenes, and fungi Aspergillus sp, Penicillium sp. and Candida albicans [12].

CONCLUSIONS

1. A direct, strong, significantly statistic correlation has been identified between the resistance of strains isolated from the medical staff and those from the air microbial flora, and a direct but moderated correlation with the resistance of strains cultivated from surfaces (supporting the colonisation of medical staff by hospital flora).
2. This study together with literature data confirm that the endogenous pathway

through which pathogenic agents reach the infection site is much more frequently involved as compared to the exogenous transmission.

3. Pointing out the endogenous route does not eliminate the possibility of punctiform exogenous route in certain patients.

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HACCP – A CONSUMER SAFETY MANAGEMENT SYSTEM

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REZUMAT

Sistemul HACCP este o normă internaţională pentru sistemul de management al siguranţei alimentelor şi siguranţei farmaceutice, reprezentând o abordare sistematică preventivă a riscurilor fizice, chimice şi biologice cu care se confruntă industria alimentară şi cea farmaceutică. În industria alimentară, HACCP este utilizat pentru a identifica posibilele riscuri pentru siguranţa alimentelor şi pentru a lua acţiunile necesare pentru reducerea şi eliminarea acestor riscuri. Sistemul este utilizat în toate etapele de producţie ale industriei alimentare, atat în procesele de preparare, dar şi ambalare, transport, depozitare etc. Devenit obligatoriu pentru toţi producătorii din industria alimentară a Uniunii Europene, sistemul de management HACCP este deosebit de important atât pentru certificarea acestora dar, mai ales, prin respectarea lui, a menţinerii producţiei alimentare la nivelul de calitate stabilit.

Cuvinte cheie: *HACCP, siguranţa alimentelor, riscuri*

ABSTRACT

Hazard analysis and critical control points (HACCP) is an international norm for the food and pharmaceuticals safety management system, representing a systematic, preventive approach for physical, chemical and biological risks confronting the food and pharmaceutical industries. In food industry, HACCP is used to identify possible risks to food safety and to take the needed actions to reduce and eliminate these risks. The system is used in all production stages of food industry, in processing, as well as in packaging, transport, storage, etc. As it became mandatory for all European Union producers in food industry, the HACCP management system is extremely important both for their certification and, especially, for maintaing the predefined quality level of food production.

Keywords: *HACCP, food safety, hazards*

INTRODUCTION

HACCP is the acronym for "Hazard Analysis and Critical Control Point". This concept has been developed in the USA at the beginning of the '60s by the Pillsbury Company in order to respond to the requirements of a NASA initiated project. The purpose of the project was to ensure the microbiological safety of foods for astronauts in the Mercury and Gemini spatial programmes.

The HACCP concept was publicly released for the first time by Pillsbury in 1971, at the National Conference for Food Protection, and 2 years later, the Food and Drug Organization introduced the HACCP system

as a mandatory requirement in the US federal legislation concerning low acid conserved products, following a severe food poisoning (the Vivant Bon Vichyssoise Soup – botulinum toxin intoxication) which resulted in deaths among consumers.

Food producers must fulfil all stated criteria throughout the entire production process, to make sure that all adjacent raw materials are in conformity, to strictly adhere to the entire applicable legislation and to verify that the end product is safe for human consumption. The sequence described by HACCP starts at the farm providing the primary food and ends with the end product reaching the consumer. The sold food product must strictly correspond with the technical specifications, physico-chemically and microbiologically.

At the same time, HACCP makes reference to prior implementation of good manufacturing practices concerning the construction of units, equipment positioning, technological processes, personnel, cleaning and disinfection, pest control, raw and auxilliary materials, including water, product traceability, transport.

HACCP PRINCIPLES AND DEVELOPING A HACCP PLAN

The HACCP Methodology has been internationally standardised by the Codex Alimentarius Commission created by the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) for developing food standards.

Codex Alimentarius elaborates: quality standards, health and security related standards, nutrition standards and methods for uniform standardisation. Food standards, guidelines and other recommendations elaborated by Codex Alimentarius rely only upon well fundamented scientific analysis and evidence involving an in depth study of all relevant information, in order for the respective standards to ensure the quality and safety of food products.

Developing a HACCP plan includes several stages which take into consideration the 7 principles of this management system:

I. Assemble the HACCP team

II. Describe the food and its distribution

III. Describe the intended use and consumers of the food

IV. Develop a flow diagram which describes the process (raw material, ingredients, packaging, expedition)

V. Verify the flow diagram

VI. Conduct a hazard analysis (Principle 1):
- Storage space: a final product must not come into contact with the raw material;
- Packaging: manual or automated, equipments used for packaging, safety system;
- Hygiene and health of staff, personal protection equipments;
- Food storage conditions until expedition.

VII. Determine critical control points (CCPs) (Principle 2)

VIII. Establish critical limits (Principle 3) – e.g. milk pasteurization, sterilisation of meat cans, pH of soft drinks

IX. Establish monitoring procedures (Principle 4) – establish responsible staff for critical control points

X. Establish corrective actions and procedures to follow in case of nonconformities (Principle 5)

XI. Establish record-keeping and preventive procedures (Principle 6)

XII. Verification of the place for HACCP functioning (Principle 7) – external experts may be involved.

Table 1. Examples of How the Stages of Hazard Analysis are used to Identify and Evaluate Hazards [4]

Hazard Analysis Stage		Frozen cooked beef patties produced in a manufacturing plant	Product containing eggs prepared for foodservice	Commercial frozen pre-cooked, boned chicken for further processing
Stage 1 Hazard Identification	*Determine potential hazards associated with product*	Enteric pathogens (i.e., E. coli O157:H7 and Salmonella)	Salmonella in finished product	Staphylococcus aureus in finished product.
Stage 2 Hazard Evaluation	*Assess severity of health consequences if potential hazard is not properly controlled.*	Epidemiological evidence indicates that these pathogens cause severe health effects including death among children and elderly.	Salmonellosis is a food borne infection causing a moderate to severe illness that can be caused by ingestion of only a few cells of Salmonella.	Certain strains of S. aureus produce an enterotoxin which can cause a moderate foodborne illness.
	Determine likelihood of occurrence of potential hazard if not properly controlled.	E. coli O157:H7 is of very low probability and salmonellae is of moderate probability in raw meat.	Product is made with liquid eggs which have been associated with past outbreaks of salmonellosis. Recent problems with Salmonella serotype Enteritidis in eggs cause increased concern. Probability of Salmonella in raw eggs cannot be ruled out.	Product may be contaminated with S. aureus due to human handling during boning of cooked chicken. Enterotoxin capable of causing illness will only occur as S. aureus multiplies to about 1,000,000/g. Operating procedures during boning and subsequent freezing prevent growth of S. aureus, thus the potential for enterotoxin formation is very low.
	Using information above, determine if this potential hazard is to be addressed in the HACCP plan.	The HACCP team decides that enteric pathogens are hazards for this product. **Hazards must be addressed in the plan.**	HACCP team determines that if the potential hazard is not properly controlled, consumption of product is likely to result in an unacceptable health	The HACCP team determines that the potential for enterotoxin formation is very low. However, it is still desirable to keep the initial number of S. aureus organisms low. Employee practices that minimize

			risk. **Hazard must be addressed in the plan.**	contamination, rapid carbon dioxide freezing and handling instructions have been adequate to control this potential hazard. **Potential hazard does not need to be addressed in plan.**

*Source: Food and Drug Administration

WHAT RISKS MAY OCCUR IN FOOD INDUSTRY?

Food products may be contaminated during processing, packaging, storage or transportation, with both microbiological and chemical risks which foods may transmit to consumers.

Of the frequently transmitted microorganisms we mention bacteria transmitted through vegetables and fruits, such as Salmonella typhi, Clostridium botulinum, Esherichia coli, Brucella melitensis, Koch's bacillus, streptococci, staphylococci, parasites transmitted with meat products, represented by Trichinella spiralis, Taenia solium, Taenia saginata larvae but also by vegetables and fruits: ascarids, nematodes or Giardia spp., but also viruses such as hepatitis A virus or aphthous fever virus.

Also, there is the risk of chemical contamination of foods with harmful chemicals, the main contamination sources being the soil, water, air chemically contaminated with further concentration of these substances in vegetal foods, and then in the food chain of animals and humans.

Chemicals may come from the use of pesticides used for pest control (insecticides, fungicides, herbicides), during certain procedures of the production process (e.g. polycyclic aromatic hydrocarbons with cancerigenic effect which result during the process of smoke treatment of various meat products) or are represented by toxic metals (lead, mercury, arsenic) coming from poor quality equipments and package materials, mycotoxins released by molds developed on the surface of products stored in improper conditions (e.g. aflatoxin B1 secreted by Aspergillius species is one of the most carcinogenetic substances known, targeting the liver).

LEGISLATION

The implementation of the HACCP system is a legal requirement, stipulated in the Government Decision 1198/2002 – General hygiene conditions for food products, art. 3 and 4 and in the Law no. 150/2004 – regarding the safety of food products. Adhering to the European Union, Romania adopted the community legislation concerning the hygiene of food products, and thus the implementation and maintenance of a food safety system based upon the HACCP principles became mandatory for all food operators (producers, processors, those acting in pre-production stages).

Table 2. The main food safety regulations

International legislation	Domestic legislation
• European Commission White Paper on Food Safety, Bruxelles 2000; • Directive 89/109/EEC of the European Council concerning materials and objects coming into contact with foods; • Regulation (EC) 1642/2003 of the European Parliament and of the European Council for the amendment of the Regulation (EC) 178/2002 laying down the general principles and requiremens of food legislation, establishing the European Authority for Food Safety and the procedures in the field of food products safety; • Regulation (EC) 852/2004 of the European Parliament and European Council regarding the hygiene of food products; • Regulation (EC) 882/2004 of the European Parliament and of the European Council on official inspections to verify compliance with legislation regarding animal feed and food products; • Regulation (EC) 1441/2007 of the Commission for amending the Regulation (EC) 2073/2005 on the microbiological criteria for food products.	• Ministry of Health (MoH) Order 1956/1995 regarding the introduction and implementation of the HACCP in the food production; • MoH Order 975/1998 approving the Hygene-Sanitary Norms for foods; • MoH Order 976/1998 approving the Hygiene Norms regarding production, processing, storage, conservation, transport and retail; • Emergency Ordinance 97/2001 regulating the production, circulation and selling of foods; • Government Decision 1197/2002 aproving the norms for materials and objects which come into contact with food products; • Government Decision 1198/2002 approving the Hygiene Norms for food products; • Government Decision 106/2002 on food labeling; • Law no. 150/2004 on food and animal feed; • Government Decision 924/2005 aproving the General Rules for the hygiene of food products; • Government Decision 984/2005 establishing and sanctioning contraventions to veterinary norms of sanitation and for food safety.

The HACCP certification organism is accredited by RENAR for certifying HACCP systems and functions in the structure of SIMTEX-OC according to the requirements of SR EN ISO 45012.

CONCLUSIONS

The advantages of the HACCP management system are numerous:
- ➢ Current and potential risks may be identified and removed;
- ➢ A higher confidence in food products safety is offered;
- ➢ The control of various parameters is easier to monitor;
- ➢ Diminishing costs by decreasing waste and rejects;
- ➢ More effective costs than those for chemical and microbiological tests;
- ➢ Continuous improvement of food safety practices;
- ➢ International acknowledgement.

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STUDY ON EXTREME HEAT BIOMETEOROLOGICAL CONDITIONS IMPACTING HUMAN HEALTH

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REZUMAT

În baza datelor zilnice pe termen lung ale temperaturii aerului prin intermediul indicilor biometeorologici, au fost evaluate evenimentele extremale de căldură în vara anului 2007 în Republica Moldova. S-a constatat că temperatura aparentă a depăşit percentila a 95-a ca şi criteriu al rarităţii evenimentului 20 zile într-o lună, în timp ce conform indicelui Humidex, în lunile iulie şi august au fost considerate cu disconfort vizibil până la 10 de zile. Creşterea valorilor deviaţiilor pozitive ale indicilor biometeorologici are cel mai mare impact asupra sporirii mortalităţii suplimentare în mediul urban şi regiunea de sud a ţării. Rezultatele obţinute pot servi drept bază pentru elaborarea Planului Naţional de Acţiuni pentru reducerea impactului negativ asupra sănătăţii publice, inclusiv pentru crearea unui Sistem Naţional de avertizare timpurie privind vremea caniculară, sistem axat pe prevenirea riscurilor pentru sănătate.

Cuvinte cheie: *temperatura aparentă, Humidex, evenimente extremale de căldură, decese în exces*

ABSTRACT

On the basis of long-term daily data of air temperature by means of two biometeorological indices the extreme heat events during the summer of 2007 in the Republic of Moldova were estimated. It was found during 20 days in a month the Apparent Temperature exceeded the 95th percentile of the event's rarity, while in accordance with Humidex index up to 10 days in July and August were considered with visible discomfort. Raising the values of positive deviations of biometeorological indices has the greatest effect on increasing mortality in the urban area and southern region. The obtained results can serve as a basis for the development of the National Action Plan on reducing the negative impacts on public health and for the creation of the National Heatwave and Health Early Warning System focused on prevention of health risks.

Keywords: apparent temperature, Humidex, extreme heat events, excess deaths

INTRODUCTION

In recent decades many scientific studies focused on the study of climate extremes, including heat waves, because of their impact on ecosystems and human society. One of the reasons for such interest is a

concern that the frequency and the severity of these phenomena have recently increased, especially in Europe, and that this trend will continue due to global warming [1]. Moreover, the unusually hot summers in recent years, more and more often observed in various regions of the world, support the idea that such a future could be not too far away. The extremely hot summer of 2003 in Western Europe claimed thousands of lives (44 000 excess deaths in 12 European countries) and caused great damage to the economy of many countries [2]. Summer heat in 2007 affected a number of countries in South-Eastern Europe, including Greece, Hungary, Romania, Bulgaria and others. This year was one of the warmest in the history of instrumental observations in the Republic of Moldova (RM), when long-term temperature records were broken during the winter, spring and especially in the summer [3]. Given the hot summer climate of the country, the continuation of this trend can lead to very negative consequences for all biological systems, primarily affecting the most vulnerable components – agriculture and human health. The hot weather of summer 2007 has led to both direct and indirect impacts on human health, reflected in the increase in ambulance calls and in the increase in total mortality, particularly from cardiovascular diseases among the elderly. As it was shown in a study of Corobov and Opopol [4,5], the direct effect of heat in the summer of 2007 in Chisinau has resulted in 200 excess deaths.

When temperature and humidity are high, people can be subjected to considerable thermal stress. In the USA, extreme heat can have a greater impact on human health [6,1] than any other severe weather, especially among the elderly [7,8].

The increase in the frequency of stressful weather days, expressed by unfavorable biometeorological indices, including very high and very low temperatures, may increase the risk for morbidity and mortality. To explain a heat stress on a human body in different environments many biometeorological indices were developed. These indices give a somewhat relative level of the human body comfort in a certain environment, e.g. PET (Physiological Equivalent Temperature), Apparent Temperature, PMV (Predicted Mean Vote) etc. Other indices not specifically designed to examine the human biometeorology have also been widely applied in studies on human comfort. A current example is the Spatial Synoptic Classification (SSC) [9], a categorization of air masses, which serves as the basis for implementation of warning systems of heat effects on public health worldwide [10,11].

In practice, two well known indices are frequently applied, which are oriented to study the human thermal comfort - Apparent Temperature (AT), used in the U.S. warning system of the National Oceanic and Atmospheric Administration (NOAA) [12] and Humidex, that is used by the Canadian Centre for Occupational Health and Safety to warn and prevent the adverse health effects of heat [13].

From this point of view, it is very important to estimate the unusually hot weather by biometeorological indices that allow us to estimate the reaction of the human body when exposed to high ambient temperatures. Using these indices allowed us to analyze the thermal characteristics of the summer of 2007, exceptional hot in the Republic of Moldova, with respect to their effect on human health, expressed as excess deaths.

MATERIALS AND METHODS

Complex effects of temperature and humidity on health can not be measured directly, but can be evaluated by calculating the Apparent Temperature developed by R. Steadman [14]. Currently, the AT is used in different variations, taking into account other parameters (wind speed, solar radiation etc.), and often referred to as the Heat Index.

In the study of R. D. Gaffen and Ross [15] by means of AT the extreme heat event is defined as any day when mean, maximum and minimum apparent temperatures exceed the 85th percentile of the baseline period (1961-1990). Biometeorological studies have shown that excess (or supplemental) deaths occur when the apparent temperature exceeds the 85th, 90th and 95th percentiles [16, 10, 17, 18]. In our analysis we used the 95th percentile, which is defined by IPCC as a threshold of very rare events [19]. Days with the mean, maximum and minimum apparent temperature exceeding the 95th percentile of the baseline period are determined as extreme heat events.

Humidex is a Canadian innovation, first used in 1965. This index was developed by Canadian meteorologists to describe how the average human experiences hot and humid weather conditions. Humidex combines temperature and humidity into a unique value reflecting the perceived temperature [20, 21]. Table 1 shows the scale of Apparent Temperature and Humidex values with a degree of precaution and comfort level for the human body.

Table 1. Scale of Apparent Temperature (ºC) and Humidex

Apparent Temperature			Humidex		
Diapason		*Level of precaution*	*Diapason*		*Level of comfort*
27–32 °C	1	**Caution** – Fatigue possible with prolonged exposure and/or physical activity	Less than 29°C	1	Little or no discomfort
			30 - 34°C	2	Noticeable discomfort
32–41 °C	2	**Extreme Caution** – Sunstroke, muscle cramps, and/or heat exhaustion possible with prolonged exposure and/or physical activity	35 - 39°C	3	Evident discomfort
41–54 °C	3	**Danger** – Sunstroke, muscle cramps, and/or heat exhaustion likely. Heatstroke possible with prolonged exposure and/or physical activity	40 - 45°C	4	Intense discomfort; avoid exertion
			Above 45°C	5	Dangerous discomfort
Above 54°C	4	**Extreme Danger** – Heat stroke or sunstroke likely	Above 54°C	6	Heat stroke probable
Exposure to full sunshine can increase AT values by up to 8ºC					

The advantage of biometeorological indices' gradations lies in estimating the body response to heat stress, which in turn determines the level of risk and appropriate preventive measures. The downside is expressed by the standardized grading scale, indifferent to the regional characteristics of the thermal regime in the studied territory. In our case, to assess the effects of extreme heat in such a small country as the Republic of Moldova, this scale is appropriate. However, a threshold temperature of excessive heat, which has impact on health, should be based on knowledge of local cause and effect relationship between temperature and mortality as an indicator of public health.

Important concepts in the study of "temperature-mortality" relationships are death associated with heat, and death from all causes. Death associated with heat is defined as death when exposure to high ambient temperatures either caused death or contributed to it. The main cause of death used in epidemiological studies is sufficient to characterize the relationship between temperature and mortality, although the associated cause of death can also be used [22].

The material of our study was represented by total daily mortality from all causes data in Chisinau and in 3 regions in the North (Falesti), Center (Anenii Noi) and South (Cahul) of the country. Data on daily mortality were obtained from the death certificates archived at the National Center for Health Management. The total population in the four studied regions is 1 million 85 thousand 400 people (1/3 of the total country population). Additional mortality (excess deaths) was estimated as the difference between the number of deaths in 2007 and the average mortality during the reference period (2001–2010, excluding 2007 as abnormal).

Meteorological daily data (mean, maximum and minimum and dew point temperatures) on four appropriate weather stations (Chisinau, Balti, Balti and Cahul) were provided by the State Hydrometeorological Service of the RM. This initial data are used for the calculation of Apparent Temperature and Humidex indices. In our study, the summer period (June-July-August) of 1961-1990 (baseline period) and the exceptionally hot year of 2007 were investigated. There are no missing values in the datasets over the studied period.

