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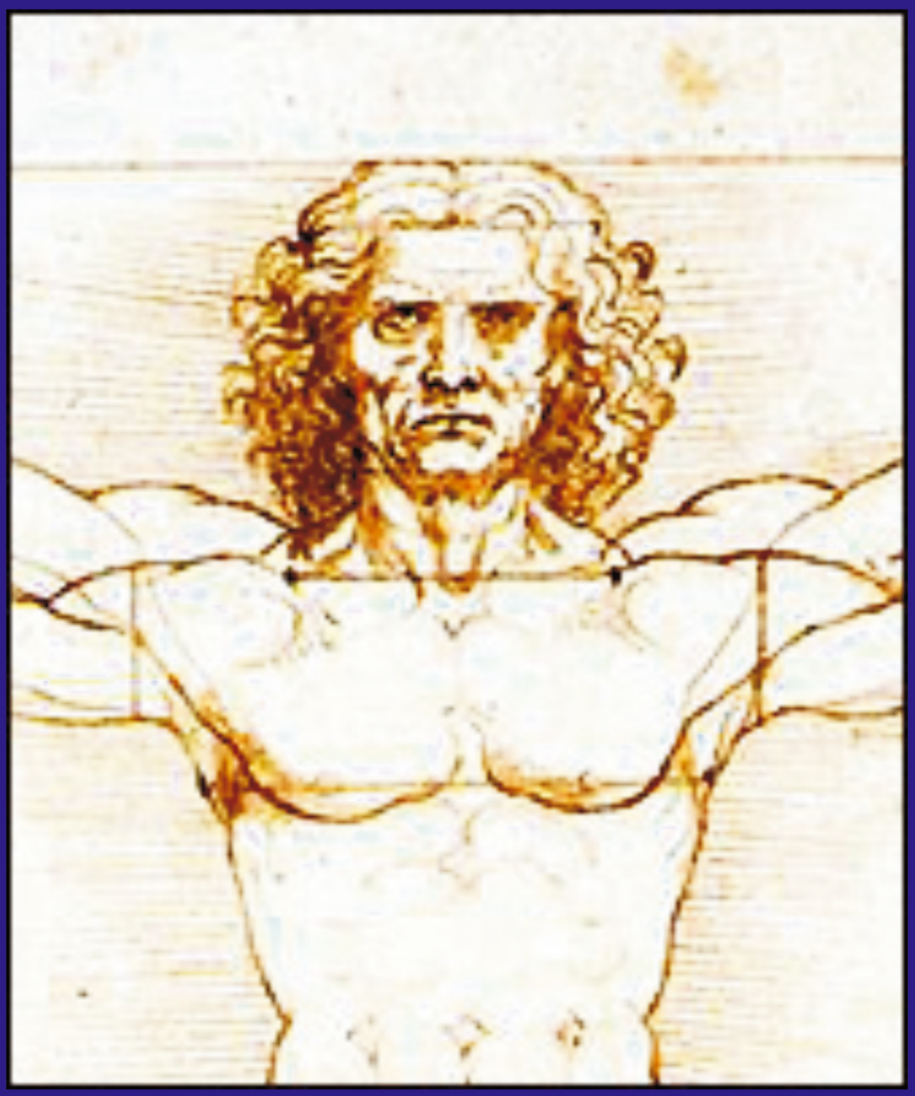

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RIJEČ UREDNIKA

Uzimajući papir da napišem par rečenica čini mi i obavezu, i zadovoljstvo da nešto kažem i osvrnem se saradnicima uredništva sa iskrenim i dužnim poštovanjem, jer oni daju poseban ton ovome što svi skupa radimo.

Kako sam po struci hirurg i slikar, podsjeti me to na jedan davni period iza nas. Postoji negde zapisano da „zlatno doba hirurgije je period poslije 1870. godine, kada se posebno izučava anatomija". Jedan paradoks tog vremjena i vremjena u kome živimo, izaziva čuđenje. Tada su se umjetnici, i to sa velikim problemima interesovali za ljudsko tijelo, njegov izgled i proporcije. „Tako je Donatelo (1386–1486), prvi slikar koji je radio disekcije ljudskog tijela. Leonardo da Vinči (1452–1519), je zasnovao portretsku i fiziološku anatomiju i tvrdio je da je sam uradio tridesetak disekcija ljudskog tijela."

Paradoks se ogleda u tome da su se ljudi koji nikada nisu imali na umu da se bave medicinom bavili ljudskim tijelom ne bi li dali svoj doprinos nauci radi bližih spoznaja u rešavanju svih tajni za to doba, u korist čovjeka, u borbi za očuvanje zdravlja. Danas, kada se tajne u medicini mijenjaju iz nedjelje u nedjelju, i kada postoje uslovi sa najsavremenijim pristupom u tehnici i kada znaju za liječenje obolelih, toliko postoji nezainteresovanost, i to baš kod onih koji su najpozvaniji da se uključe u razne programe i postanu deo medicinske nauke za dobrobit društva. Tragično je što je opao taj tonus i mnogi lekari zaustavljaju sebe u daljem radu na prvoj stepenici obrazovanja, na koju stanu po završenoj specijalizaciji.