To establish the relationship between biometeorological indices and excess deaths the simple linear regression was used as a suitable statistical instrument, showing the power, significance and value of such relation.

Statistical computations were performed by means of StatGraphics Centurion Data Analysis and Statistical Software.

RESULTS AND DISCUSSION

The recent scientific studies [23,24] have shown that the Republic of Moldova is already living in new climate conditions caused by the global warming, that leaves little hope for adapting the natural and social systems [25]. One of the features of this climate is the thermal regime toughening during the summer heat – frequent heat waves and prolonged high temperatures.

The estimation of the unusually hot summer in RM in 2007 as compared to the baseline period was performed by using the Apparent Temperature index (AT).

Threshold values of Apparent Temperature (the 95th percentile) as a criterion of rarity are shown in Table 2. As can be seen, the highest average AT value is observed in July across the territory of the Republic of Moldova. However, the values of Chisinau weather station, located in the centre of the country, are very close to those in the South, because urban infrastructure, consisting in asphalt, concrete and metal, accumulates and stores the heat.

Table 2. Threshold values (95 percentile) of Apparent Temperature (ºC) in summer months for the baseline period (1961-1990)

Location	AT mean			AT maximal			AT minimal		
	June	*July*	*August*	*June*	*July*	*August*	*June*	*July*	*August*
Chişinău	21.0	22.2	21.9	26.4	27.9	27.9	15.9	17.2	17.1
North	20.3	21.6	21.3	26.3	27.6	27.9	14.5	16.0	15.1
Center	20.8	22.1	21.5	26.8	28.3	27.5	14.8	16.2	15.7
South	21.0	22.6	22.1	26.9	28.5	27.9	15.9	17.6	17.0

In the summer of 2007, in the Republic of Moldova, the number of extremely hot days determined by AT, was very high and during July-August it increased up to 20 days per month in the South.
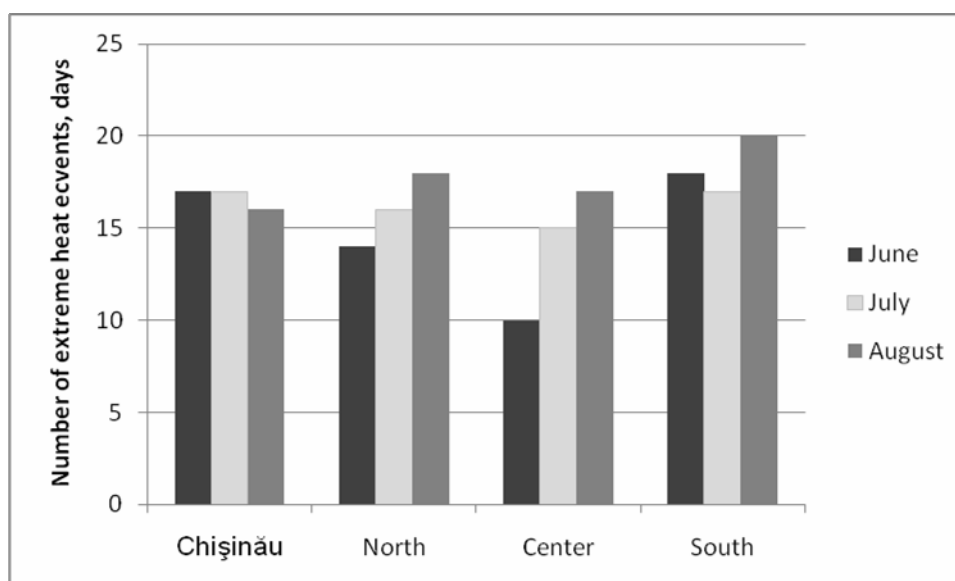
Figure 1. Number of extreme heat events in the summer of 2007, identified by the 95th percentile of the apparent temperature

However, in Chisinau, the number of days with extreme heat values during the three summer months remained almost at the same level – 16-17 days (Figure 1), despite the fact that AT values as a rare phenomenon (the 95th percentile), during the thirty years of the baseline period were observed only once or not recorded at all.

AT values in the summer of 2007 reached a caution degree of 1, which in case of prolonged sun exposure and physical activity can lead to fatigue, with further work possibly leading to heat cramps. However, the current trend of increasing air temperature and the number of extreme heat events associated with anthropogenic climate change, may maintain a reserve for more severe values of apparent temperature.

Another biometeorological index, estimated for the summer of 2007, also confirming the danger of anomalous heat to human and other biological systems, is the Humidex index. Positive anomalies of Humidex over several days already occurred in May (Figure 2) and lasted until the last third of June, with the longest duration recorded i.e. 47 days! During the period from May to August, deviations of this index reached a difference of 12°C (North), demonstrating the severity of extreme heat events.
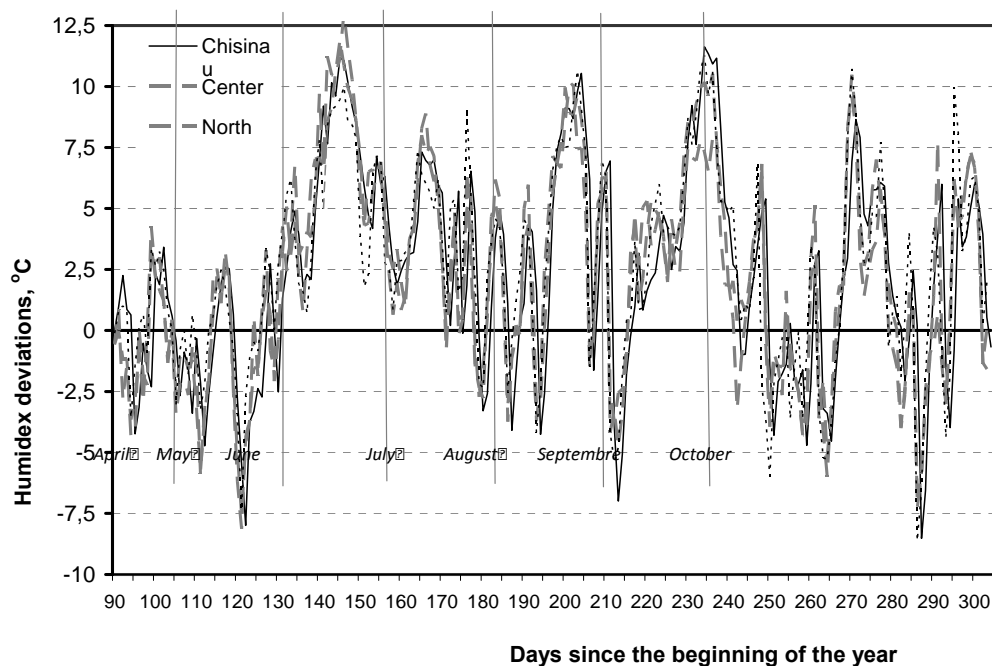
Figure 2. Regime of the Humidex deviations as compared to the baseline period (1961-1990) in the Republic of Moldova in a warm period of 2007 (April - October)

According to the Humidex discomfort scale, the highest number of days with visible discomfort was observed in July and August, reaching a maximum in the South and in the capital of RM – 10 days (Table 3). At the same time, despite the fact that in June there was a high number of positive

Humidex anomalies, basically no days with discomfort were recorded. However, the persistent warm weather for a very long time contributed to the accumulation of heat and therefore increased the number of days with noticeable discomfort during the following months.

Table 3. Number of days with noticeable discomfort and positive deviations of the Humidex index (as compared to the baseline period) in the summer of 2007

Location	June		July		August	
	30-34ºC Noticeable discomfort	*Days with positive deviations*	*30-34ºC Noticeable discomfort*	*Days with positive deviations*	*30-34ºC Noticeable discomfort*	*Days with positive deviations*
Chişinău	0	26	10	25	8	26
North	0	25	8	23	8	27
Center	0	27	9	23	7	26
South	1	28	10	25	10	28

Thus, the unusually hot summer of 2007 is characterized by a large number of extreme heat events, estimated by two biometeorological indices that allow us to appreciate the human body reactions when exposed to high temperatures and to propose concrete measures to prevent risk.

The quantification of the health impacts of extreme heat events by means of linear regression has shown that positive deviations of both biometeorological indices above the threshold of caution (for AT) or discomfort (for Humidex) cause the increase of excess deaths in urban areas and in the South of the country (Table 4).

Table 4. Parameters of linear regression of Excess deaths on deviations of biometeorological indices (AT>27ºC, Humidex>30ºC) during the hot summer of 2007 in the Republic of Moldova

Statistics	Chisinau		North		Center		South	
	AT	Humidex	AT	Humidex	AT	Humidex	AT	Humidex
Coefficient of regression (b)	0.29	0.25	0.06	0.04	0.03	0.02	0.17	0.16
Coefficient of correlation (r)	0.207	0.186	0.093	0.066	0.059	0.039	0.321	0.317
Statistical significance (p)	0.048	0.076	0.376	0.531	0.575	0.713	0.002	0.002

The urban population is more sensitive to high ambient temperatures due to the significantly pronounced heat storage by urban buildings and large areas of asphalt, creating a "heat island". In Moldova, this relationship is confirmed by a low but statistically significant correlation coefficient both for AT and Humidex in Chisinau ($r \approx 0.2$). In turn, the Southern region, due to its hotter climatic regime, also shows the statistical significant relationship ($r \approx 0.2$). So, the 1ºC deviations of AT and Humidex contribute to 0.3 excess deaths in Chisinau and 0.2 in the South (the statistical level of confidence is 90%).

CONCLUSIONS

The caution degrees of both Apparent Temperature and Humidex represent a signal for public health institutions, where not only preventive measures but also measures to mitigate the negative effects of heat waves on human health are needed. To this end, the RM MoH Order No. 547 of 06.08.10 "On organizing the health care activities during hot weather", contains a number of preventive measures and medical recommendations for hot weather period.

It is obvious that not only the evaluation of extreme temperature parameters, but also the study of complex biometeorological indices contribute to the characterization of the abnormally hot summer of 2007 in Moldova, supplementing it with such an important aspect as the impact of weather conditions on the human body.

Moreover, these estimates can serve as a basis for developing the National Action Plan for reducing the negative impact of heat on human health and to create a national surveillance system, oriented on early warning of health risks.

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THE PLACENTA: A MARKER OF PRENATAL DISORDERS WITH POSTNATAL MANIFESTATIONS

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REZUMAT

Studiul sistematic şi standardizat al placentei nu a reprezentat o preocupare majoră pentru majoritatea grupurilor de specialişti obstetricieni şi cercetători din acest domeniu. Cu toate acestea, numeroase lucrări au atras atenţia asupra acestui subiect şi au readus în planul cercetării acest organ indispensabil creşterii şi dezvoltării fetale normale. Mai mult, s-a remarcat faptul că între unele leziuni sau asocieri lezionale placentare şi o anumită patologie a nou-născutului ar exista corelaţii semnificative, iar cercetările ultimelor decenii duc mai departe aceasta idee şi stabilesc corelaţii interesante între diverse manifestări patologice placentare şi unele boli ale adultului. Din aceste motive, studiul sistematic al acestui organ la cazurile cu risc de patologie neonatală (în special hipoxică) a devenit o preocupare majoră a medicinii perinatale. Lucrarea subliniază cele mai importante argumente care susţin acest demers şi necesitatea ca aceste studii să contribuie la elucidarea unor manifestări patologice postnatale neexplicate sau insuficient explicate.
Cuvinte cheie:

ABSTRACT

A systematic and standardized study over the placenta was not the aim of most obstetricians and researchers in this field. Nevertheless, numerous papers highlighted this subject and brought this organ back into the light of research, as it is indispensable for a normal fetal growth and development. Moreover, it has been observed that there are significant correlations between certain placental lesions or lesional associations and certain newborn pathologies. Thus researches conducted during the last decades continued this idea and established interesting correlations between various placental pathological manifestations and some diseases in the adult. For these reasons, systematic studies over this organ in the cases associated with risks of neonatal pathology (especially hypoxia) became a major concern for perinatal medicine. This paper underlines the most important arguments supporting this approach and the necessity of these studies, in order to shed light on some unexplained or insufficiently explained postnatal pathological manifestations.
Keywords:

INTRODUCTION

It is clear that most newborns are normal, healthy and, thus, most placentas are normal, accordingly. Many, but not all (5-15%), newborns are labeled as high risk newborns, a category mostly represented by preterm newborns and newborns with intrauterine growth restriction that manifest multiple neonatal diseases some of which with a reserved prognosis. These numbers show that, at least in theory, the placentas of these fetuses/newborns cannot be ignored and thrown away as useless. A systematic and standardized study conducted over them may offer useful information at least for confirming a diagnosis and explaining some pathological manifestations which may even generate conflicts between obstetricians and neonatologists.

The opinion that a systematic study of the placenta is not important has been expressed in 1991 by the American Board of Obstetrics and Gynecology, in a published practical bulletin [1]:"The benefits of routine collection of security histologic slides have not yet been proven and we can recommend no standardized study on the pathology of the placenta". This opinion practically discouraged the routine research of the placenta. Despite this, evidence always showed that when a newborn is affected, the placenta played an important role in elucidating the cause of fetal sufferance and abnormal deliverance, and this aspect came to support obstetricians, neonatologists and other persons involved in fetal/newborn care [2] (malpractice suspicions included). Fortunately, during the last two decades and especially in recent years, the interest for the study of the placenta increased especially due to the increase in the number of medico-legal cases in which the placenta is a main witness and marker. One of the most important litigations worldwide is represented by the unexpected adverse outcome and especially cerebral palsy together with other types of neurologic injuries (motor, sensitive, cognitive, communication and perception associated, behavioral). These may start early in the postnatal period and may evolve progressively or non-progressively during early childhood.

Even if there are controversies regarding the causes of cerebral palsy, most authors agree that an important number of cases are related to perinatal events, with a sufficiently long period (between the 22nd gestational week and the 7th day of postnatal life) to include pathological events and conditions. As we know, the placenta is the most important fetal organ as it performs the gaseous, nutritive and fluid exchanges between the mother and the fetus. Underlining the fact that it is the most important fetal organ makes us understand that its study after birth may offer valuable information on the entire history of the pregnancy, but especially on the perinatal period and on the harmful effects of some perinatal pathological events. Offering a series of retrospective information the placenta may be considered a true "gestational diary" as is has been suggestively named by Altshuler G [3].

Equally, the placenta may also offer prospective and prognostic information. Being a fetal organ it expresses a fetal genotype and may be considered a fetal genetic print which can offer valuable information on some genetic chromosomal or congenital disorders. This capacity of the placenta is also argued by the fact that chorionic villous sampling, although invasive, is one of the usual methods for prenatal genetic diagnosis.

Summing up all the presented data, it may be stated that the placenta – as the most important fetal organ – may witness fetal pathologic processes, and fetal unfavorable consequences which determine the practitioner to pay a greater attention to its examination. We further present the main lesions and pathological processes of the placenta which impose its macro- and

microscopic morphological investigation, offering important arguments for postnatal diagnosis and approach of the fetus/newborn. These lesions or pathological processes may be primary or acquired, acute or chronic, isolated or extensive, influencing in various degrees and ways the fetal homeostasis.

Primary placental lesions are represented by a heterogeneous group of diseases which interfere with the maternal-fetal blood flow or lead to the destruction of the villi. The most important lesions with harmful fetal effects are: placental bed infarcts, chronic villitis and meconium myonecrosis.

Vascular bed infarcts represent a group of etiologically unlabeled lesions characterized

by marked intervillous fibrinoid or fibrin deposition. This material coats the surface of chorionic villi and decreases, in variable degrees, the placental oxygen and nutrient transport capacity. The fetal unfavorable consequences are represented by intrauterine growth restriction, but may also lead to fetal death depending on the degree of placental parenchyma impairment and on the reduction of the exchange surface of the placenta [4,5]. On long term, these lesions are frequently associated with neurologic disorders [5]. Even though the etiology is not certain, it is suggested that these are mediated by immune response type lesions, when the mother "rejects" the placenta [5, 6].
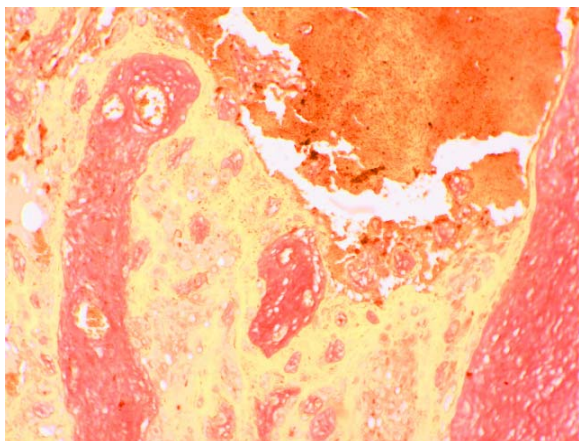
Infarction of the maternal side of the placenta, with

Van Gieson X 20 (dr. ILIE R. collection)
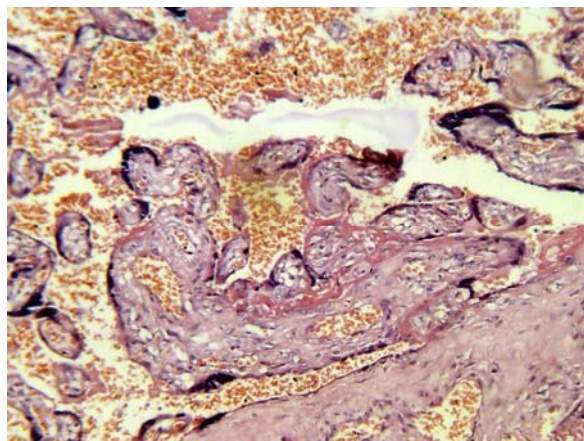
Clot, with compression of the fetal villous tissue – fetal

vascular fibrosis – H.E. X 10 (dr. ILIE R. collection)

Chronic villitis is defined by the presence of chronic inflammatory infiltrate in the chorionic villi. It may be of infectious or unknown etiology (more frequent, affecting around 5% of placentas). It is frequently associated with the maternal vascular bed infarct, and inflammatory cells have been proven to be of maternal origin [6]. Histologically, chronic villitis is characterized by a lympho-histiocytic infiltrate in the chorionic villi and in the intervillous spaces. The association to the infarct of the maternal vascular bed suggests the same immune mediated etiology. In

severe forms, chronic villitis is significantly associated to cerebral palsy and other severe neurologic injuries [7,8].

The elimination of meconium (fetal stool) in the amniotic fluid is a pathologic situation occurring in cases of fetal hypoxia. Even though it is frequently encountered, this manifestation poses severity problems: when the meconium is aspirated by the fetus and causes the meconium aspiration syndrome with severe pneumonia and risk of neonatal death. If the meconium is released in the amniotic fluid long before

birth, it may organize in larger particles (plugs) which may aggravate the aspiration syndrome. Additionally, meconium being the content of fetal intestines, containing bile salts and enzymes, may cause lesions to the amniotic cavity, umbilical cord and fetal blood vessels. The umbilical cord is affected 12-24 hours after meconium elimination, leading to the necrosis of the smooth muscles in the umbilical vessels, most frequently in the umbilical arteries. Additionally, in vitro studies reported that meconium causes umbilical vessel constriction with reduction of the fetal blood flow [9,10]. For these reasons, meconium myonecrosis is significantly correlated to cerebral palsy and other postnatal cerebral injuries.