Pa dobro, nijesu motivisani da pišu, da stvaraju, ali je još tragičnije što neki baš tada pomisle da oni već sve znaju i da su se već umorili za dalje usavršavanje. Neki su i opasni po druge jer su se uvrstili u one ljude koji „ne znaju, a misle da znaju", i njih se treba kloniti.

Takvi pojedinci su izbrisali hijerarhiju, oni bi da gaze po učiteljima, misle da je njih sam Bog poslao da rešavaju probleme, a pacijent im je noćna mora, i on je taj koji mora da trpi, čeka i traži spas. Šta bi rekao Leonardo da Vinči kada bi video hirurga koji ne zna anatomiju a ide da operiše čovjeka?

To je taj paradoks za koji ne znam da li sam ga plastično prikazao, ali znam da sam ga upotrijebio namjerno, želeći da se osvrnem na naš rad od prvog broja SANAMED-a, kada smo ga izdavali jednom godišnje i koji je od tada sazreo i stao u red časopisa starih nekoliko decenija i sada već izlazi tri puta godišnje, a po kvalitetu mnogi nam već i zavide, i većina nam čestita na njegovom uzrastu.

Po ko zna koji put moram da zahvalim našim saradnicima, a posebno sadašnjoj ekipi mladih lekara koji svojim entuzijazmom potvrđuju, kroz kvalitet onoga što čine, da je vjera u čovjeka vrijedna samo onda kad, „znaš da zna, a on zna da zna" i toga treba slijediti.

Sam život predstavlja vječitu borbu da bi se stiglo na vrh. Ako ste riješili da budete učesnik u toj borbi, budite ponosni što imate izazov, bez obzira što ćete do tog vrha biti mnogo puta povređeni i neshvaćeni.

U našem časopisu ima mnogo mesta za takve entuzijaste.

Koristim priliku da svima čestitam Novu Godinu i poželim puno uspeha u profesionalnom i privatnom životu.

Srdačan pozdrav,
Prim. dr Avdo Ćeranić
glavni i odgovorni urednik

Čitaj da shvatiš

Piši da preneseš

Uradi da te pamte

Avdo Ćeranić

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THE EFFECTS OF CHRONIC LEAD POISONING ON THE VALUES OF HYPERTENSION IN CHILDREN

Zivkovic Jovan,[1] Savic Zoran[2]

[1] Faculty of Medicine, University of Priština, based in Kosovska Mitrovica
[2] Health Center Kosovska Mitrovica

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Abstract: **Introduction:** During the treatment of Roma children from Kosovska Mitrovica suffering from chronic lead poisoning (which began in the second half of the last decade), hypertension has also been observed. The examination and treatment were conducted under the patronage of World Health Organization, Ministry of Health of the Republic of Serbia and local administration. **Aim of this work** is show correlation between lead levels in blood and hypertension in children. **Materials and methods:** Lead from capillary blood flow was measured by Lead care analyzer. Extracted blood from a vein measured lead level in the toxicological laboratory of the Institute „Karajović" Belgrade. The pressure was measured by standard devices with changeable cuffs and has been expressed in mmHg. Hypertension has been observed in 159 children. They were divided into four groups. First group: non-Roma children (n = 32) with blood lead level of up to 10 mcg/dl. Second group: Roma children (n = 31) with blood lead level of up to 10 mcg/dl. Third group: Roma children (n = 53) with blood lead levels of 10–45 mcg/dl. Fourth group: Roma children (n = 43) with blood lead levels more than 45 mcg/dl, with an average value of 61.6 mcg/dl. **Results:** There is a statistically significant difference in the elevation of systolic blood pressure between group (chi-square = 31,179; p < 0,001), the first ($\bar{x}$ = 107,2 mmHg) and the fourth group ($\bar{x}$ = 114,6 mmHg), the second ($\bar{x}$ = 104,5 mmHg) and fourth group, third ($\bar{x}$ =106,4 mmHg) and fourth group. There is a statistically significant difference in the elevation of diastolic blood pressure between group (chi-square = 32,028; p < 0,001), the first ($\bar{x}$ = 67,7 mmHg) and the fourth group ($\bar{x}$ =73,4 mmHg), the second ($\bar{x}$ = 66 mmHg) and third group ($\bar{x}$ = 69 mmHg), second and fourth group, third and fourth group of children. It is concluded that when the value of lead in the blood was higher its effect on blood pressure was more pronounced. **Conclusion:** Most children with lead levels over 45 mcg/dl have developed an increased blood pressure as well, which required further observation and testing. Twelve of the children from the fourth group have significant hypertension. But, none of the children have shown severe hypertension values.