Acute chorioamnionitis is histologically defined by the presence of inflammatory cells among the amnion and chorionic fetal membranes, as an indicator of ascendant bacterial infection of the amniotic cavity. The ascendant bacterial infection occurs in the case of prematurity and/or early rupture of the amniotic membranes, with or without labor. In the absence of labor, the ascendant infection will produce an initial response with inflammatory cells of maternal origin, but if the infection persists, an inflammatory response with acute fetal inflammatory cells migrating from the fetal vessels towards the umbilical cord and the chorionic plate will occur. If the infection persists for several days, it escapes control and may infect the fetus causing fetal bronchopneumonia and/or sepsis which will evolve in the postnatal period.

The ascendant infection is the most frequent cause of premature labor and birth, but the most plausible sequence a maternal infection may trigger is the following: maternal infection → premature amniotic membranes rupture → ascendant infection in the amniotic cavity → labor → premature birth (with the entire range of prematurity related risks). Even in the absence of fetal infection, fetal exposure to bacteria will induce a fetal inflammatory response with release of inflammatory mediators and cytokines. A severe fetal inflammatory response associated to thrombosis is significantly correlated to cerebral palsy and other harmful neurologic consequences by: alteration of the blood-brain barrier permeability; vasoactive effects leading to brain hypoperfusion; direct toxic effects on the nervous tissue caused by inflammation mediators [11].

Abnormal (unfavorable) intrauterine environment. The environment of the fetus is the amniotic fluid. Quantitative and/or qualitative changes of the amniotic fluid render it the status of "abnormal intrauterine environment" or even pathological environment with consequences upon the fetal development and homeostasis. The direct or indirect consequence of unfavorable intrauterine environment is intrauterine hypoxia, and in the placenta this is shown by two main characteristics: increase of the nucleate red blood cells in the fetal blood stream and chorioangiosis. The increase in the number of nucleate red blood cells in the fetal blood stream may be observed on the microscopic examination of the placenta. It is caused by fetal hypoxia which induces the increase of erythropoietin production in the fetal kidney and the increased production of red blood cells in the fetal hematopoietic organs in order to compensate fetal hypoxia. In order to demonstrate this characteristic, at least 12-24 hours of hypoxia are needed. An absolute measured value greater than 2500/cm3 is considered a significant indicator for fetal hypoxia if the measurement is performed as early after birth as possible or even from the umbilical blood [12]. **Chorioangiosis** as an indicator of fetal hypoxia represents an adaptive response of the placenta, characterized by proliferation of villous capillaries in an attempt to increase the oxygen transport capacity [12,13]. In order for those placental changes to occur (formation of new blood vessels) the hypoxic stimulus needs to act for a longer

period (weeks). The two characteristics of feto-placental blood circulation are

frequently associated to unfavorable perinatal consequences up to neonatal death.
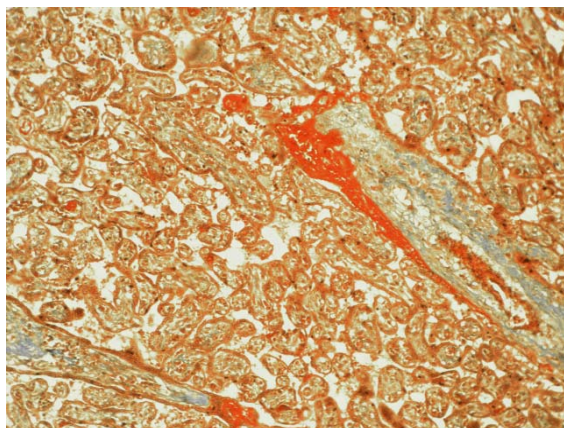
Syncytial vasculopathy with a great number of syncytial knots – Trichrome Masson X 10 (dr. ILIE R. collection)
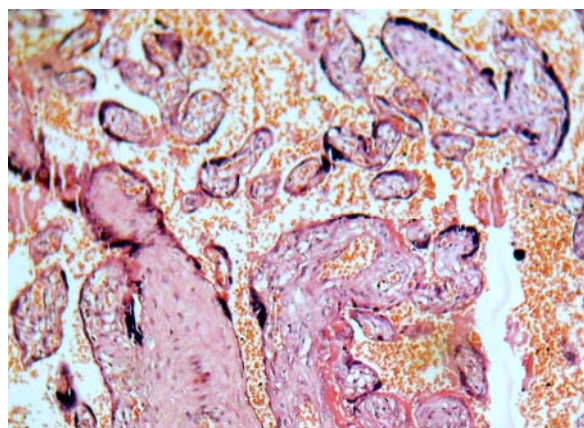
Thrombosis of fetal chorionic vessels – H.E. X 10 (dr. ILIE R. collection)

Acute and/or chronic placental lesions. The types of lesions [13] as well as the main acute and/or chronic pathologic events which may cause these lesions are illustrated in Table 1. The same types of lesions may be encountered in both situations, the difference between acute and chronic being due to the time factor, e.g. in acute placental pathology lesions occur suddenly or rapidly while in chronic pathology these take days

or weeks. A brutal reduction of the fetal blood flow will cause fetal death or severe fetal neurologic lesions (e.g. uterine rupture). A rapid decrease by 50% of the placental exchange surface (e.g. acute placental abruption) will determine the death of the fetus inside the uterus, and if this occurs in a lower proportion it will cause sublethal lesions with variable degrees of severity.

Table 1. Categories of placental pathology

LESION TYPE	ACUTE PLACENTAL PROCESSES	CHRONIC PLACENTAL PROCESSES
Impaired maternal blood flow	Uterine rupture	Low maternal perfusion
Impaired fetal blood flow	Acute placental abruption	Chronic placental abruption
Primary placental lesions	Acute obstruction of the blood flow	Ischemic/infarct type changes
Inflammatory/infectious processes	Occlusion of the umbilical cord	Villous morphological changes
Abnormal intrauterine environment	Acute fetal hemorrhage	Accelerated villous maturation
	Extensive necrosis in the fetal blood vessels, especially in fetal capillaries	Increase in the number of syncytial knots
	Velamentous vessels	Syncytial vasculopathy
	Fetal-maternal hemorrhages	Meconium myonecrosis
	Fetal traumatisms	Infarction of the maternal side of the placenta
	Acute chorioamnionitis	Chronic villitis

The obstruction or interruption of the blood flow towards the umbilical vessels may have major fetal consequences, from complete and unresolved obstruction leading to fetal or neonatal death to partial or incomplete obstruction which results in fetal/neonatal neurologic disorders with variable severity. There are studies showing that cerebral palsy is significantly more frequently associated to long, excessively coiled umbilical cords, as well as to velamentous insertion of the umbilical cord [14]. The most frequent umbilical cord obstructions are mechanical and they are associated to its compression. In any type of compression, the umbilical vein, being more elastic and with a wider caliber, will initially be the most compressed, inducing a reduction of the oxygenated blood flow towards the fetus. The physiopathological consequences of this mechanism are represented by a venous congestion of placental capillaries as well as by a variable degree of fetal hypovolemia, anemia and hypoxemia, implicitly.

The most frequent cause for large umbilical cord vessel hemorrhage is the rupture of velamentous vessels. In order to demonstrate the presence of velamentous vessels and their interruption with hemorrhage, an examination of the placenta is needed. Moreover, the clinician must communicate to the pathologist the suspicion of velamentous vessels rupture in order for the latter to carefully conserve the anatomopathological characteristics. Umbilical cord rupture is a rare pathologic situation and it may be caused by an abnormal traction of a short cord or by pathologic processes which may fragilise the umbilical cord (e.g. necrotizing funisitis, meconium induced ulceration, or trauma produced during collection of fetal blood samples). Depending on the celerity and severity of the hemorrhage, severe neurologic lesions or even fetal death may occur [14,15]. A particular aspect of exsanguination occurs in monozygotic twins with monochorial placentas, when one fetus is the donor (transfusor) and the other is the receiver (transfused). In the placenta, anastomosis of various sizes will be detected, their number and size determining the degree of exsanguination. If one of the twins dies in utero, this will become a drainage pit for the other and will contribute to the severe exsanguination of the surviving twin. When both twins survive such a situation, they will both be finally severely affected, one with anemia and hypovolemia, the other with usually severe hypervolemia and polycytemia.

Fetal-maternal hemorrhage is a rare entity, being increasingly observed in the presence of placental choriocarcinoma and hemangioma (chorioangioma).

For diagnostic purposes, the Kleihauer-Betke test is needed to identify fetal cells in the maternal circulation, but this may give false results. Blood loss occurs in several episodes, and the recorded placental changes are represented by massive and multiple intervillous thrombi in evidence of fetal and neonatal anemia.

Chronic placental lesions are easily identifiable upon pathologic examination. Under physiological conditions, even when affecting 1/3 of the placenta, chronic lesions do not significantly influence blood gas exchanges. When the injured placenta is unique, there is a reduction of the total exchange surface for gases and nutrients, which will lead to an intrauterine growth restriction. Even when the placenta has a normal size, its function is diminished if chronic lesions are present, due to the reduction of placental parenchyma and fetal reserves. The most frequently diagnosed chronic lesion is the decidual vasculopathy consisting of various decidual alterations or utero-placental vessels changes: fibrinoid necrosis, ateromatosis, mural hypertrophy, and the absence of any physiologic conversion. The primary manifestation consists of villous agglutination with collapse and, finally, infarction of the

intervillous spaces. The expansion of the nonfunctional placental parenchyma contributes to the reduction of maternal-fetal perfusion and may lead to acute or chronic placental abruption with consecutive aggravated malperfusion. The chronic obstruction of the fetal circulation blood flow may also be caused by fetal circulation thrombosis or fetal thrombotic vasculopathy [16,17]. This group includes several types of thrombotic lesions, some also macroscopically recognizable: occlusive and nonocclusive thrombi, mural thrombi, avascular villi, hemorrhagic endovasculopathy. Calcified thrombi are the oldest, indicating a period of several weeks from onset [18]. All these lesions may cause a substantial reduction in the oxygen transport capacity (fetal hypoxemia and hypoxia with variable neurologic consequences) as well as a reduction of the fetal reserves with restricted intrauterine growth accompanied by its metabolic and neurologic complications.

CONCLUSIONS

1. In at least 10-15% births, the placenta and umbilical cord are important witnesses and markers of certain abnormalities affecting the normal fetal growth and development. If we add the fact that an important number of children with cerebral palsy or neurologic disorders do not present a perinatal history, possibly explaining this pathology, we may consider that the percent of marker-placentas might be higher.

2. In current practice, this important witness of fetal and perinatal pathology is, unfortunately, totally ignored, by obstetricians and pathologists alike. Consequently, an important database, incorporated in this organ, vital for the prenatal life of the individual, is lost.

3. If we admit that placental lesions may occur in a certain sequence and that their timing can be very precisely assessed, we consider that a systematic pathologic examination in cases of high risk pregnancy and/or newborn becomes a fundamental practical procedure. This practice must be implemented with the highest priority in all maternities. For this, our team initiated a centre where placentas collected from such cases are conserved for 7-10 days while the evolution of the newborn will determine whether its placenta will require a systematic histological examination.

4. Recent researches bring important arguments regarding the value of placental printing for the postnatal evolution of the child and future adult. These studies bring an additional argument for the inestimable value of this true "diary" of human prenatal evolution.

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TOTAL HYPERCHOLESTEROLEMIA IN THE PRACTICE OF PRIMARY CARE

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REZUMAT

Hipercolesterolemia totală reprezintă un factor de risc major cardiovascular implicat în evaluarea riscului total cardiovascular, adesea neglijat de pacient, de familia pacientului, fără suferinţe, cu evoluţie spre complicaţii aterosclerotice deosebit de grave şi care poate fi uşor depistat în asistenţa medicală primară. Depistarea, evaluarea şi combaterea sunt la îndemâna medicului de familie. Asocierea şi altor factori de risc cardiovascular, creşte exponenţial riscul.
    Cuvinte cheie: *hipercolesterolemie totală, risc cardiovascular, prevalenţe*

ABSTRACT

Total Hypercholesterolemia is a major cardiovascular risk factor involved in assessing total cardiovascular risk, often ignored by the patient, the patient's family, without suffering atherosclerotic ascending to very serious complications that can be easily detected in primary care. Detection, assessment and control are at hand for the family doctor. Association of other cardiovascular risk factors increases the risk exponentially.
    Keywords: *total hypercholesterolemia, cardiovascular risk, prevalence*

MOTIVATION OF THE PAPER

Total hypercholesterolemia is a major risk factor in the onset and complicated evolution of diseases with atherosclerotic etipathogeny. These diseases prevail in the foreground of morbidity and mortality in our country (cardiovascular diseases, cerebrovascular diseases).

Total hypercholesterolemia can remain undetected in the general population, in the absence of symptoms determining a patient to seek medical attention, until the moment when severe complications occur, and that is the reason why it is necessary to detect as early as possible the disease by primary prevention activities, through active screening.

Early screening is in the hand of the family doctor and relatively easy to achieve by the adult patients' screening in the entire community (patients from the family doctor's list) or by selected screening that refers to patients with increased risk (family histories of atherosclerotic diseases, obese – overweight people, diabetes, other metabolic diseases: hypertriglyceridemia, gout, etc.)

Early screening of patients with total hypercholesterolemia constitutes the basis of elimination and fight against the risk through lifestyle, diet and proper treatment.

METODOLOGY OF THE PAPER AND STUDY POPULATION

The adult population, aged over 20 years, in a family doctor's practice was included into the study.

The medical records of all adult patients over the age of 20, with known pathology were analysed, highlighting the cardiovascular, cerebrovascular and metabolic diseases, relevant family histories, data regarding smoking, nutrition, body mass index and the laboratory investigations carried out in the primary medical care: total cholesterol levels, HDL cholesterol, triglycerides and glucose levels divided into three risk ranks.

The study population consisted of 1238 people including 654 men and 584 women, divided into three age groups.

The results were processed to reveal the prevalence index and the conclusions were formulated and represented as graphs.

RESULTS
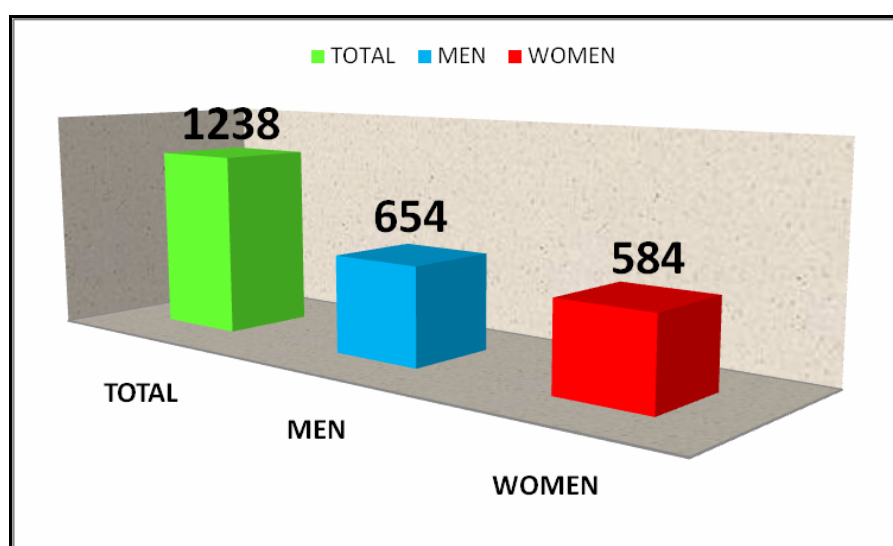
Figure 1. Numerical and gender distribution of the overall study group
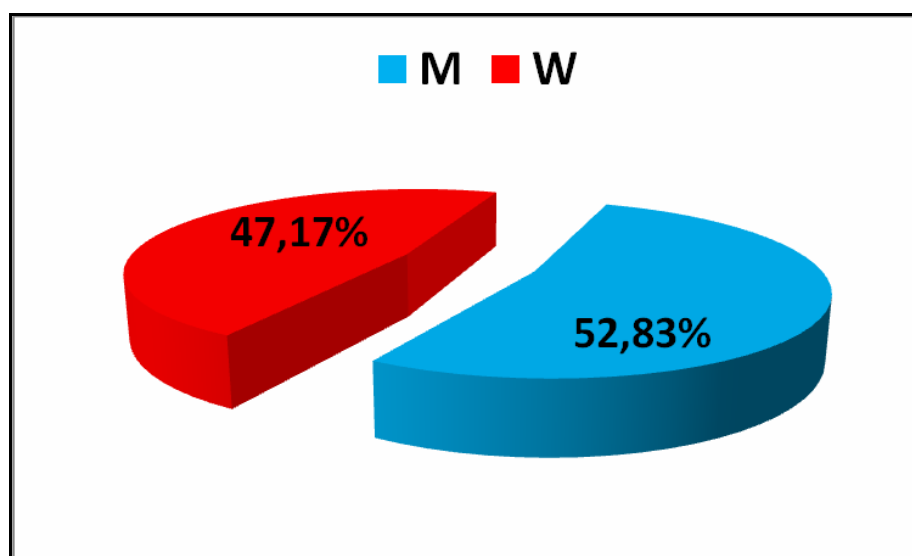
Figure 2. Percent gender distribution of the study group

We can observe a slight predominance of the male population due to the neighbourhood characteristics, where the constructors prevail.

Table 1. Numerical and percent age group distribution

Age (years)	20 - 29	30 - 39	40 - 49	50 - 59	60 - 69	≥ 70
No	225	234	228	216	201	134
%	18.17	18.90	18.42	17.45	16.24	10.82
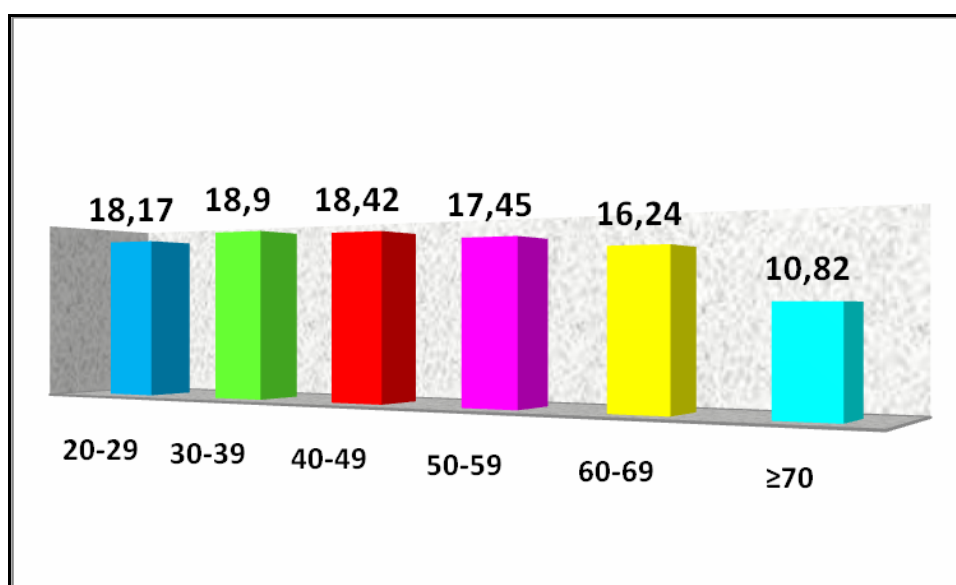
Figure 3. Age group distribution of study group
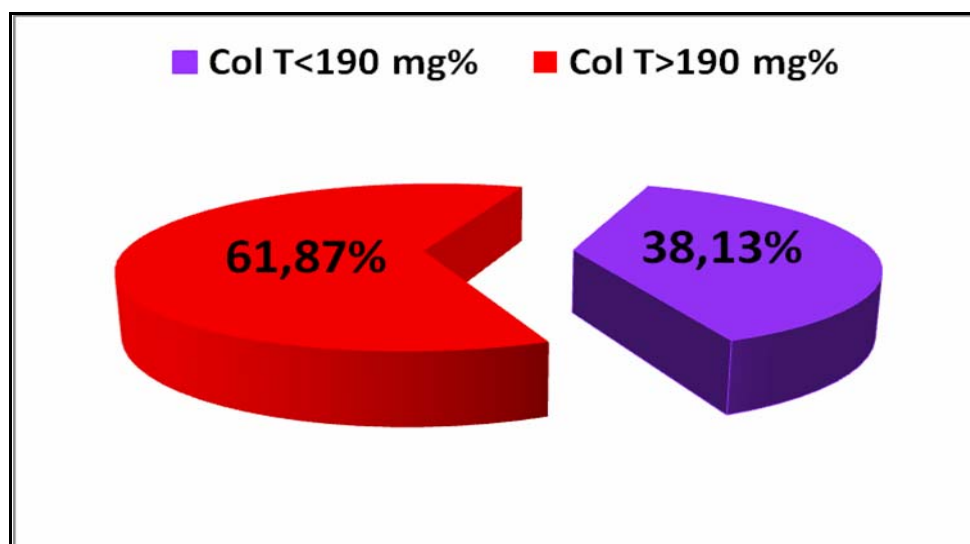
Figure 4. Prevalence of the total hypercholesterolemia in the study group

Total hypercholesterolemia reaches increased values 38.13%.
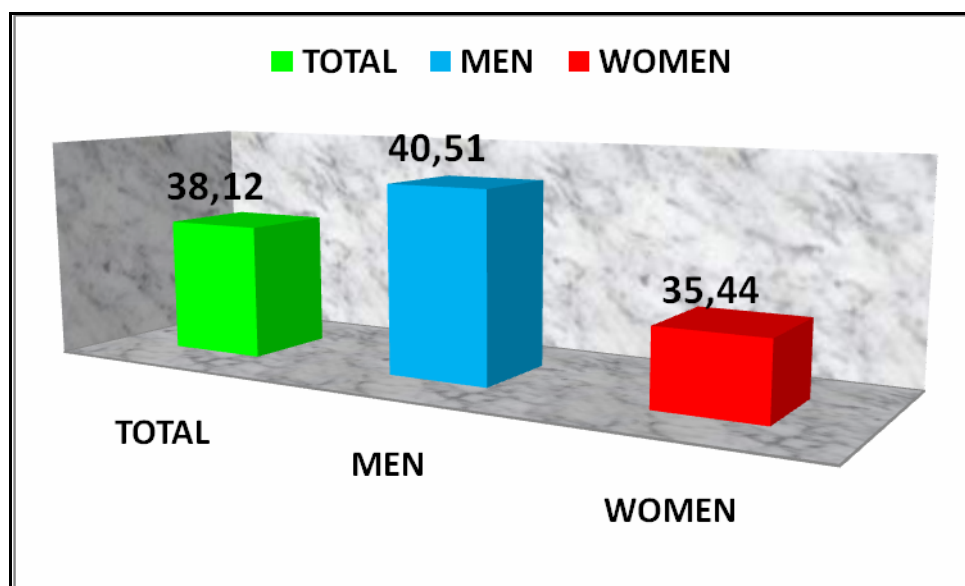
Figure 5. Hypercholesterolemia prevalence by gender

A significantly higher prevalence in the male (40.51%) as compared to the female population was observed (35.44%).
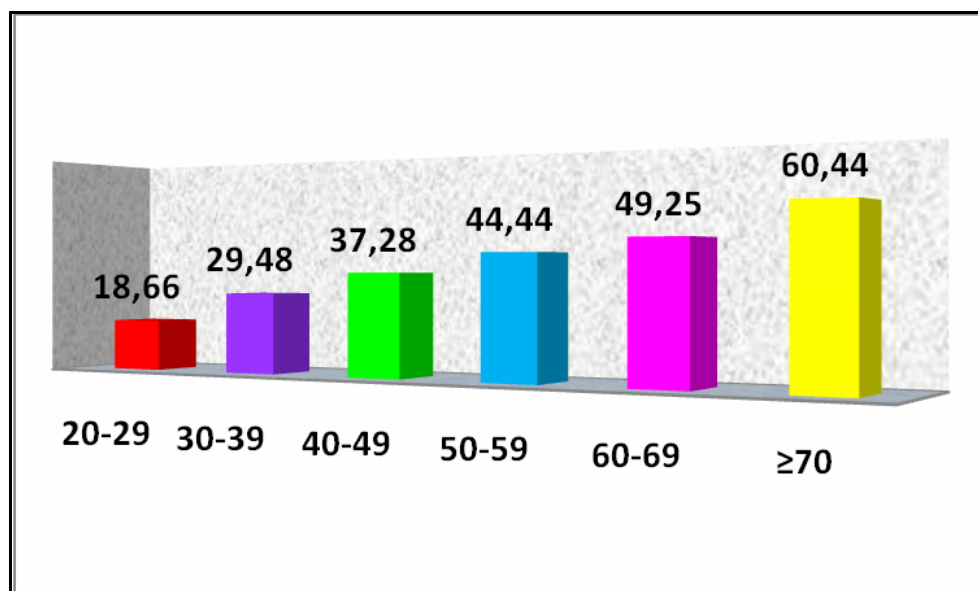
Figure 6. Total hypercholesterolemia prevalence by age groups

The total hypercholesterolemia prevalence increases with age becoming an important risk factor.
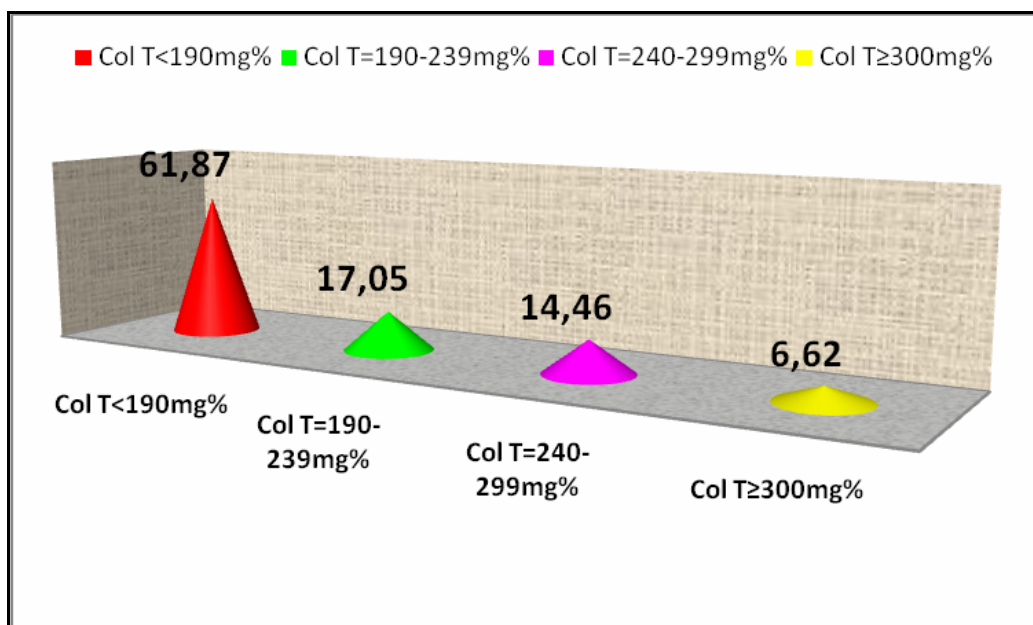
Figure 7. Total cholesterolemia prevalence according to risk factors
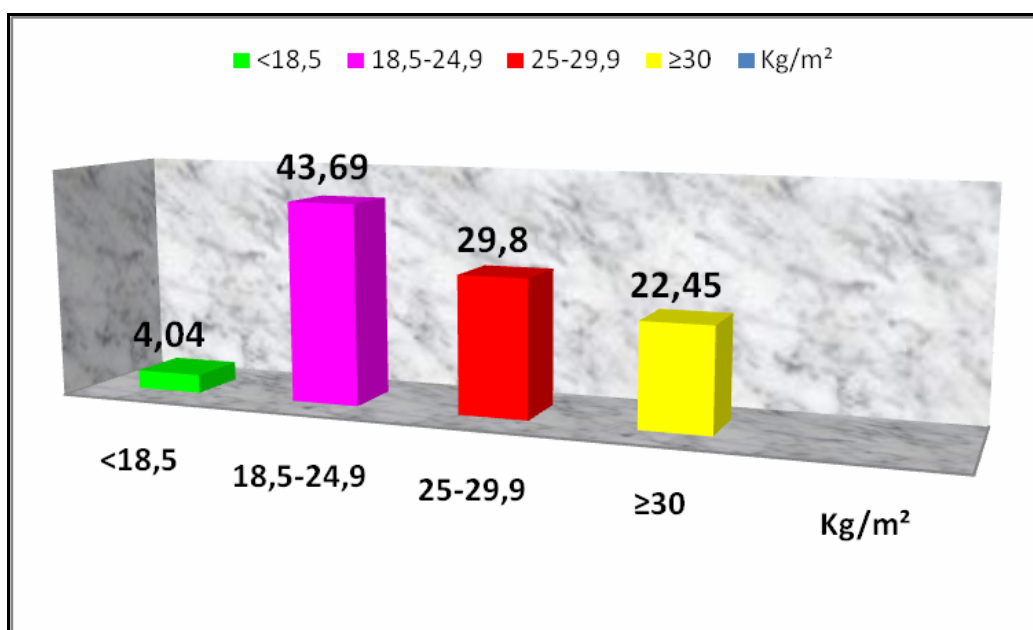
Figure 8. Distribution of the study population according to the body mass index

- < 18.5 underweight
- 18.5-24.9 normal weight
- 25-29.9 overweight
- ≥ obese people

Thus, the overweight population exceeds ½ of total adult population (52.25%).
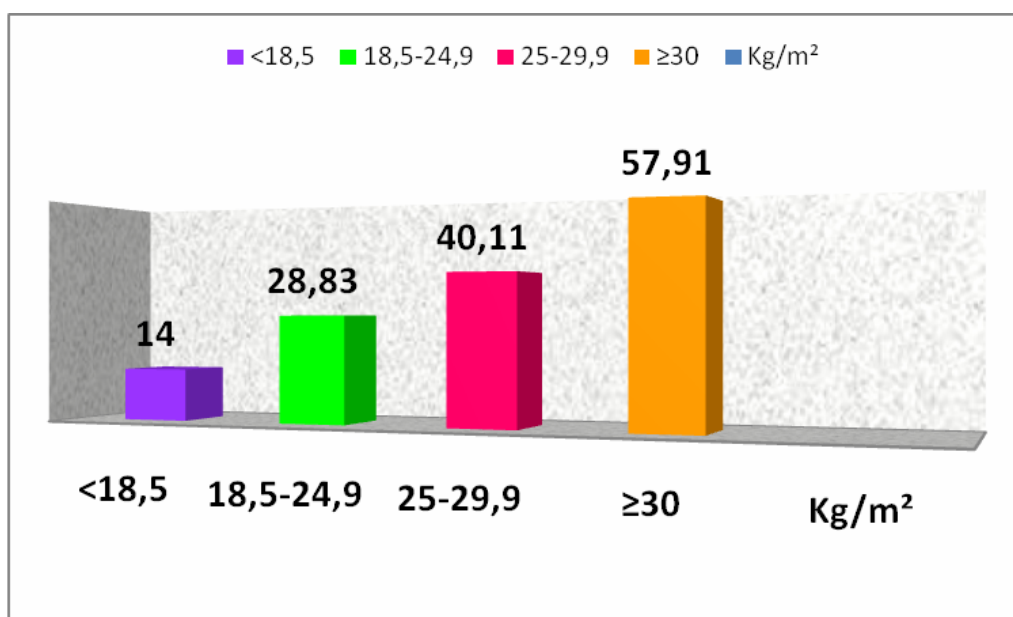
Figure 9. Hypercholesterolemia prevalence according to body mass index

The prevalence of total hypercholesterolemia increases with the body mass index.
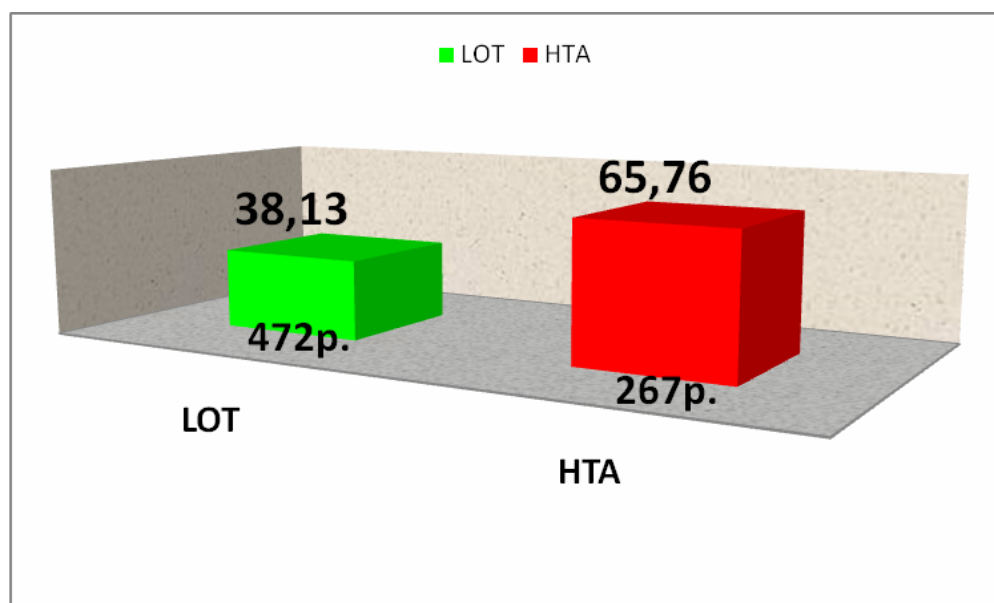
Figure 10. Comparative prevalence of hypercholesterolemia in the study group and in a hypertensive population

Total hypercholesterolemia has higher prevalence values in hypertensive people.
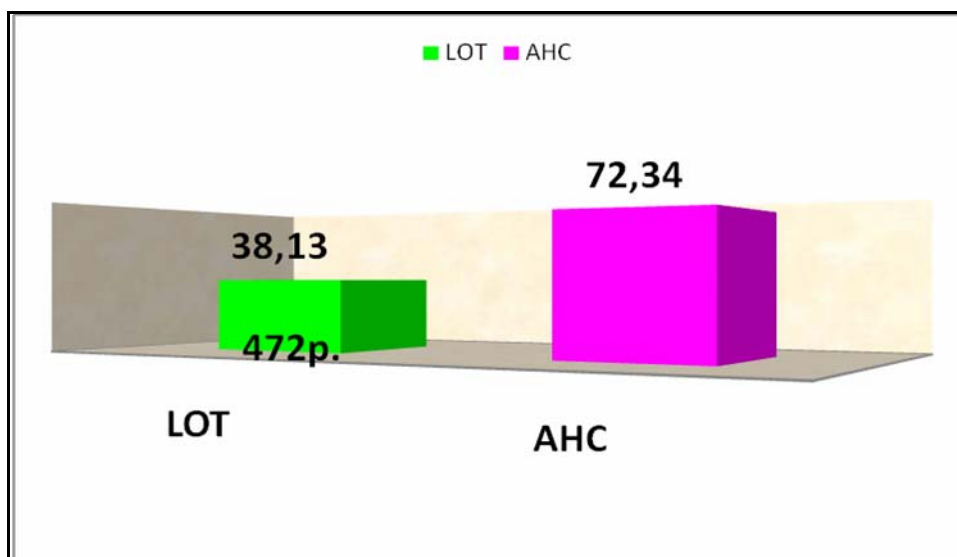
Figure 11. Comparative prevalence of total hypercholesterolemia in the study population and in patients with cardiovascular pathology in their family histories (myocardial infarction, sudden death, obstructive arteriopathy)

Patients with high risk family histories present very high prevalence levels.
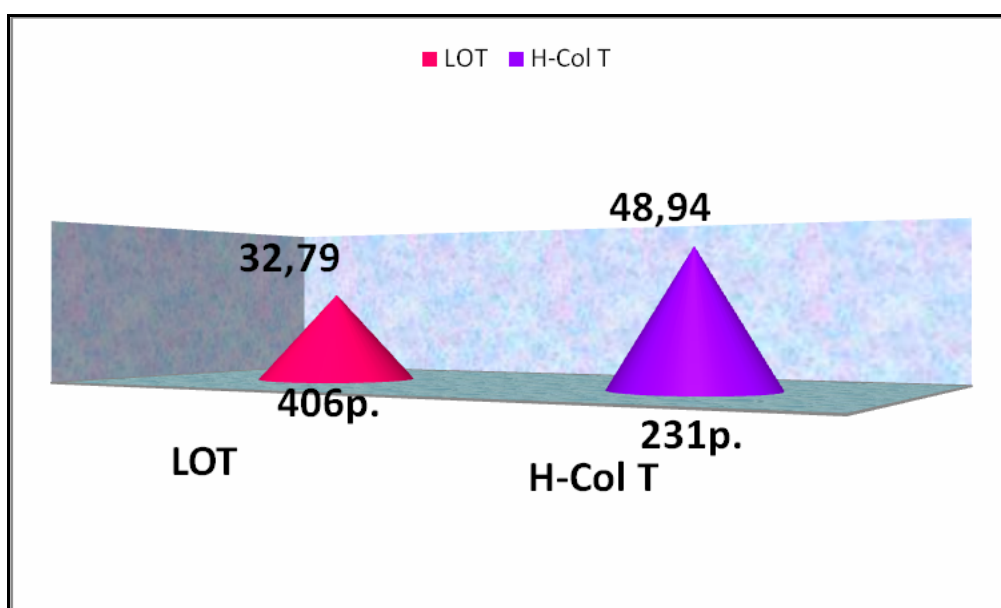
Figure 12. High blood pressure prevalence in the study group and in a high risk population with pathologic levels of total hypercholesterolemia

But also HTN records high prevalence at people with total hypercholesterolemia.
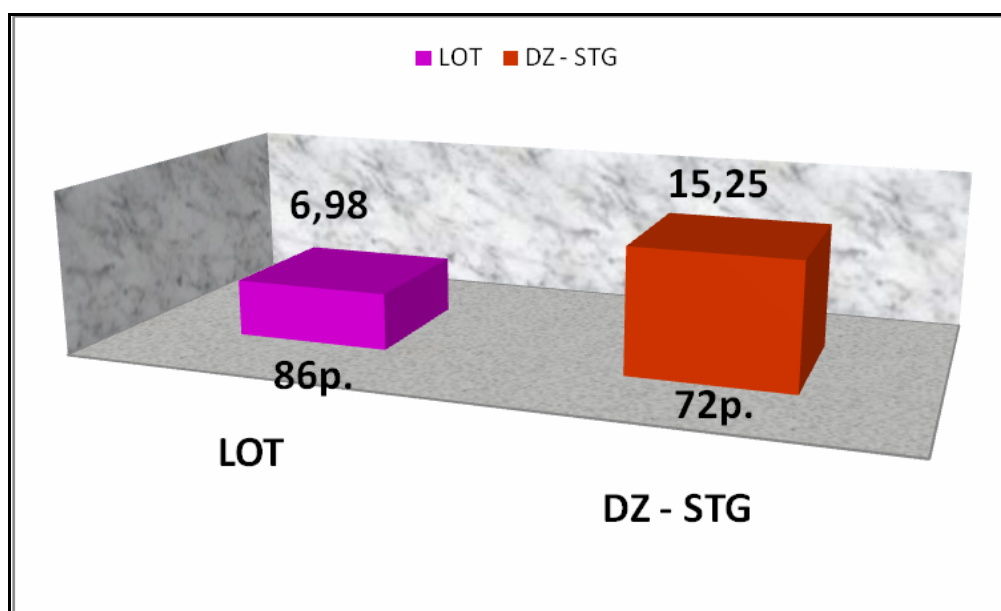
Figure 13. DM and STG prevalence in the study group and in a high risk population with pathologically increased levels of total cholesterolemia