Key words: children, lead in the blood, hypertension.

INTRODUCTION

Lead has been known to man before all other metals. It has been used widely for a very long time. Ever since the ancient and Roman times, the production and use of lead have been constantly increasing throughout history (with only slight oscillations). Many of the ancient civilizations, such as Egypt, Greece, Rome and Phoenicia, were familiar with lead (1). There is historical evidence that indicates the exploitation of lead in pre-Roman times in the northern region of Kosovo and Metohija (today's territory of Trepča). Year 1927 is considered a milestone — the English company "Trepca Mines Limited" began working on the opening of the mine, while the production started in 1939 when the lead smelter was built (2). Lead can enter the body by inhalation and ingestion, while the absorption of lead through undamaged skin is insignificant. Lead can also be transported transplacentally (3). When lead is inhaled, the absorption occurs within the whole respiratory tract, especially in bronchioles and alveoli (4). After the absorption, lead is transported by blood, mostly by erythrocytes (about 95% of the intake), then by protein fractions of plasma, and minimally in terms of ionic transport. Ionized lead represents metabolically active nucleus of the entire amount of lead in the body responsible for toxic effects. Lead toxicity may have multiple mechanisms. As other heavy metals, lead

forms a series of complexes with ligands that contain sulphur, nitrogen or oxygen. The interaction of lead with sulphur groups, amine and simple amino acids (inhibition of enzyme activity) is especially significant (5, 6).

Chronic lead poisoning is common, especially in children. Lead affects many systems and organs in human body: hematopoietic system, hearing, peripheral and autonomic nervous system, skeletal system, liver, kidneys, reproductive system, metabolism of vitamin D, etc (7). There is no hard evidence of heart damage due to chronic lead poisoning. Lead poisoning causes spasms of the smooth muscles of blood vessels (especially of smaller blood vessels of the central nervous system, kidneys and bowels). The main effect of lead poisoning on the cardiovascular system is hypertension with all its consequences (8).

Hypertension is a health problem of national significance. It is one of the main risk factors for atherosclerosis and consequential cardiovascular, cerebrovascular and renal diseases, which are the leading cause of morbidity and mortality in our country, as well as other developed countries and many developing countries.

The primary goal of pediatricians and other child care medical personnel is to recognize children and adolescents who either have the risk factors for developing hypertension, or have already developed it, and take preventive and therapeutic measures in a timely manner (since hypertension in childhood and adolescence is one of the strongest predictors of adult hypertension) (9).

AIM OF THE STUDY

The aim of this study is to process and represent the test results of examined children chronically poisoned by lead in Kosovska Mitrovica, using statistical-epidemiological methods, as well as to show correlation between lead levels in blood and hypertension in children.

MATERIALS AND METHODS

Examination and treatment of Roma children, identified as the group with the highest risk for lead poisoning by the World Health Organization, started in the second half of the last decade. The investigation included almost all Roma children from North Kosovska Mitrovica within the age group of 1–14. The research also included two control groups- Roma children from Leposavić and non-Roma children from Kosovska Mitrovica.

Lead Care Analyzer (No 70–2233) at Kosovska Mitrovica Public Health Institute was used for determination of capillary blood lead levels. Venous blood lead levels were determined in toxicological laboratory of the Institute for Occupational Health “Karajović”, Belgrade.

Basic hematological and biochemical analyses were performed in the central laboratory of Health Center Kosovska Mitrovica (Le, Le formula, Er, Hb, Hct, MCV, MCH, MCHC, Tr, feritin, AST, ALT, Urea, Cr, serum Fe). Children with lead levels above 40 microgr/dl were treated with “Chemet”, a medication used for the first time in Europe with these children.

For analysis of obtained data, descriptive-statistical methods were used, as well as methods for testing the statistical hypotheses. Among the descriptive methods, measures of central tendency (arithmetic mean) were used and measures of variability (standard deviation) and relative numbers. The methods used for testing statistical hypotheses were: Kruskal-Wallis with Mann-Whitney post hoc test and chi-square test. For analysis of correlation, the Spearman’s rho test was used. For variable of age in children, ANOVA was performed. Distribution of results was normal. For the rest of analysis Kruskal-Wallis test was performed. After the application of Bonferroni correction, there was no change in significance. Statistical processing was done by SPSS21 software program. Statistical hypotheses were tested at a significance level of 0.05.