A two times higher prevalence was observed in patients with total hypercholesterolemia with glucose metabolism disorders (DM, STG).
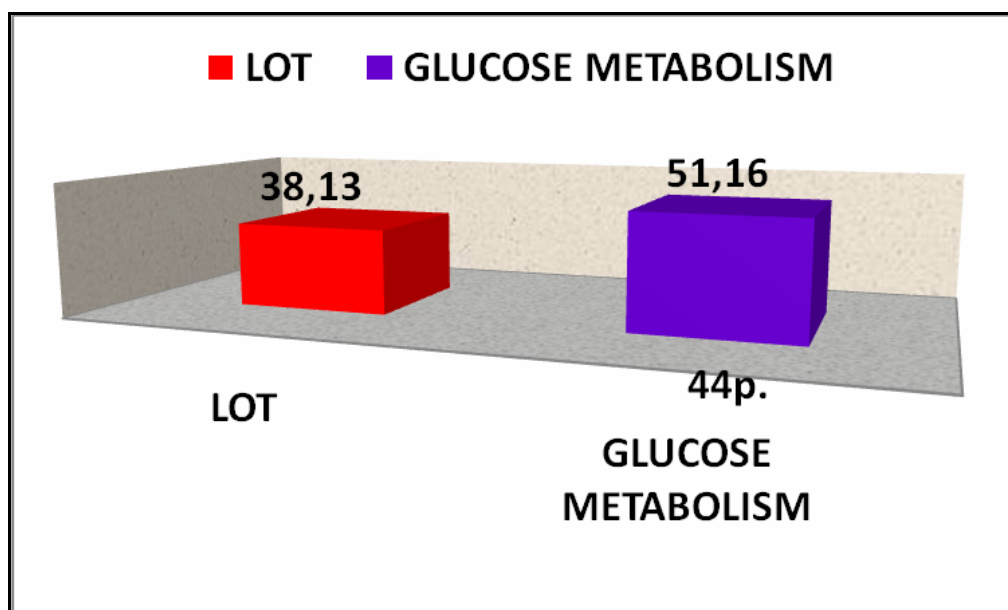
Figure 14. Total hypercholesterolemia prevalence in the study group and in a population with glucose metabolism disorders

Total hypercholesterolemia prevalence is significantly higher in patients with DM and STG.
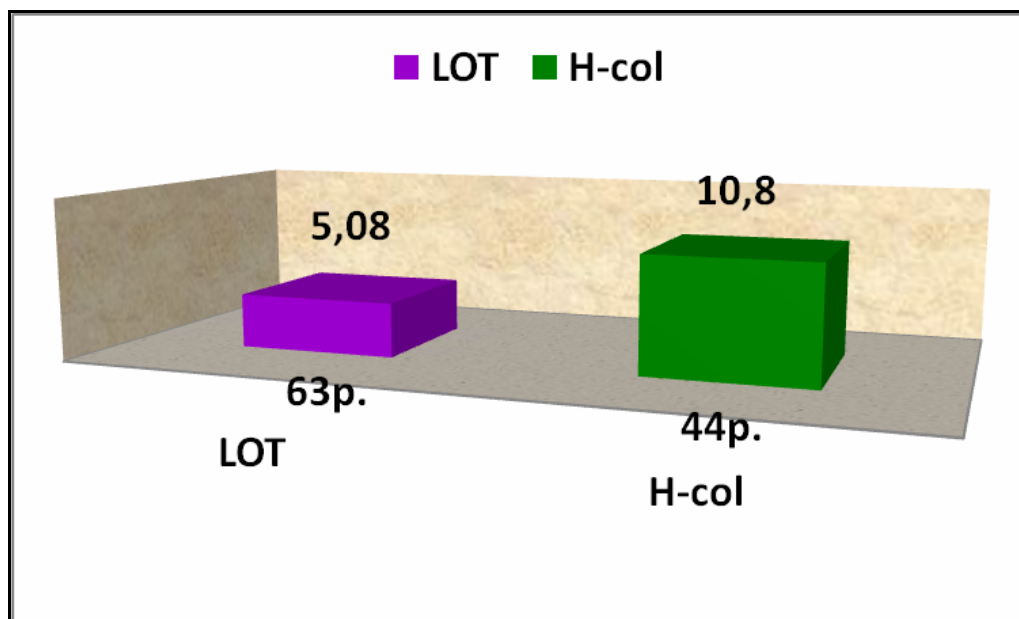
Figure 15. Dyslipidemia prevalence by decreased HDL cholesterol in the study population and in patients with hypercholesterolemia

Increased prevalence of DL by HDL cholesterol decrease is associated with high H-Col.T values.
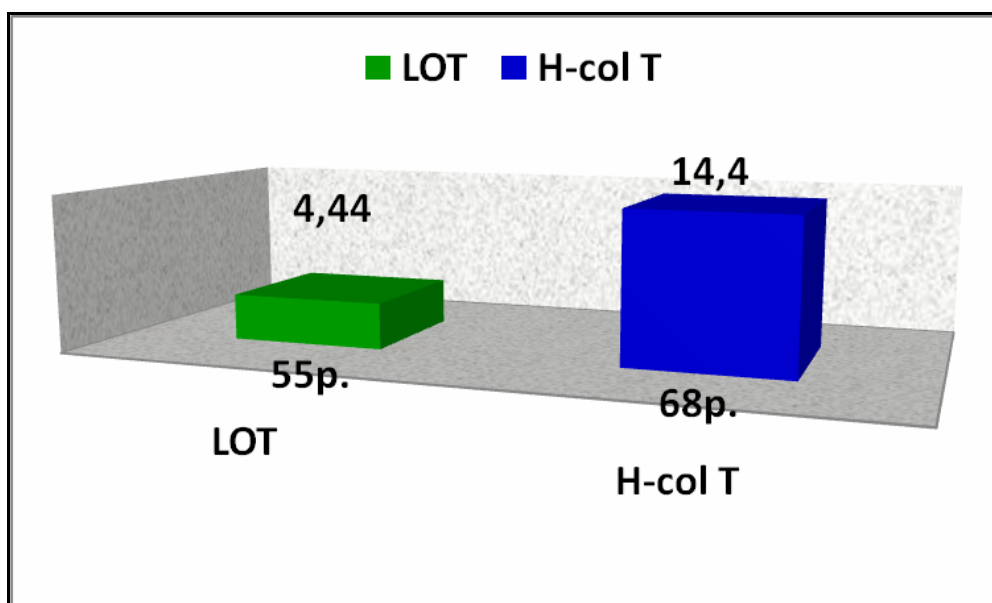
Figure 16. Atherogenic index prevalence in the study group and in patients with total hypercholesterolemia (Total Col/HDL-col≥5)

Atherogenic index is three times higher in patients with total hypercholesterolemia.
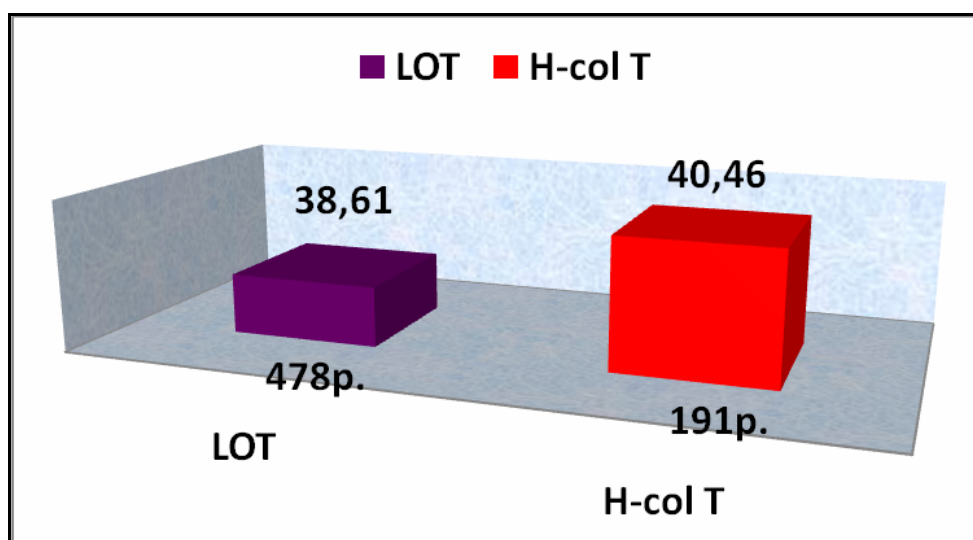
Figure 17. Prevalence of smoking in the general population and among total hypercholesterolemia subjects

Unfortunately the smokers' prevalence among those with total hypercholesterolemia is not lower but even slightly higher.
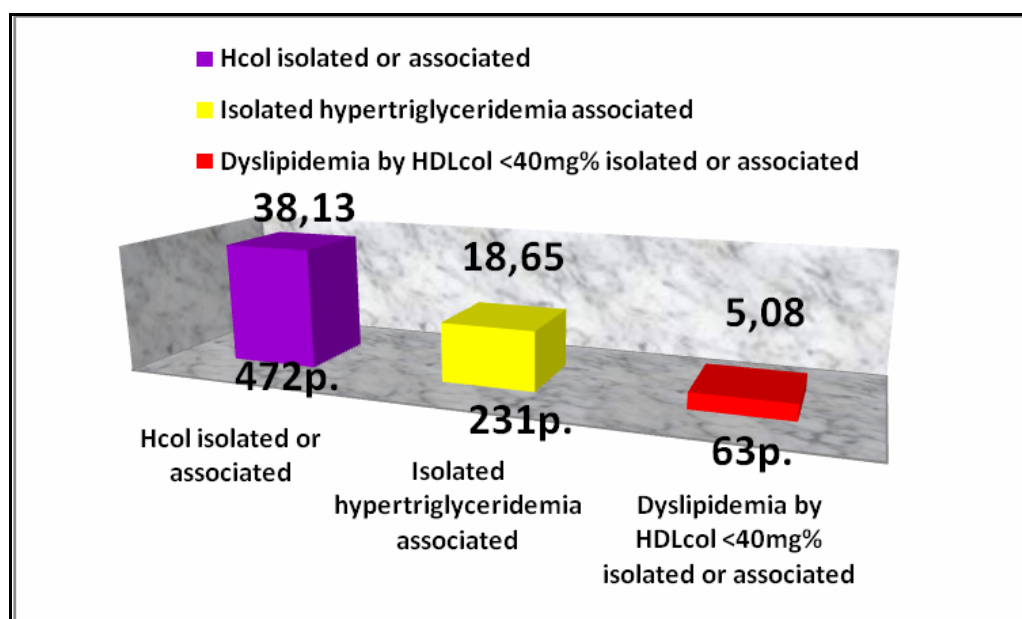
Figure 18. Prevalence of different dyslipidemic disorders associated or not with hypercholesterolemia in the study group

CONCLUSIONS

✓ Total hypercholesterolemia prevalence in the adult population over the age of 20 records increased values 38.13%.

✓ The prevalence of high risk hypercholesterolemia (total cholesterol > 190 mg%) is higher in men (40.51%) than in women (35.44%).

✓ The prevalence of hypercholesterolemia increases with age reaching (60.44%) at those ≥ 70 years old.

✓ The prevalence of pathologic hypercholesterolemia records 21.08% of which 6.62% with very high risk (≥300 mg %).

✓ The prevalence of hypercholesterolemia increases according to body mass index, reaching 57.91% in obese people.

✓ A significantly higher prevalence in people with high blood pressure (65.76%) is recorded.

✓ A very high prevalence is also recorded in people with family histories of cardiovascular and cerebrovascular diseases.

✓ The population prevalence of high blood pressure associated to hypercholesterolemia records increased values (48.94%).

✓ The glucose metabolism disorders (GMD) i.e. DM and STG also record almost three times higher prevalence levels in patients with total hypercholesterolemia.

✓ In these patients with GMD, hypercholesterolemia reaches high values 51.16%.

✓ The decrease of HDL cholesterol in patients with total hypercholesterolemia is doubled as prevalence in comparison to the study group (10.80%).

✓ The atherogenic index records increased prevalence, three times higher in those with total hypercholesterolemia (14.40%).

✓ In these patients, instead of decreasing, smokingrecords slightly increased prevalences in comparison to the study group (40.46% vs. 38.61%).

✓ These hypercholesterolemia-associated risk factors must be taken into account for the correct evaluation of the global cardiovascular risk.

MANAGERIAL REFERENCES

Adequate treatment of total hypercholesterolemia through:

➢ physical activity of 30min/day, walking in an alert rhythm or other activities, physical education, sport

➢ limitation of high exogenous cholesterol intake (or foods like: eggs, sausages)

➢ substitution of saturated fatty acids with foods rich in unsaturated fatty acids (vegetable fat, fish, lean white meat, etc.)

➢ increase of food intake rich in ethyl esters/sterols (special margarine, special fortified orange juice, special chocolate bars)

➢ avoidance of food rich in refined carbohydrates

➢ food with soy bean protein content (containing isoflavones) although the tracks exist, but they are limited

➢ consumption of food rich in dietary fibers (vegetable, fruit, cereal)

➢ fight against smoking

➢ fight against alcohol abuse (>30 g/day)

Medicinal treatment involves:

▪ statins of first choice, with an assessment after three months of treatment in adequate doses in order to achieve the therapeutic goals

▪ treatment with fibrates associated to statins with the notification of a specialist physician

▪ clinical control at assessment and transaminase laboratory control

▪ CPK control only in case of reminiscent symptoms (myalgia, cramps)

▪ in case of failure when doses are increased and the statins class is changed, other hypolipemiants are worth taking into consideration:
- resins
- inhibitors of cholesterol intestinal absorption
- nicotinic acid

The need of an accurate management of patients with total hypercholesterolemia also involves:

- an exact non-pharmacological and medicinal treatment of high blood pressure
- treatment of glucose metabolism disorders
- treatment and correction of body mass index by complex activities (physical activities, diet, medication

- and surgery for the BMI ≥ 40 Kg/m^2 value)
- correction of some dyslipidemic disorders associated to total hypercholesterolemia

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SCHOOL ABSENTEEISM IN SECONDARY SCHOOL PUPILS

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REZUMAT

Scopul acestui studiu, ca parte a unei investigaţii mult mai ample, constă în determinarea cauzelor care stau la baza absenteismului şcolar şi în acelaşi timp identificarea unor măsuri pentru reducerea şi chiar eradicarea acestuia. Lotul este alcătuit din 216 şcolari mijlocii, cu o medie de 50 elevi pentru fiecare an de vârstă, de la 11 la 14 ani. Metoda de lucru se bazează pe aplicarea unor chestionare având la bază respectarea principiului anonimatului, cu întrebări legate de prezenţa elevilor la şcoală, absentarea, cauzele absentării, factori de influienţă ai absentării, modul de petrecere a timpului în timpul absentării, informarea părinţilor, atitudinea acestora legată de absentarea copiilor la şcoală şi în final. Am constatat că un număr destul de mic de elevi recunosc că absentează de la ore. Totuşi, motivele principale ale celor care absenteaza sunt lipsa interesului pentru anumite ore, plictiseala, colegii fiind principalul factor de influenţă, iar locul preferat pentru a petrece acest timp este casa, parcul, sau la internet cafe.

Cuvinte cheie: absenteism, şcolari, situaţie şcolară

ABSTRACT

The purpose of this study, as part of a much wider investigation, consists of establishing the causes of school absenteeism and also identifying some measures to reduce or even eliminate it. The group includes 216 middle school pupils, with an average of 50 pupils for each age, from 11 to 14 years. The working method is based upon anonymous questionnaires, with questions on the school attendance, absenteeism, its causes, factors influencing absenteeism, ways time is spent during absence from school, informing the parents, their atitude regarding their children being absent from school. We found that a relatively low number of pupils admit to be absent from classes. Still, the main reasons of those who are absent are lack of interest for certain classes, boredom, peers being the main influence factor, and the favourite place to spend this time is the home, the park or the internet cafe.

Keywords: absenteeism, pupils, school situation

INTRODUCTION

During recent years, school absenteeism has become increasingly spread, even among middle school pupils, reflecting their lack of interest for school, lack of motivation or even the lack of confidence in school education. If, in the case of elder pupils, the predominant absenteeism is generalized, in young pupils the selective abesnteeism is

specific, pupils only missing one or several disciplines [1-4].

The causes of school absenteeism may be related to the child's personality – lack of interest, tiresom, pasivity, family - parents' indiference, poor material status, disorganised families, lack of surveillance and, finally, causes which may be connected to school – malfunctioning teacher-pupil relationship, school overload, ineffective communication between pupil and teacher, and even the lack of interest of teachers for the preoccupations and wishes of children or even an insufficient psycho-pedagogical training of teachers, disregard for age related peculiarities in pupils [5-7].

In order to solve the problem of school absenteeism, it is imerative to first identify the causes and to establish an intervention plan. For this, anonimous questionnaires might be applied to reveal the true problems underlying absenteeism. The strict monitoring of absences by the class master, as well as the cooperation between the class master and the parents and avoiding the teacher-pupil conflicts may lead to the decrease or even the elimination of absenteeism. Also, complying to certain internal norms, maintaining an affectionate atmosphere for pupils, attractive teaching methods, a wide teacher-pupil communication and even counselling of pupils are imperative [8-13].

OBJECTIVES

Revealing the causes and methods to reduce and even eliminate absenteeism in this category of middle school pupils in order to prevent school dropout which is specific for elder pupils.

MATERIAL AND METHOD

A group of 216 Vth-VIIIth grade pupils in Oradea were included into the study. The study relied on anonimous questionnaires, with questions on school attendance, absenteeism, its causes and influencing factors, ways of spending free time during absence from school, information of parents and their position regarding their children missing classes [14,15].