During the investigation, the blood pressure of 159 children (ages 5–14) was monitored in order to determine the effects of chronic lead poisoning. The groups were formed based on the recommendation by The World Health Organization. The children were divided into four groups. The first group (n = 32) consisted of non-Roma children with blood lead levels of up to 10 mcg/dl (the average lead level of 7.78 mcg/dl). Roma children from Kosovska Mitrovica and Leposavic were first joined based on the capillary blood lead level, and then divided into the remaining three groups: the second group (n = 31) consisted of Roma children with blood lead levels of up to 10 mcg/dl (the average lead level being 7.7 mcg/dl); the third group (n = 53) consisted of Roma children with blood lead levels between 10 and 45 mcg/dl (the average lead level value of 25.47 mcg/dl); the forth group (n = 43) consisted of Roma children with blood lead levels greater than 45 mcg/dl (the average lead level of 61.70 mcg/dl).

Each child’s blood pressure was measured several times and the average values were calculated. The blood pressure was measured using the auscultatory method. The values are expressed in millimeters of mercury (mmHg).

The following table provided by WHO was used for blood pressure interpretation:

Table 1. *Normal blood pressure values in children (mmHg)*
(upper limits of normal blood pressure — recommended by WHO)

AGES	**BOYS**		**GIRLS**	
Years of age	Systolic	Diastolic	Systolic	Diastolic
5	104	65	103	66
6	105	68	104	68
7	106	70	106	69
8	107	71	108	71
9	109	72	110	72
10	111	73	112	73
11	113	74	114	74
12	115	74	116	75
13	117	75	117	76
14	120	75	119	77

Table 2. *Average values of arterial blood pressure (mmHg) and blood lead levels (mcg/dl)*
(SBP — systolic blood pressure, DBP — diastolic blood pressure, Pb — blood lead level)

Ages	Group I			Group II			Group III			Group IV		
years of age	SBP	DBP	Pb	SBP	DBP	Pb	SBP	DBP	Pb	SBP	DBP	Pb
5	102	62	7	99	60	7	100	64	25	106	69	60
6	103	65	7	100	62	8	102	65	25	108	70	60
7	104	65	8	101	63	7	103	65	25	110	69	62
8	105	68	8	103	65	8	103	67	26	110	70	62
9	105	68	7	105	66	7	105	69	26	112	72	61
10	108	69	8	106	68	7	106	70	25	115	72	62
11	110	70	9	107	68	7	108	72	25	115	75	62
12	110	71	9	107	70	8	110	72	26	120	75	65
13	113	71	7	110	70	8	110	73	26	120	78	65
14	118	72	7	112	70	8	114	73	26	125	81	65

These values represent the lower limits of high blood pressure in accordance with the age and gender of the children. Each value, equal or higher, represents marginal blood pressure, HTN degree I or II and requires further examination.

It is evident from Table 1 that gender does not affect the blood pressure values, and was therefore disregarded from further research (recommended by WHO).

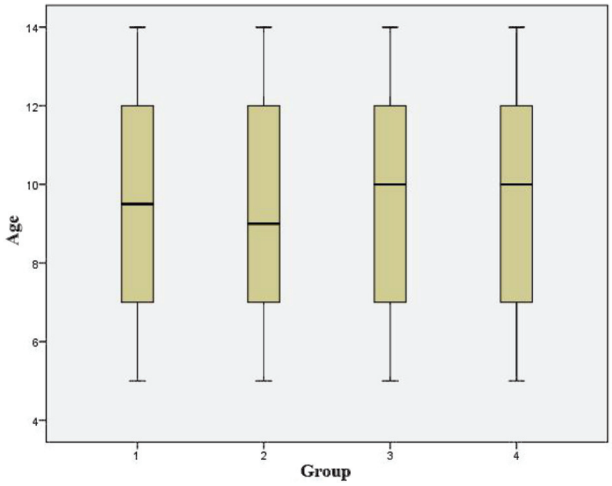
RESEARCH/INVESTIGATION RESULTS

Blood pressure values and average blood lead levels in examined children are outlined in Table 2.

The average age of examinees in the research was 9.6 ± 2.9 years of age. The youngest examinee was 5 years old, while the oldest was 14 years of age (Table 3, Graph 1).

Table 3. *Ages of examined children*

Group	**n**	**$\bar{x}$**	**SD**	**Med**	**Min**	**Max**
1	32	9.4	2.9	9.5	5	14
2	31	9.3	2.9	9	5	14
3	53	9.7	2.9	10	5	14
4	43	9.5	2.9	10	5	14
Total	159	9.6	2.9	10	5	14



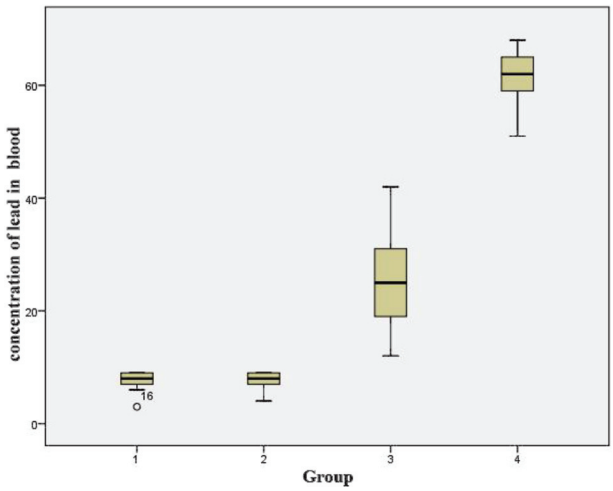
Graph 1. *The average age of examined children*

The first control group consisted of children of similar age as other examined children.

Average values of blood lead levels in examined groups of children are presented in Table 4 and Graph 2.

Table 4. *Blood lead levels*

Group	n	$\bar{x}$	SD	Med	Min	Max
1	32	7.9	1.4	8	3	9
2	31	7.6	1.4	8	4	9
3	53	25.4	7.5	25	12	42
4	43	61.6	4.2	62	51	68
Total	159	28.2	22.3	20	3	68



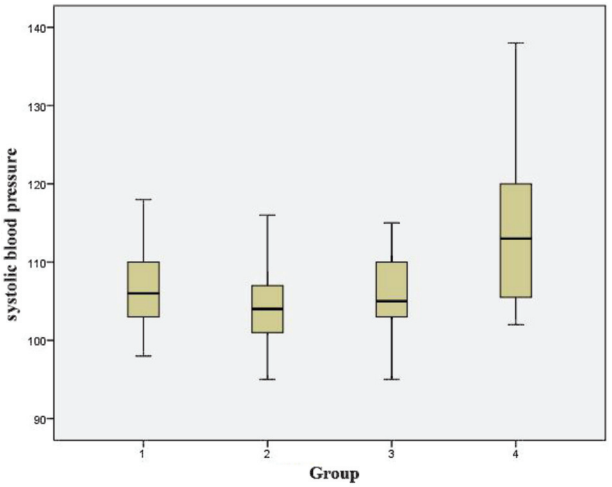
Graph 2. *Blood lead levels*

Blood lead levels in the third group of children exceed the (upper) limits of normal values (25.4). The treatment with diet was applied. Blood lead levels in the children from the fourth group was very high (61.6). These children were treated with Chemet.

Average values of systolic blood pressure of examinees are shown in Table 5 and Graph 3.

Table 5. *Average values of systolic blood pressure*

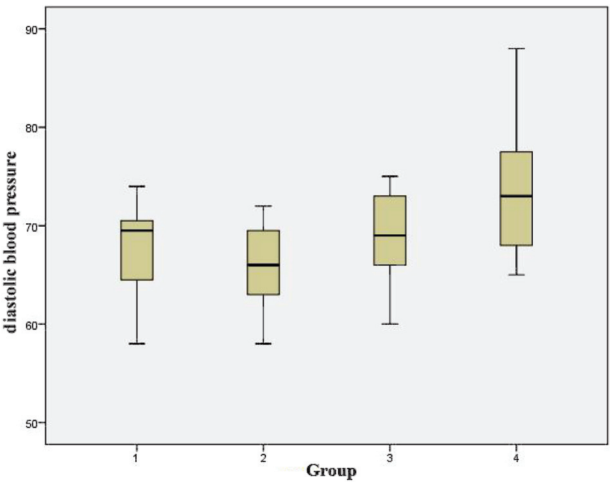
Group	n	$\bar{x}$	SD	Med	Min	Max
1	32	107.2	5.2	106	98	118
2	31	104.5	4.6	104	95	116
3	53	106.4	4.9	105	95	115
4	43	114.6	9.5	113	102	138
Average	159	108.4	7.5	106	95	138



Graph 3. *Values of systolic blood pressure*

Table 6. *Average values of diastolic blood pressure*

Group	n	$\bar{x}$	SD	Med	Min	Max
1	32	67.7	4.2	69.5	58	74
2	31	66	4.0	66	58	72
3	53	69	3.7	69	60	75
4	43	73.4	5.9	73	65	88
Total	159	69.4	5.3	69	58	88



Graph 4. *Values of diastolic blood pressure*

The values of diastolic blood pressure in children from the fourth group are increased with regard to their

age. The increase of diastolic blood pressure is less noticeable than the increase of systolic blood pressure.