RESULTS

A very low number of pupils admit to be absent from school. Nevertheless, according to the questionnaire, even if they do not admit it, 25% of pupils in the VIIth and VIIIth grades still miss classes (Figure 1).
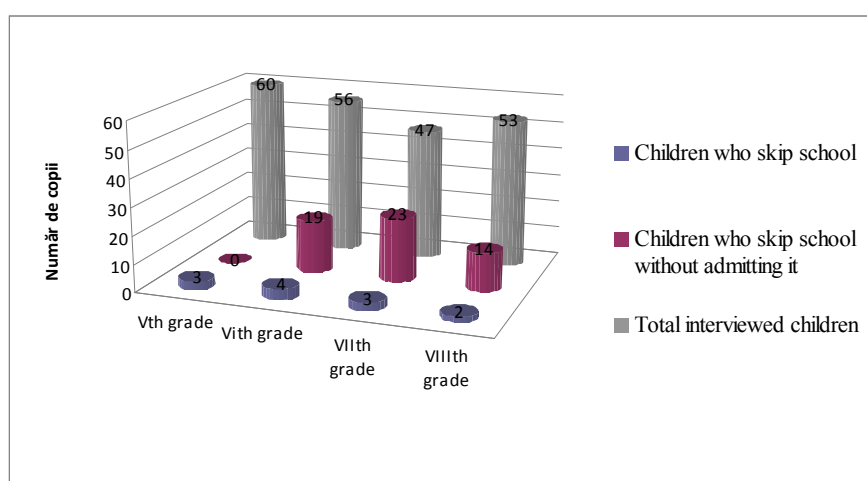

Figure 1. Distribution of children according to school attendance

The reasons given by those who do not attend school are boredom (21% in VIth grade pupils), lack of interest for school (17% in VIIth grade pupils) or for certain

topics (30% in VIIth grade pupils), but the highest percent occurs for other causes (78% in VIIIth grade, 40% in VIIth grade pupils, respectively) (Figure 2).
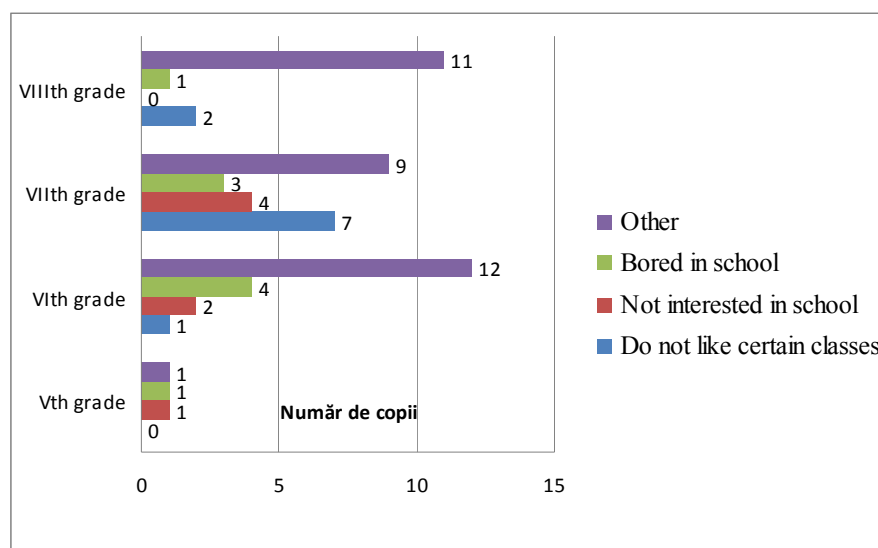

Figure 2. Distribution of pupils according to reasons for not attending classes

Most children who do not attend school spend the time on their own (43% in the case of VIIth grade pupils), but there is also a rather important percent of those who declare they spend the time with colleagues (in the case of VIIth and VIth grade pupils), or with other people (42% of the VIIIth grade pupils) (Figure 3).
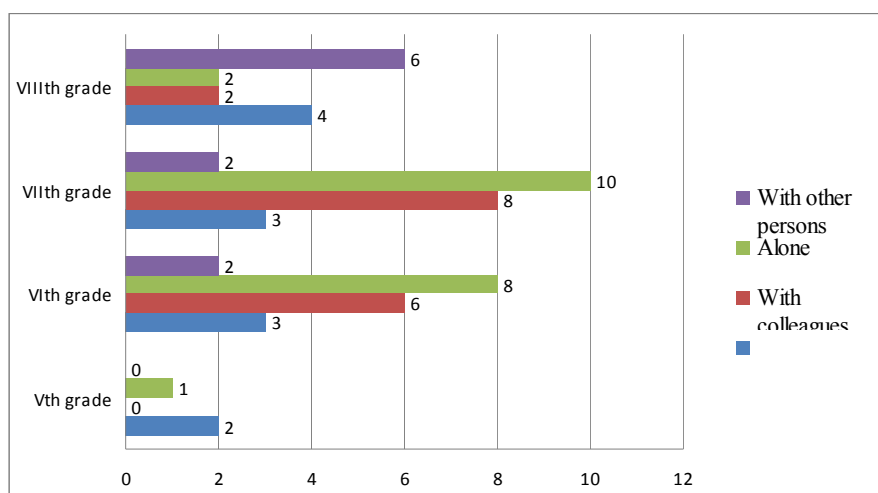
Figure 3. Distribution of pupils according to the entourage during the time they do not attend school

Colleagues and friends are those with the greatest influence on VIth and VIIth grade absentees, but surprisingly, in the case of elder pupils of the VIIth and VIIIth grades, there are pupils who declare that parents also have an influence (13% in VIIIth grade and 7% in VIIIth grade pupils, respectively) (Figure 4).
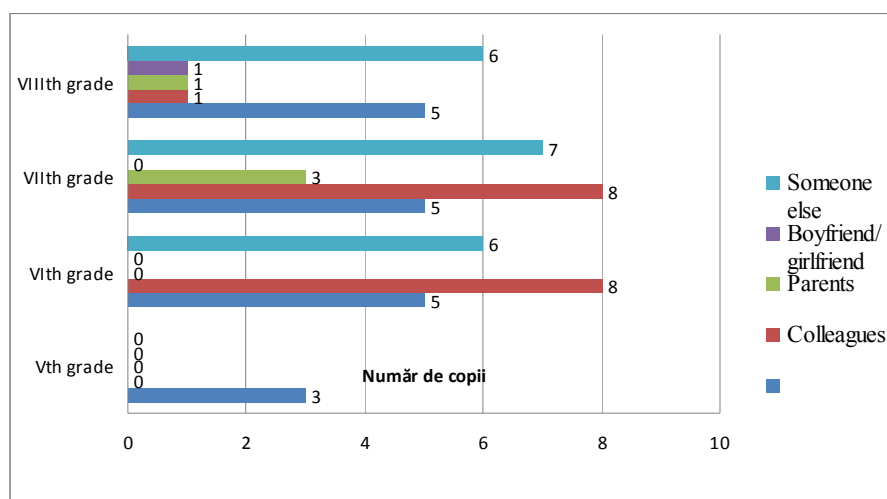
Figure 4. Distribution of pupils according to the person influencing absentees

The highest percent of VIIth and VIth grade absentees spend the time at home, and for Vth grade pupils the percent is 100%. There is a rather high percent spending the time in an internet café or in the park (21% in VIIth grade and 42% in VIIIth grade pupils, respectively, for the internet café, the percents for the park being slightly lower) (Figure 5).
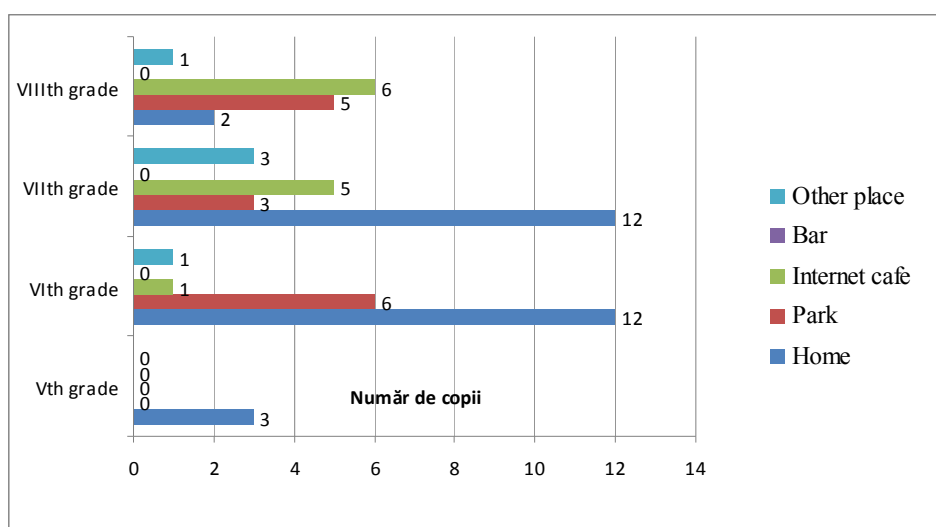

Figure 5. Distribution of pupils according to the place they spend their time while not attending school

In each age group, informing the parents on school absenteeism is predominant, and it is done by the child himself, but in the case of elder pupils, there is a rather high percent of cases when parents are not informed (21% in the case of VIIth grade, 14% in the case of VIIIth grade children, respectively). The class master informs the parents in 15% of the cases of VIth grade pupils, 17% of the cases of VIIth grade pupils (Figure 6).
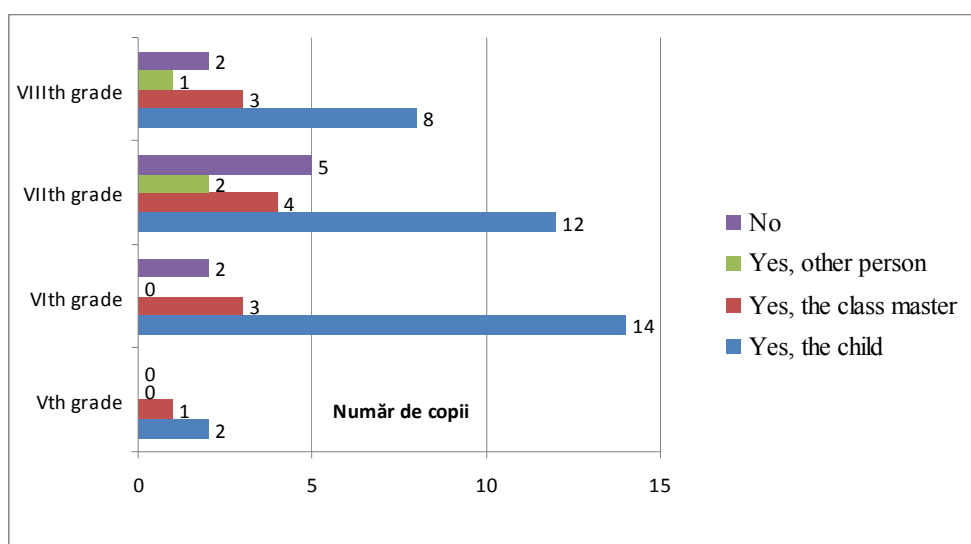
Figure 6. Distribution of pupils according to the way parents are informed on absenteeism

Parents are upset by the child's behaviour, but a much too low number (15%-17% in the case of elder pupils) talk to the child in order to find out what causes the situation and to look for solutions together with the child (Figure 7).
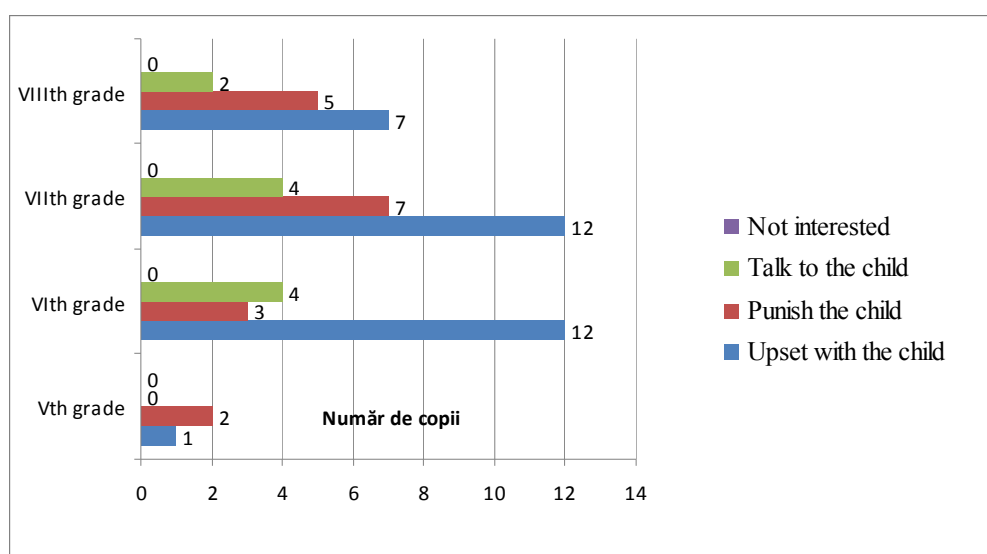

Figure 7. Distribution of pupils according to the position of parents regarding absenteeism

A proportion of 80-100% of Vth and VIth grade pupils consider they have a lot to lose if they do not attend school, but for those in the VIIth and VIIIth grades the percent abruptly decreases (Figure 8).
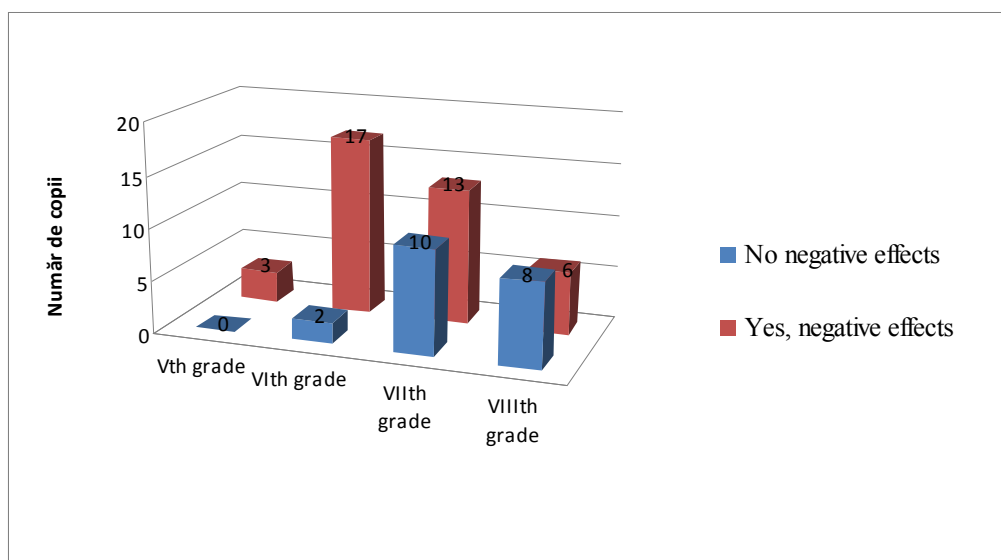
Figure 8. Distribution of pupils according to their opinion on the effects of absenteeism

CONCLUSIONS

According to the study, the main measures to be taken may be grouped according to their targets: pupil, school, family. Thus, school motivation must be increased and also it must increase self esteem in pupils, together with their intelectual stimulation and integration in the collectivity, identification of sources of stress in school, adaptation of school curricula to the peculiarities of the new generations of pupils, increasing school reliability, improvement of the pupil-school-parent relation, creation of a family environment favourable for intelectual development [14,16]. The way these measures should be developed will constitute the subject of a future thesis.

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ANTHROPOMETRIC INDICATORS IN MIDDLE SCHOOL PUPILS FROM ORADEA

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REZUMAT

Datorită marilor modificări de dezvoltare care survin în perioada şcolarului mijlociu, în contextul fenomenului de acceleraţie a creşterii, tema studiului este una mereu în actualitate, cu toate că fenomenele creşterii şi dezvoltării la om au fost în atenţia specialiştilor de peste un secol, existând un număr impresionant de studii, lucrări, programe de sănătate. Noile date permit crearea unei date de baze actualizate care să ofere suport pentru programele de sănătate. Reconsiderarea metodelor de prevenire şi corecţie, dezvoltarea unei strategii de informare şi formare, stau la baza promovării unui stil de viaţă sănătos. Obiectivul lucrarii - studiul dezvoltării fizice la şcolarul milociu. Metodologie: studiul se efectuează pe o populaţie reprezentativă de elevi din ciclul gimnazial din municipiul Oradea. Unitatea de eşantion este clasa de elevi. Antropometria permite evaluarea corpolenţei, a proporţiilor şi a compoziţiei corpului uman. Indicatorii antropometrici principali utilzaţi, raportaţi la vârstă şi sex sunt talia şi greutatea. Prelucrarea, analiza şi interpretarea statistică a datelor foloseşte metodele moderne de statistică medicală. Rezultate: studiul permite o menţinere în actualitate a evaluării stării de sănătate în perioada şcolarului mijlociu pe plan naţional, evaluare începută în România în 1950 prin măsurători antropometrice efectuate la fiecare 7 ani pentru aprecierea creşterii şi dezvoltării copiilor şi adolescenţilor între 0 – 18 ani. Studiul continuă şi augmentează cercetările efectuate în zona de vest a României, la populaţia şcolară.

Cuvinte cheie : şcolar, creştere, dezvoltare, antropometrie

ABSTRACT

Due to the multiple development changes occuring during the middle school period, in the context of the accelerated growth phenomenon, the topic of the study remains of high interest, despite the fact that human growth and developemnt have been constantly under the attention of specialists for over a century, with an impressive number of studies, papers, health programmes. New data allow the creation of an up to date database to offer support for health programmes. Reconsidering prevention and corrective methods, developing a strategy for information and training, are fundaments for promoting a healthy life style. Objective of the paper: the study of physical development in middle school pupils. Methodology: the study is conducted in a representative population of gymnasium pupils in the municipality of Oradea. The sampling unit is the classroom of pupils. Anthropometry allows the assessment of the human body mass, proportions and composition. The main

anthropometric indicators used, reported to age and gender, are height and weight. Data processing, analysis and statistical interpretation uses modern methods of medical statistics. Results: the study allows constant focus on the health status assessment during middle school on a national level, which has been initiated in Romania after 1950 by anthropometric measurements performed every 7 years to evaluate growth and development of children and adolescents aged between 0 and 18 years. The study continues and augments the researches performed in the Western area of Romania, in school aged population.

Keywords: *pupil, growth, development, anthropometry*

INTRODUCTION

In our country, a series of studies on pupil growth and development have been conducted beginning with the researches of Valeria Roşca in 1926. Starting with the year 1950, in Romania, health surveillance programmes have been conducted every 7 years in children, using somatoscopic, somatometric and physiometric indicators. During recent years, these studies intensified, Brigitha Vlaicu focusing with special attention on this growth and development phenomenon, in all regions of Romania, performing laborious studies since 1994 and up to the present. The results of these studies reveal the following average values of height and weight in middle school pupils, boys and girls, urban residents (Tables 1, 2).

Table 1. Dynamics of the height anthropometric indicator in middle school pupils, boys and girls, in our country, 1992

Growth period	Age	Boys	Girls
		Average values (cm)	Average values (cm)
Middle school 11 – 14 years	11 years	142.02	142.74
	12 years	147.52	149.71
	13 years	154,46	155.04
	14 years	161.97	156.06

The height and weight growth are relatively slow and stable during the first years of the interval. A sudden intensification, with a growth increase, occurs during the prepubertary period and towards the end of the middle school stage, during early adolescence. Thus, if the annual height growth rate is reduced at the age of 6-9 years, it reaches 5-6 cm per year until the age of 10-11 years and 6-7 cm per year during the immediately following period. Height accumulation is mainly achieved by elongation of the lower limbs and later by the growth of the torso.

Regarding height, there are several differences, both between the two genders, as well as between children from urban versus rural areas. Thus, if between 6-10 years, figures on the height of boys are higher than in girls, the latter present a more obvious height growth than in boys around the ages of 10 and 14 years, respectively. Also, in our country during recent years a decrease of the period when girls had a

better satural development than boys has been observed. Average data on height

development in rural areas are 4-7 cm lower for the same age group.

Table 2. Dynamics of the weight antrhopometric indicator in middle school pupils, boys and girls, in our country, 1992

Growth period	Age	Boys	Girls
		Average values (Kg)	Average values (Kg)
Middle school 11 – 14 years	11 years	33.98	34.26
	12 years	37.88	39.05
	13 years	43.05	44.07
	14 years	48.87	48.80

In Romania, weight gain is maximal between 11-14 years in girls and between 12-15 years in boys, with an annual growth rate of 2-3 kg between 7-11 years, followed by a more rapid growth of 6 kg per year in the 14-15 years age interval. The weight growth rhythm is more intensified during the first period in girls. The weight of boys is clearly superior as compared to girls, except for the 11-13 years age interval in urban areas and 12-14 years in rural areas, due to differences in the onset of puberty [1-3].

OBJECTIVE

Determining the anthropometric indicators for the study of physical development in middle school pupils.

MATERIAL AND METHOD

A number of 216 Vth to VIIIth grade pupils in Oradea were included into the study. The study was based upon specific anthropometric measurements, height and weight [4-6].

RESULTS

Following the anthropometric measurements performed in the 216 middle school pupils, we found 159 children with a harmonious physical development and 57 children with a disharmonious physical development. Differences between these children may be observed in Table 3.