DISCUSSION

Lead can enter the body by ingestion and inhalation. It is distributed to almost all tissues and organs and has adverse effects on them. These effects are mostly reversible, however, in cases of longer and intense poisoning, irreversible changes can occur. In children, the central nervous system is the most vulnerable and severe changes can be manifested. Chronic lead poisoning is more common than acute lead poisoning in children. The clinical picture does not show anything specific that can indicate chronic poisoning. The only means of diagnosing chronic lead poisoning is by determining the blood lead level. All other examinations are of less importance, or even irrelevant.

However, the fact that there were about 200 deaths from chronic lead poisoning among children per year in the United States during the mid 20th century is astonishing. The children who suffered from chronic lead poisoning lived in wooden houses painted with lead colors (lead-based paint) (10).

The investigation of blood lead levels of 92 immigrant children from Africa, and 401 control group children, was conducted in 2004 in New Hampshire. The blood lead levels above 10 mcg/dl were found in 29% of immigrant children and only in 1.5% of the control group children. The reasons were the residential area (residence near the industrial zone), lifestyle and diet (11).

An examination conducted in India in 2007 included 107 children who lived near the lead mine. Blood lead levels between10 and 20 cmg/dl were found in 43% of the children, while 39% of the children had blood lead levels greater than 20 mcg/dl. Only 18% of the examined children had normal blood lead values (12).

Similar research was published in 2008 in Columbia. The examined group consisted of 110 children whose parents were involved in battery recycling. Blood lead levels between 10 and 20 mcg/dl were found in 25% of the children. Almost half of the children (49%) had blood lead level of 20 mcg/dl. Only 26% of examinees had the allowed blood lead level values (13).

Two separate investigations were conducted in Germany (Duisburg). The first one, performed in 1983, included 843 children with place of residence in the city centre and 872 children from the suburbs. The average blood lead level in children from the city center was 5.3 mcg/dl, as opposed to 1.8 mcg/dl found in children who lived in the suburbs. The second investigation took place in 2008. The children who lived in the city center had the average blood lead level of 2.2 mcg/dl, while the average blood lead level in children from the suburbs was 1.4 mcg/dl. The reduction was achieved by the use of unleaded fuel and driving restrictions in the city center (14).

According to the standards of the World Health Organization (WHO), the optimal blood lead level is up to 5 mcg/dl. The values up to 10 mcg/dl can be tolerated. Blood lead levels of 10–45 mcg/dl indicate chronic lead poisoning. These values do not require medicamentous treatment, but only the change of residence and proper diet. Blood lead values of above 45 mcg/dl demand urgent medical treatment.

During the 50 years of his work, Howard performed longitudinal monitoring of 192 lead-intoxicated (former) children. He concluded that there was a high risk for the development of hypertension (15).

Ho H. and associates concluded that the long term exposure of children to lead and the accumulation of lead in bones represent high risk factors for developing hypertension (16).

The US national poison control center (DCC) published that the blood lead level higher than 10 mcg/dl was found in 310.000 children in the period 1999–2002 (17).

Kopp and associates came to a conclusion that the exposure of children to lead can induce significant changes in cardiovascular system functioning and hypertension. Myocarditis, ECG changes, increased catecholamines, hypertension, hypercholesterolemia, atherosclerosis, and vascular degeneration signs are associated with lead poisoning which has been proved in clinical and experimental studies. Morphological and biochemical postmortem changes in the myocardium have been proved in humans, whereas cardiovascular changes have been established in animals (18).

The American Academy of Pediatrics announced in the journal “Pediatrics” in 2005 that the lead level in blood decreases in children in America, but 25% of them still lives in houses painted with lead paint. In the samples taken it was recorded over 10 mcg/dl lead level, resulting in weakened cognitive functions and other consequences (19).

Binns et al are announcing that the Center for Disease Control and Prevention (CDC) reported that in studies from 1991 children with increased lead in the blood showed that physical and mental health of children may be affected even when lead level is below 10 mcg/dl. In children throughout the USA with increased lead level in blood were recorded weakened cognitive functions, functions of motor skills, reduced physical abilities and changed behavior. Accordingly CDC proposed training measures, prevention and enhancement of awareness of health centers, families and local health programs (20).

Lyn Patrick amounts that even smaller amounts of lead in the blood, over a long period of time, result in disorders in cognition, neuro-behavioral disorders, neurological damages, hypertension, and kidney failure (21).

Shiring Weng et al during the six years of monitoring the levels of lead in the blood in middle age people found a significant interaction with hypertension and increased level of serum creatinine. They conclude that diabetes and hypertension are the consequences of short-term and long-term exposure to lead (22).

Barbosa et al claim that there is no lower limit safety of lead level in blood. Bad influence on health, including intellectual deterioration in young children, occurs when the lead level is less than 10 mcg/dl (23).

By examining the blood lead levels in Roma children who live in camps in Kosovska Mitrovica, and by comparing the obtained results with the results of many authors who investigated this problem, the same conclusion is reached: the two main risk factors for chronic lead poisoning in children are the place of residence and lifestyle. Primitive battery recycling has a special significance as a risk factor for chronic lead poisoning in children.