Table 3. Physical development in Oradea gymnasium pupils

Physical development	Vth grade	VIth grade	VIIth grade	VIIIth grade
Total number of examined subjects	60	56	47	53
Total number of examined subjects with a harmonious physical development	45	41	31	42

Total number of examined subjects with a disharmonious physical development	15	15	16	11
Excessive weight	14	13	12	9
Underweight	1	2	4	2
Weight indicators				
Very low	0	0	1	1
Low	1	2	3	1
Medium	45	41	31	42
High	10	3	8	7
Very high	4	10	4	4
Height indicators				
Very low	0	0	1	1
Low	3	4	2	2
Medium	45	41	31	42
High	5	6	6	3
Very high	7	5	7	5
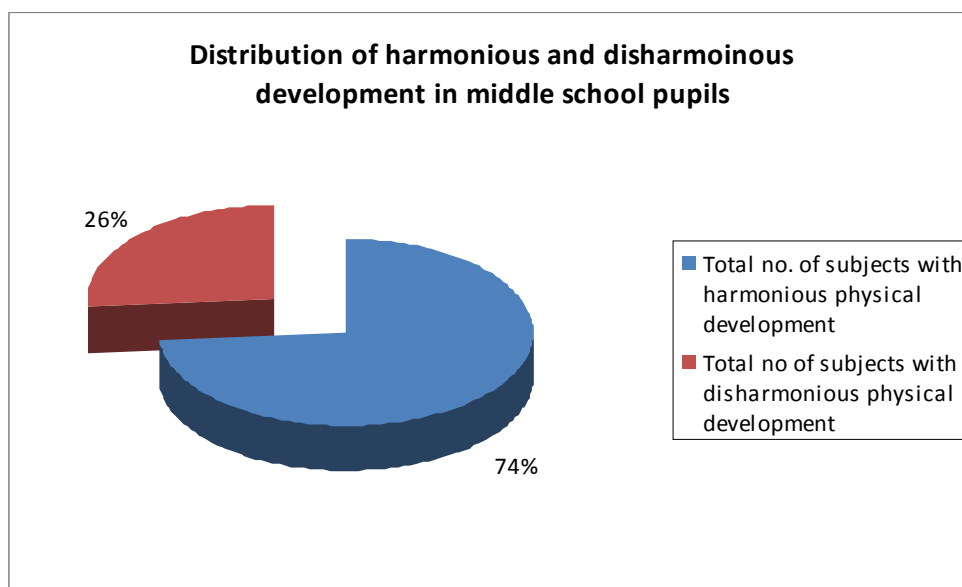
Figure 1. Percent distribution of middle school pupils with harmonious and disharmonious development

The above figure shows that one quarter of the examined children have a disharmonious physical development. The proportions of children with a harmonious and disharmonious physical development are

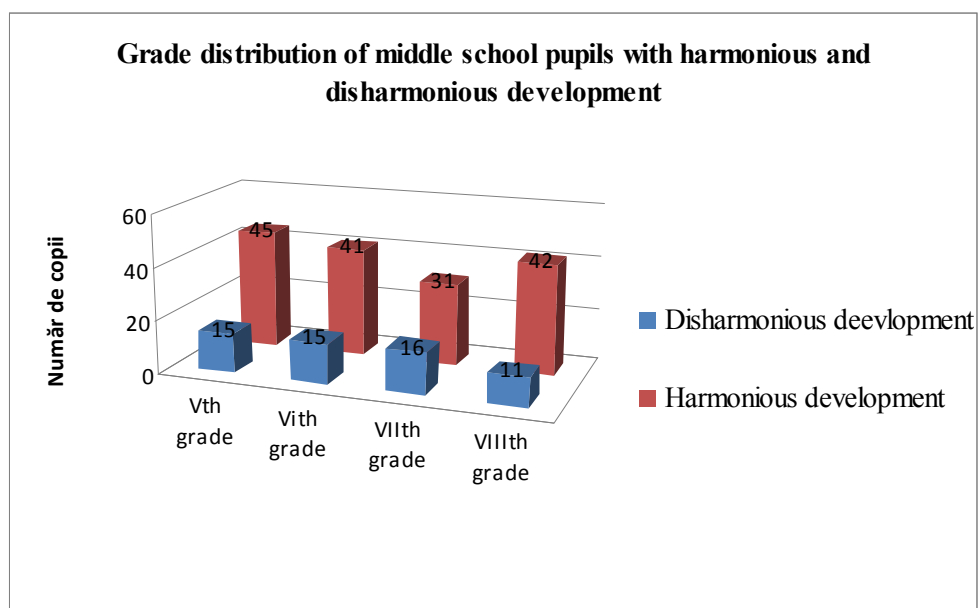approximately the same for each grade   (Figure 2).

Figure 2. Percent grade distribution of middle school pupils with harmonious and disharmonious development

In the group of children with dsharmonious physical development, overweight subjects are predominant for the entire group and in all grades (Figures 3,4).
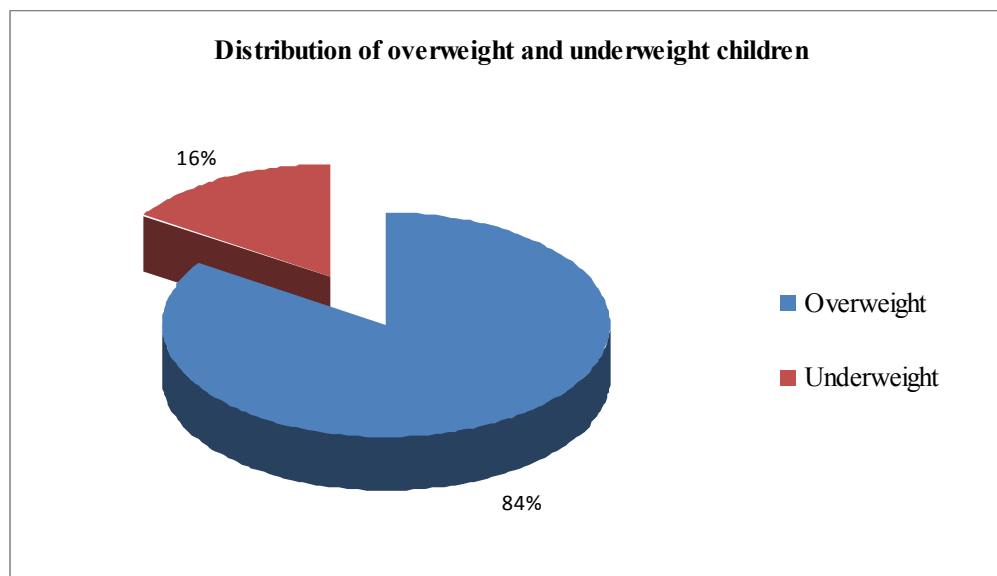

Figure 3. Percent distribution of middle school pupils with disharmonious development
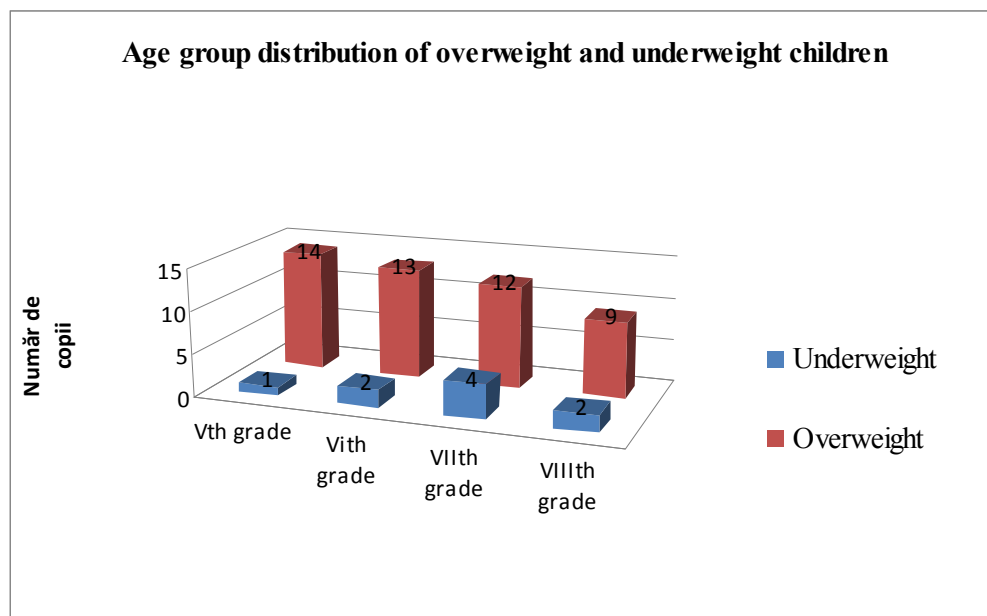
Figure 4. Grade specific percent distribution of middles school children with disharmonious development

The figure below shows that the number of children with a medium weight indicator is predominant, with still several cases with high and very high indicator levels, especially in the Vth and VIth grades, as well as a small number of low and very low indicator values (Figure 5).
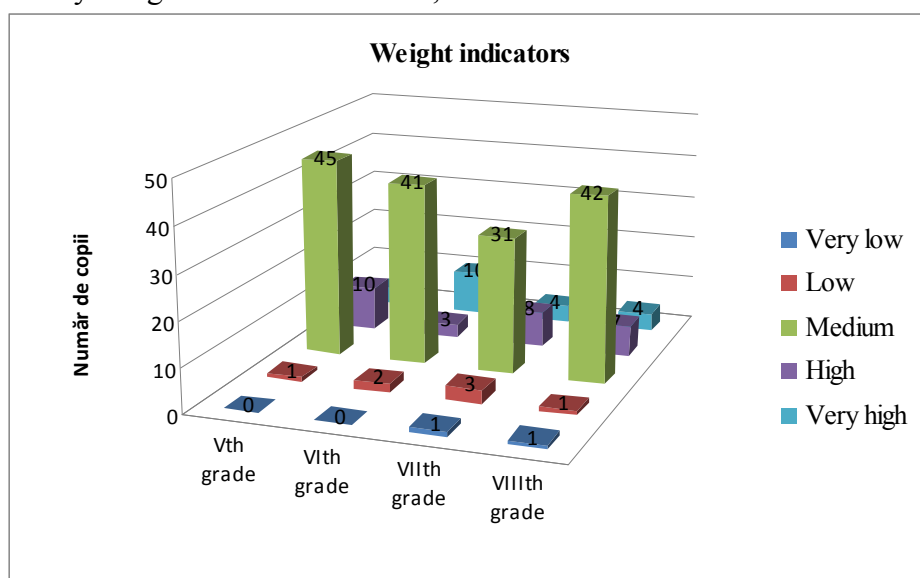

Figure 5. Percent, grade specific distribution of middle school pupils according to the weight indicator
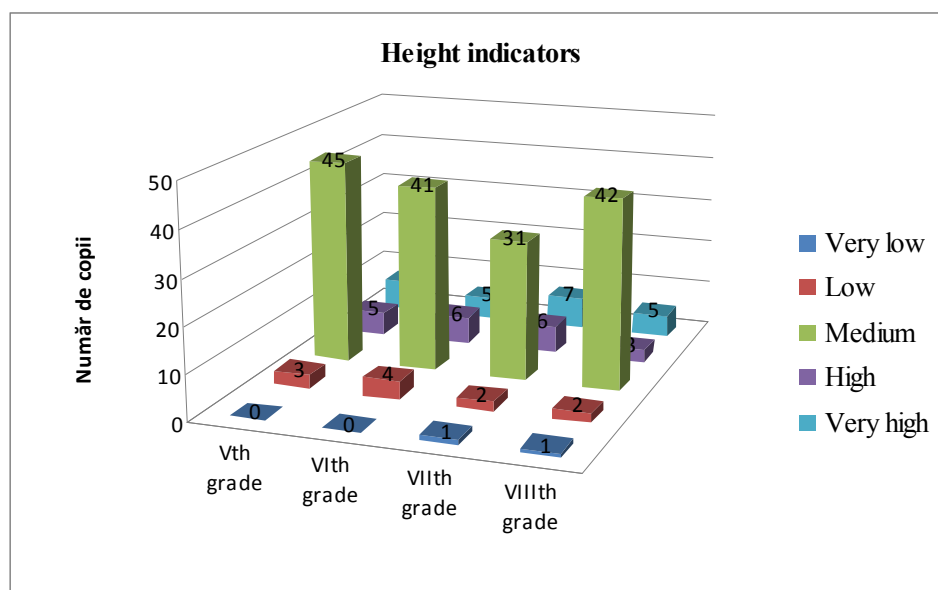
Figure 6. Percent, grade specific distribution of middle school pupils according to the height indicator

The figure above shows that the number of children with a medium height indicator is predominant, with still several cases with high and very high values, as well as with a small number of low and very low indicator values (Figure 6).

CONCLUSIONS

One quarter of the examined children have a disharmonious physical development. In this category of disharmonious children, those with overweight are predominant in each age group of the middle school category.

Starting from these results, health programmes linked to the information and training of pupils on healthy lifestyles, especially on nutrition, sports and actively spending free time, may be implemented [7-10].

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CLINICAL AND PERSONALITY CORRELATES IN MAJOR DEPRESSIVE DISORDER COMORBID WITH CHRONIC MEDICAL DISEASES – A PILOT STUDY

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REZUMAT

Introducere. Tulburarea depresivă majoră, cea mai prevalentă afecţiune psihiatrică în populaţia generală, ridică mai multe probleme clinice, comorbiditatea cu afecţiunile medicale cronice fiind una dintre acestea. Obiectivul principal al prezentului studiu, a fost acela de a identifica factorii referitori la caracteristicile clinice şi cele de personalitate, ce ar putea fi asociaţi în mod semnificativ cu apariţia comorbidităţii medicale la pacienţii cu depresie majoră. Material şi metodă. A fost realizat un studiu transversal ce a inclus 32 de pacienţi spitalizaţi în Clinica de Psihiatrie Timişoara, în perioada 2011 – 2012. Toţi subiecţi au îndeplinit criteriile diagnostice a DSM-IV-TR pentru tulburarea depresivă majoră. Ulterior, din lotul iniţial de 32 subiecţi au fost generate două subloturi inegale. Sublotul studiat, a fost alcătuit din 22 de subiecţi ce au prezentat şi comorbidităţi cu afecţiuni medicale, în timp ce sublotul de control, format din restul de 10 subiecţi nu au prezentat nici o comorbiditate cu vreo afecţiune medicală. Severitate depresiei a fost auto-evaluată psihometric cu Invetarul Beck de Depresie, iar severitatea simptomelor anxioase a fost auto-evaluată cu Inventarul Beck de Anxietate. Pentru evaluarea trăsăturilor de temperament şi caracter, s-a administrat Inventarul de Temperament şi Caracter versiunea 9, a cărui autor este Cloninger. Rezultate. Existenţa comorbidităţilor medicale cronice a fost un fenomen clinic mai frecvent decât lipsa acesteia (71% din numărul total de subiecţi), iar 3 subiecţi (9%) au prezentat două sau mai multe afecţiuni medicale cronice. Surprinzător, severitatea simptomelor depresive şi anxioase nu s-a corelat semnificativ statistic cu prezenţa comorbidităţilor medicale la subiecţii cu depresie majoră. Cu toate acestea, mai multe dimensiuni temperamentale şi caracteriale au prezentat diferenţe semnificative statistic între subiecţii cu şi cei fără afecţiuni medicale comorbide depresiei majore. Concluzii. Prezenţa comorbidităţii cu afecţiunile medicale cronice constituie mai degrabă o regulă decât o excepţie. Apariţia comorbidităţilor medicale cronice la pacienţii cu depresie majoră ar putea fi mai bine explicată prin profilul de personalitate a acestor pacienţi. Este cunoscut faptul că,

trăsăturile de personalitate îşi poate avea fundamentele lor inclusiv în substratul neurobiologic al individului şi că acestea preced cu mult timp apariţia primului episod depresiv major.

Cuvinte cheie: comorbiditate medicală, tulburare depresivă, personalitate

ABSTRACT

Background. Major depressive disorder, which is the most prevalent psychiatric disorder among the general population, raises several clinical challenges, medical comorbidity being one of them. Our main objective was to identify those clinical and personality factors that are closely related to medical comorbidity occurrence in major depressed subjects. Subjects and methods. A cross-sectional study was conducted on 32 patients who received hospitalization in Timişoara Psychiatric Clinic from 2011 to 2012. The subjects met the DSM-IV-TR diagnostic criteria for major depressive disorder. Subsequently, the initial sample of 32 patients was divided in two uneven subsamples. The subsample representing the study group comprised 22 subjects who presented medical comorbidities while the other subsample was made up of 10 subjects who showed no sign of such comorbidities. The latter constituted the control group. The severity of depression was measured by means of the self-reported Beck Depression Inventory while the severity of anxiety symptoms was assessed by the Beck Anxiety Inventory. The Temperament and Character Inventory version 9, conceived by Cloninger was employed as a self-reported personality inventory. Results. The co-existence of chronic medical comorbidities was more frequent than their lack (71% of the total number of subjects), and 3 subjects (9%) have had more than one chronic medical condition. Surprisingly, the severity of depressive symptoms and of anxiety did not correlate with the presence of chronic medical diseases. However, several dimensions of temperament and character have manifested significant statistical difference in subjects suffering from Major Depressive Disorder, and who presented or not comorbid physical illnesses. Conclusions. The presence of chronic medical comorbidity in subjects who also have major depressive disorder is rather a rule than an exception. The occurrence of chronic medical comorbidity in major depressive patients could be better explained by the personality profile. It is well-known that the personality profile has deep extensions in the neurobiological substrate of individuals and that precedes long before the first major depressive episode.

Keywords: medical comorbidity, Major Depressive Disorder (MDD), personality

INTRODUCTION

As regards the prevalence of morbid conditions among the U.S. general population, during the period 2001- 2003, the results provided by National Comorbidity Survey – Replication have revealed that 58% of the adult population suffers from at least one medical disease while 25% are affected by at least one mental illness. Indeed, what was striking was that most individuals suffering from mental disorders (68%) were also affected by one simultaneous medical comorbid disease. Hence, we can objectively draw the conclusion that mentally ill subjects are more prone to medical comorbidity in comparison with those subjects with no psychiatric conditions [1]. We shall mention from the very beginning that the terms "medical diseases" and "physical diseases" will be used interchangeably in the present article.

Closely following the survey mentioned above, other several studies pointed out that the presence of depressive symptoms, irrespective of their severity, will increase the incidence of certain medical diseases which have the tendency to become chronic. Thus, the meta-analysis performed by Van

der Kooy et al., has revealed that subclinical depression moderately increases the risk of coronary heart disease, myocardial infarct and cerebrovascular diseases. The same study has indicated that major depression or clinically significant depression represents a risk factor for cardiovascular diseases, and it is at least as significant as smoking or as diabetes mellitus [2].

Once the coronary heart syndrome is installed, the subsequent occurrence of depression symptoms increases by three times the death rates for this category of patients [3]. Moreover, the depression symptoms are a strong predictor of hypertension in young adults [4].

A large population-based study, conducted prospectively and over a period of ten years, has revealed that the presence of depression symptoms and of anxiety were predictors of the development of diabetes mellitus type 2 [5].

From another perspective, the presence of medical comorbidity in major depressive patients may as well be considered a significant factor and resistance to antidepressant treatment [6].

Last but not least, the connection between certain chronic medical diseases and major depression should be analyzed according to the personality terrain of the subject. Thus, some studies have failed to demonstrate a linear correlation between the severity of depression symptoms and both the magnitude of medical comorbidity and the physical health decline [7,8]. Hence, it is very likely that temperament and character traits of personality, which have the deep extensions in biologic level of individuals, could explain better than clinical features of depression, the higher comorbidity of major depressed subjects with certain medical diseases. Moreover, the long lasting biological substrates of personality traits could be considered as a common terrain with increased diathesis for both major depression and certain medical diseases.