Our results of the blood lead levels in Roma children show that the children from the first and second group do not suffer from chronic lead poisoning. The children from the third group suffer from low-intensity chronic lead poisoning. However, chronic lead poisoning in children from the fourth group is of very high, even alarming, intensity (up to 65 mcg/dl).

In the course of our research, no statistical significance in the age of examined groups was established ($F = 2.332$; $DF = 3$; $p = 0.916$).

Statistical significance was found in the level of diastolic blood pressure among the examined groups (chi-square = 32.028; $p < 0.001$), especially between the first and the fourth group ($p = 0.001$), the second and the third group ($p = 0.002$), the second and the fourth group ($p < 0.001$), and finally the third and the fourth group ($p = 0.001$). The median diastolic blood pressure value is statistically significant in the fourth group of examinees.

There is a positive correlation between the values of blood lead levels and diastolic blood pressure ($r = 0.48$; $p < 0.001$). High blood lead level is followed by the increase in diastolic blood pressure.

Statistical significance was established in blood lead levels among the examined groups (chi-square = 140.2; $p < 0.001$). The median blood lead value is statistically significant between the first and the third, the first and fourth, the second and third, the second and the fourth, and the third and the fourth group ($p < 0.001$).

Statistical significance was found in the level of systolic blood pressure among the examined groups (chi-square = 31.179; $p < 0.001$), especially between the first and the fourth group ($p = 0.001$), the second and the fourth group ($p < 0.001$) and the third and the fourth group ($p < 0.001$). The median systolic blood pressure value is statistically significant in the fourth group of examinees. A positive correlation between the values of blood lead levels and systolic blood pressure ($r = 0.42$; $p < 0.001$) has also been proven. High blood lead level is followed by the increase in systolic blood pressure.

CONCLUSION

There is evidence of significant lead poisoning in Roma children who live in camps in the north region of Kosovo and Metohija. Lead poisoning was determined by the reliable methods of measuring the blood lead levels.

Chronic lead poisoning, especially if significant, leads to the increase of blood pressure values, both systolic and diastolic.

The higher the blood lead levels, the greater the effects on the blood pressure. The blood pressure values in the majority of children with high blood lead levels (higher than 45 mcg/dl) required detailed examination and further observation.

Abbreviations

WHO — Word Health Organization
CDC — Center for Disease Control and Prevention
Er — red blood cell (RBC)
Le — white blood cell(WBC)
Le — formula = WBC formula
Hb — hemoglobin
Hct — hematocrit
MCV — mean corpuscular volume
MCH — mean corpuscular hemoglobin
MCHC — mean corpuscular hemoglobin concentracion
Tr — trombocit
AST — aspartat aminotransferaza
ALT — alanin aminotransferaza
Fe — iron
Pb — lead
Cr — creatinin
HTN — high hypertension
SBP — systolic blood pressure
DBP — diastolic blood pressure

Sažetak

DEJSTVO HRONIČNOG TROVANJA OLOVOM NA VREDNOST KRVNOG PRITISKA KOD DECE

Živković Jovan,[1] Savić Zoran[2]

[1] Medicinski fakultet Univerziteta u Prištini, sa sedištem u Kosovskoj Mitrovici
[2] Zdravstveni centar Kosovska Mitrovica

Uvod: Tokom projekta lečenja romske dece, iz Kosovske Mitrovice, hronično trovanih olovom (započetog u drugoj polovini prošle decenije), praćena je i hipertenzija. Ispitivanje i lečenje je vršeno pod patronatom Svetske zdravstvene organizacije, Ministarstva zdravlja Srbije, lokalne administracije. **Cilj** rada je da se utvrdi korelacija između povišenog nivoa olova u krvi dece i hipertenzije. **Materijal i metode:** nivo olova iz kapilarne krvi je određivan na aparatu Lead care analyzer. Nivo olova iz venske krvi određivan je u toksikološkoj laboratoriji Instituta „Karajović“ u Beogradu. Pritisak je meren standardnom metodom. Praćena je tenzija kod 159-ro dece. Podeljena su u četiri grupe. Prva grupa: ne-romska deca (n = 32) olovo u krvi do 10 mcg/dl. Druga grupa: romska deca (n = 31), olovo do 10 mcg/dl. Treća grupa: romska deca (n = 53) olovo u krvi 10–45 mcg/dl. Četvrta grupa: romska deca (n = 43), olovo u krvi veće od 45 mcg/dl, sa srednjom vrednošću 61,6 mcg/dl. **Rezultati:** Postoji statistički značajna razlika u visini sistolnog krvnog pritiska između ispitivanih grupa (hi-kvadtat = 31,179; p < 0,001). Između prve (X =107,2 mmHg) i četvrte grupe (X = 114,6 mmHg), druge (X = 104,5mmHg) i četvrte grupe, treće (X = 106,4 mmHg) i četvrte grupe. Postoji statistički značajna razlika u visini dijastolnog krvnog pritiska između grupa (hi-kvadrat = 32,028; p <0,001). Između prve(X = 67,7 mmHg) i četvrte grupe(X = 73,4 mmHg) druge (X = 66 mmHg) i treće (X = 69 mmHg) druge i četvrte, treće i četvrte grupe dece. **Zaključak:** Što je veća vrednost olova u krvi njegovo dejstvo na krvni pritisak je izraženije. Deca sa olovom iznad 45 mcg/dl imaju povećane vrednosti krvnog pritiska i kod njih je indikovano dalje praćenje i detaljnije ispitivanje. Dvanaestoro dece iz četvrte grupe ima signifikantnu hipertenziju. Ni jedno dete nema vrednosti ozbiljne hipertenzije.