When discussing on the dimensional perspective of personality, one study has emphasized the higher death rates caused by medical diseases in subjects with higher levels of neuroticism [9]. On the other hand, following the categorical perspective of personality in DSM-IV-TR, several studies have indicated the strong connection between the borderline type of personality and medical diseases; a link mainly explained by the unhealthy habits of the subjects [10].

The main aim of the present study was to investigate the possible links between clinical features of major depressive episode and personality traits on the one hand, and the presence of chronic medical diseases, on the other hand in patients who suffer from Major Depressive Disorder.

SUBJECTS AND METHODS

Design
A cross-sectional research was performed on subjects hospitalized in Timişoara Psychiatric Clinic during 2011 – 2012. The patients met the DSM-IV-TR diagnostic criteria for Major Depressive Disorder (MDD) [11]. Although the ICD – 10 diagnostic criteria are used at the level of our national health system, we believe that the DSM – IV TR diagnostic criteria are more adequate for research purposes.

From the initial sample of 83 eligible subjects, only 63 gave their informed consent to take part in the study. Out of 63 patients, 16 presented partial remission from major depression and that is why they had to be excluded from our study. Another 15 subjects provided incomplete responses to administered inventories and so their data could not be processed.

The initial sample of 32 subjects was further on subdivided in two subsamples according to the presence or the absence of medical comorbid diseases. Thus, one subsample

encompassed N=22 subjects with MDD and at least one medical comorbidity, too. The other subsample comprised the remaining 10 subjects, who presented MDD but no medical comorbidity. The two subgroups were relatively homogeneous in terms of age and sex distribution, and therefore open to comparisons.

Among inclusion criteria we mention the following: a diagnostic of MDD, except the presence in the current or previous episode of psychotic features, age structure between 18 and 65, and the informed consent to participate in the study. Exclusion criteria were mainly as follows: the presence of another psychiatric disease (besides MDD), patients over the age of 65, the presence of organic diseases which could lend a better explanation for the mood episode, patients following medication already accepted as facilitating or determining the onset of depression, the lack of informed consent, smoking habits and the presence of psychotic symptoms during the previous mood episodes. The latter necessitated the treatment with antipsychotics for a period of time. The last two exclusion criteria could be considered confounding factors for the developing of certain chronic medical diseases.

Measures
The clinical symptomatology of major depressive episodes was recorded during the subjects' admission in Timisoara Psychiatric Clinic while their personality profile was assessed in ambulatory psychiatric service as soon as the depressive episode remission was achieved. The Beck Depression Inventory (BDI) was used as an instrument for measuring the severity of depressive symptoms. At the same time, the Beck Anxiety Inventory (BAI) was employed for measuring the anxiety symptoms. Temperament and Character traits of personality were dimensionally assessed by means of the Temperament and Character Inventory (TCI) version 9, conceived by Cloninger. As already pointed out, TCI has

been developed in order to evaluate both the temperament and the character domains of personality.

The research datasheet was filled out in order to collect all clinical and anamnesis information about each patient. The socio-demographical, family and personal historical of diseases along with other important clinical information resulted from anamnesis.

Data Analysis
Data were processed using SPSS Statistics 17.0, and the method involved the use of descriptive statistics, and by applying statistical tests such as unpaired t test (CI=95%).

First, we performed a statistical analysis on the entire or the initial sample, which included all subjects suffering from MDD, and with or without medical comorbidity. At this phase, we employed methods which consist in descriptive statistics.

Subsequently, we applied a comparative analysis to the two subsamples (one which presented medical comorbidity while the other did not). As the samples were uneven, the unpaired t test (CI=95%) was used for comparing several items of these subgroups.

RESULTS

The results of the entire sample
As easily noticed, the vast majority of subjects were females, and mostly living in urban areas. The mean age for the initial sample was 52. The premorbid skills underlying the social interactions were fairly good as compared with other categories of subjects suffering from major psychiatric disorders. The fact is revealed in the higher percent of married subjects. The descriptive data referring to premorbid academic skills also show that the majority of subjects have at least a medium level of education so a good functioning level (Table 1).

Table 1. Characteristics of the initial sample during their admission in Timişoara Psychiatric Clinic

Characteristic	n = 32	Range
Female, *n (%)*	23 (72)	
Age (years), M ± SD	51.78 ± 12.05	28 - 74
Married, *n (%)*	25 (78)	
Education (Gymnasium), n (%)	18 (56)	
Urban residence, *n (%)*	23 (72)	

M ± SD = mean ± standard deviation

It should be noted that the dynamics of professional performance over the period marked by MDD had negative outcomes. Major depression bore a significant impact on the subject's life, even though the results didn't achieve statistical significance (Figure 1).
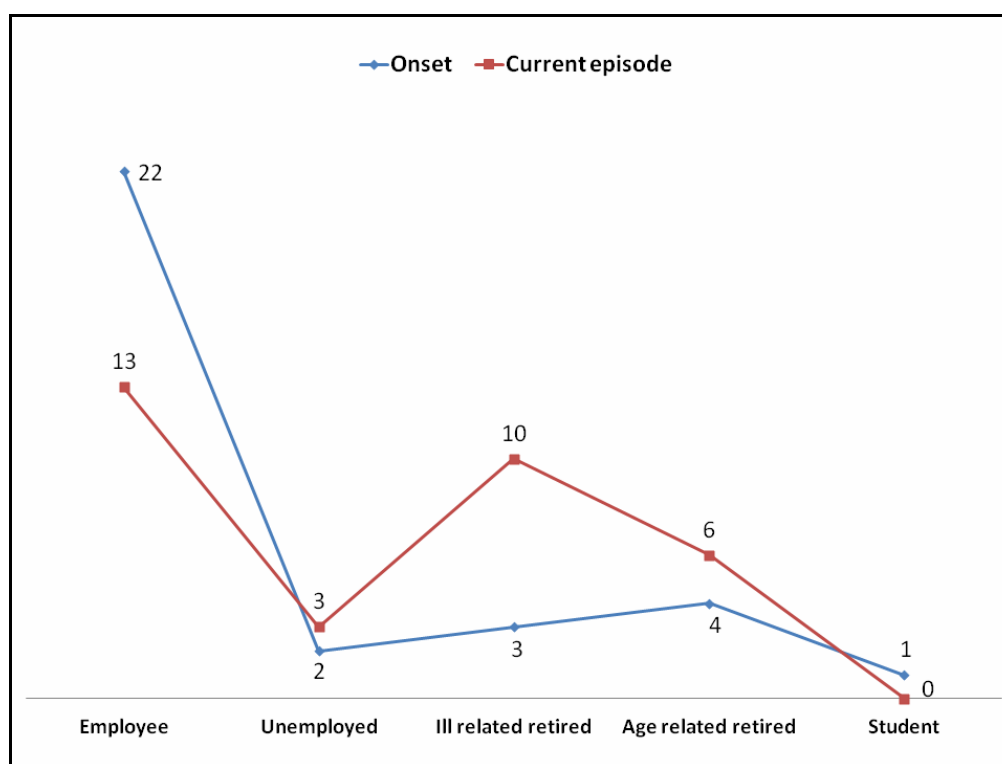
Figure 1. The professional outcomes in subjects with MDD during their psychiatric illness

Scholarly literature has shown that major depression carries a significant genetic load when compared with other psychiatric disorders [12]. Taken into consideration were the psychiatric disorders present in first degree relatives of the subjects with MDD. Thus, the initial sample comprised almost one fifth of subjects having at least one first degree relative suffering from major depression (documented by medical

records). At the same time, there were three subjects with positive family history of alcohol dependence while one patient had one relative who suffered from bipolar affective disorder (Table 2).

Table 2. The family history of psychiatric disorders among the initial sample diagnosed with MDD

Positive familial history of psychiatric disorder	n (%)
Without any psychiatric disorder	22 (69)
Major Depressive Disorder	6 (19)
Alcoholism	3 (9)
Bipolar Affective Disorder	1 (3)

Medical comorbidity was rather a rule than an exception with (n = 22) more than two-thirds of major depressed subjects having had at least one chronic medical disease. Moreover, three subjects have presented two comorbid medical diseases. As regards the types of medical diseases affecting subjects with MDD, we encounter the same tendency as in the general population: cardiovascular diseases have been ranked first. Digestive diseases come second, while musculoskeletal diseases come third. There still remains as an open question the extent to which the aforementioned musculoskeletal diseases were truly organic diseases or whether they rather were functional disorders, or even epiphenomena associated with depressive experience.

Table 3. Chronic medical comorbidities in subjects with MDD

Chronic medical comorbidity (types)	n (%)
Without medical comorbidity	10 (31)
Cardiovascular diseases	11 (34)
Digestive diseases	9 (28)
Musculoskeletal diseases	3 (9)
Diabetes Mellitus type 2	1 (3)
Bronchial Asthma	1 (3)
More than 1 medical comorbid disease	3 (9)

Results based on the presence versus the absence of medical chronic comorbidity
In order to simplify the labeling of the two samples, we shall further on use the label of studied subjects for the subjects with MDD and chronic medical comorbidity while the label of controls will be used for the subjects who suffer from MDD and no chronic medical comorbid disease.

The research maps no statistical correlation between the severity of depression and/or anxiety symptoms and the presence of medical comorbidity. This result could be better explained by the small size of the samples. However, rather as a tendency, it can be noticed that the severity of depressive symptoms have had a greater weight on the presence of medical comorbid

diseases than the severity of anxiety symptoms.

Table 4. The correlation between the severity of depressive and anxiety symptoms and chronic medical comorbidities in subjects with MDD

		Levene's Test for Equality of Variances		t-test for Equality of Means				95% Confidence Interval of the Difference	
		F	Sig.	t	Sig. (2-tailed)	Mean difference	Std. Error Difference	Lower	Upper
DEPRESSIVE & ANXIETY SYMPTOMS	Total score of Beck Anxiety Inventory	0.221	0.642	-0.386	0.702	-2.1	5.445	-13.221	9.021
	Total score of Beck Depression Inventory	1.353	0.254	1.071	0.293	3.036	2.835	-2.753	8.826

As concerns the three life domains, the Sheehan Disability Scale has indicated that medical comorbidity has a more negative impact on studied subjects than on controls. But the differences didn't achieve statistical significance. Also, rather as a tendency, we have registered that the work/school and social life domains are more impaired than family life/home responsibilities.

Table 5. The impact of chronic medical comorbidity on work / school, social life and family life/home responsibilities

		Levene's Test for Equality of Variances		t-test for Equality of Means				95% Confidence Interval of the Difference	
		F	Sig.	t	Sig. (2-tailed)	Mean difference	Std. Error Difference	Lower	Upper
SHEEHAN DISABILITY SCALE	Work / School	0.18	0.674	1.356	0.185	1.309	0.965	-0.662	3.281
	Social Life	0.672	0.419	1.353	0.186	1.182	0.873	-0.602	2.965
	Family Life / Home Responsibilities	0.511	0.48	0.885	0.383	0.873	0.987	-1.142	2.888

Further down we shall present the temperament and character features associated with a higher level of physical diseases in subjects having MDD.

As already pointed out, the subjects' temperament and character have been assessed with the aid of the Temperament and Character Inventory (the 240-item version). This tool measures four temperament dimensions (novelty seeking, harm avoidance, reward dependence and persistence) and three character dimensions (self-directedness, cooperativeness and self-transcendence).

When comparing the two categories of subjects - the subjects with MDDs but no medical disorders and the subjects with comorbid physical diseases - we notice that the latter present significantly higher scores in the temperamental dimension of Harm Avoidance; more precisely, at the level of the following items: Shyness with Strangers and Fatigability vs. Vigor (Table 6).

When all character dimensions are considered (that is, Self-Directedness, Cooperativeness and Self-Transcendence), we may conclude that subjects having MDD and comorbid medical diseases present significantly higher total scores as compared with those without any medical diseases.

Table 6. The interpretation of scores referring to the temperament and character dimensions of personality; a comparison between individuals who suffer from MDDs and chronic medical comorbid diseases and subjects with MDDs and no chronic medical comorbid diseases

		Levene's Test for Equality of Variances		t-test for Equality of Means				95% Confidence Interval of the Difference	
		F	Sig.	t	Sig. (2-tailed)	Mean difference	Std. Error Difference	Lower	Upper
HARM AVOIDANCE	HA1 Anticipatory worry and Pessimism vs Uninhibited Optimism	0.389	0.537	-0.393	0.697	-0.345	0.878	-2.139	1.448
	HA2 Fear of Uncertainty	0.002	0.966	1.084	0.287	0.636	0.587	-0.563	1.835
	HA3 Shyness with Strangers	0.133	0.717	2.877	0.007	1.791	0.622	0.52	3.062
	HA4 Fatigability vs Vigor	1.714	0.2	2.628	0.013	1.873	0.713	0.417	3.328
	HA Harm Avoidance total	2.234	0.145	1.863	0.072	3.955	2.122	-0.38	8.289
SELF-DIRECTEDNESS	S1 Responsibility vs Blaming	1.772	0.193	0.702	0.488	0.5	0.712	-0.954	1.954
	S2 Purposefulness vs Lack of Goal Direction	1.525	0.226	0.991	0.33	0.609	0.615	-0.646	1.864
	S3 Resourcefulness vs Inertia	0.288	0.596	1.384	0.177	0.673	0.486	-0.32	1.666
	S4 Self-Acceptance vs Self-Striving	0.512	0.48	3.912	0.0001	3.282	0.839	1.568	4.995
	S5 Congruent Second Nature vs Bad Habits	0.211	0.649	2.29	0.029	1.482	0.647	0.16	2.803
	S Self-Directedness total	1.299	0.263	3.163	0.004	6.545	2.07	2.319	10.77
COOPERATIVENESS	C1 Social Acceptance vs Social Intolerance	0.006	0.939	2.763	0.01	1.7	0.615	0.443	2.957
	C2 Empathy vs Social Disinterest	0.135	0.715	-0.167	0.868	-0.1	0.599	-1.322	1.122
	C3 Helpfulness vs Unhelpfulness	2.494	0.125	0.56	0.579	0.3	0.535	-0.793	1.393
	C4 Compassion vs Revengefulness	14.61	0.001	1.384	0.177	1.073	0.775	-0.511	2.656
	C5 Integrated Conscience vs Self-Serving Advantage	1.262	0.27	1.132	0.266	0.682	0.602	-0.548	1.911
	C Cooperativeness total	0.171	0.682	2.158	0.039	3.745	1.735	0.202	7.289
SELF - TRANSCENDENCE	ST1 Creative Self-Forgetfulness vs Self-Consciousness	0.679	0.417	-2.688	0.012	-2.727	1.015	-4.8	-0.655
	ST2 Transpersonal Identification vs Personal Identification	1.363	0.252	-1.408	0.169	-1.091	0.775	-2.673	0.491
	ST3 Spiritual Acceptance vs Rational Materialism	4.986	0.033	-1.441	0.16	-1.418	0.984	-3.428	0.591
	ST Self -Transcendence total	1.625	0.212	-2.285	0.03	-5.236	2.292	-9.917	-0.555

DISCUSSION

The present paper has drawn attention to several facts. As already pointed out by other studies, it is females and people in urban areas that are more likely to suffer from MDD. These results are consistent with other prestigious studies performed in the U.S. [13]. Several explanations can be offered: subjects living in urban areas are

confronted with more economic problems than the people who live in rural settlements. As regards the gender vulnerability to depression, in Romania, this factor should be considered (at least partially) as being caused by cultural factors. Like in other Eastern European countries, in Romania, as well, women usually fulfill more duties than males do; these duties are related to housekeeping, childcare and profession.

The functional remission from major depressive episodes (not only the clinical remission of symptomatology) still remains an open and thought-provoking issue on MDD. The current paper indicates that MDD has a negative impact on professional abilities. Unfortunately, most depressed subjects - engaged in professional activities at the moment of the index episode of clinical depression - cease to remain professionally active after several years of MDD [14, 15].

As expected, the presence of at least one other medical disease in MDD subjects was rather a rule than an exception. Moreover, the following come in support of our findings: the neurobiological fundaments of MDD, which partially overlay with factors involved in several medical diseases (such as inflammation markers, platelet activity, coagulation factors dysfunction, endothelial dysfunction, cortisol activity) and more specifically with psychosocial contributors like personality, coping style, unhealthy behaviors, social support etc [16, 17, 18, 19]. Like in the case of the general population, cardiovascular diseases are the most frequent among MDD while digestive diseases came second. Still open to research is whether those functional digestive disorders should be considered rather a somatic projection related to depressive experience in our cultural space.

Somewhat debatable, the present study did not indicate a significant correlation between the severity of depressive and / or

of anxiety symptoms and the presence of comorbid physical diseases. This result is line with other studies which have pointed out that depression could increase the risk of medical diseases without a linear relation with its severity [20]. On the other hand, further studies are necessary in order to quantify if the negative experience of anxiety in MDD patients – most likely associated with increased physical illnesses - should be perceived rather as a trait than as a state factor.

Without achieving statistical significance, comorbid physical diseases had a differentiated impact, nevertheless. The strongest (negative) impact was on Work/School and on Social Life than on the Family Life/Home Responsibilities domains of functioning. The result may rather be a characteristic of the psychiatric disorder than the effect of medical diseases. Moreover, an analysis of the marital status category (applied to all subjects) leads us to believe that patients with MDD also have better premorbid and subsequent family functioning than subjects suffering from other severe mental illnesses.

The most important results of the current research are drawn from the dimensional aspects of personality. On the one hand, subjects having MDD comorbid with medical diseases scored higher in some of the Harm Avoidance items. Based on these findings, we can infer that subjects who experienced negative emotions during their childhood and during their adult premorbid period are also more likely to develop physical health issues. According with Cloninger, the higher scores in Harm Avoidance are rather correlated with serotoninergic dysfunction [21]. This may be the common substrate of depression and physical disease.

On the other hand, subjects with MDD and physical comorbidities have obtained higher scores in all three character domains. The higher scores for Self-Directedness could be

translated as follows: this subgroup of patients has a more pronounced sense of responsibility and of self-confidence. The higher scores in Cooperativeness could mean that the subgroup of studied subjects is more socially tolerant, emphatic, helpful and compassionate. The higher scores in Self-Transcendence reveal that the subgroup of MDD subjects, who also have medical comorbid diseases, are more open to the spiritual experience and their cognition is rather intuitive than analytical or deductive. To add more, it may be that the subjects use more passive than active coping styles when they are faced with different types of difficulties.

The limitations of our study can be related to the sample size. Further studies are needed to clarify the clinical and personality-related issues that could be correlated with increased comorbidity between MDD and chronic medical diseases.

CONCLUSIONS

Beside the epidemiological magnitude of MDD, this psychiatric condition also raises the clinical challenge of presenting a high risk of developing chronic medical comorbidities. Hence, medical comorbidities should be considered rather a rule than an exception in subjects with MDD. Therefore, clinicians should pay more attention to the physical examination of these patients and they should also ask for paraclinic investigations whenever the clinical situation indicates a suspect physical condition. Undoubtedly, medical comorbidity will affect unfavorably the prognosis of MDD; it may even be a therapeutically resistant factor.

The presence of medical comorbidities in subjects with MDD may be considered rather a result of personality issues than the direct effect of clinical symptoms. Starting from the psychobiological assumption of personality traits, it is very plausible that certain temperament traits act as an unfavorable terrain for the development of subsequent physical comorbid diseases in subjects with MDD. On the other hand, the character profile of these patients can also play a major role in the aforementioned predisposition.

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