Ključne reči: deca, olovo u krvi, hipertenzija.

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Correspondence to /Autor za korespondenciju
Prof dr Jovan Živković
Donjovrežinska 10/13
18000 Niš,
Mob. Tel.063/408-694
Email: drjovanzivkovic@gmail.com

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CORRELATION BETWEEN DOMESTIC VIOLENCE AGAINST WOMEN AND NEUROTICISM

Numanovic S. Almedina,[1] Jovicic M. Milena[2]

[1] International University of Novi Pazar, Novi Pazar, Serbia
[2] Clinical Center Kragujevac, Psychiatric Clinic, Kragujevac, Serbia

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Abstract: **Objective:** The aim of the study was to determine the degree of correlation between domestic violince against women and neuroticism. Socio-demographics characzeristics were also compared.

Method: This research included 120 women from Novi Pazar and Sjenica, 60 women who were victims of domestic violence and 60 women who were not violence victims. The degree of neuroticism has been tested with general neuroticism test.

Results: There is significant difference between women who were violnce victims and those who were not, on 0.05 level (with 5% risk), t = 2.112, p = 0.039. Arithmetic mean of the degree of neuroticism of women who were violence victims is 78,89, for those who were not is 38,69. The difference is important (about 40). There is statistically significant difference between married and single women who were violence victims. Married examinees have higher degree of neuroticism than single ones. Examinees with higher degree of neuroticism have been suffering from domestic violence longer than those with less degree of neuroticism. There is no statistically significant difference in the the degree of neuroticism between different categories of examinees, according to the degree of profesional qualifications.

Conclusion: It remains an open question, and it is necessary to longitudinally examine what is the role of violence against women in the emergence neurotic and other disorders.

Key words: violence against women, neuroticism, neurosis.

INTRODUCTION

Violence is the use of an absolute or psychological force to another person. The violence is a pervasive phenomenon that manifests itself in a number of forms: physical violence, verbal abuse, domestic violence, violence against children, violence in the workplace, instrumental violence, actual violence, potential violence, motivated violence, etc. (1).

Domestic violence always represents an abuse of power and the exercise of control over family members who have less power and have less resources (2).

Domestic violence is the behaviour of a family memeber endangering the physical integrity, mental health or tranquility of another family member according to Legislation on Domestic Violence in Serbia (article 197, pg 3) (3). Domestic violence is a term that usually refers to violence between spouses or spousal abuse, but it can also applies to unmarried intimate partners or just people who live together. Domestic violence is a phenomenon that is present in all countries and in all cultures; people of all races, ethnicities, religious, and political and sexual orientation, social and cultural levels and genders can be perpetrators of domestic violence.

The awareness of domestic violence as well as understanding and documentations of this offense vary from country to country. It is estimated that in the United States and Great Britain only a third of cases of domestic violence reported to the police (4).

The most common victims of domestic violence are women and that is the reason we call it even gender based violence. The family is a social institution with most violence cases, except for the army during the war. According to the UN, the leading cause of death and disability for women between 15–45 years are not an illness or a car accident, but the violence, and the most dangerous place for a woman is her own home (5).

Women are often victims of their loved ones. Domestic violence is the most common form of the more general problem of violence against women, which speak in favor of the statistics: between 40% and 70 %

of murders where the the victims were women, the perpetrators were their husbands or fiancés. It was also reported that it is not always about physical violence, but also mental or verbal. Violence against women exercising their sentimental partners most often unreported to the police, so that experts believe that the number of women victims of domestic violence is much higher than when the statistics show that it is difficult to assess.

Although this problem is presented as a problem within heterosexual relationships, it still exists among lesbians, or between mother and daughter, between two women who share a flat or in any other relationship between the two women living under the same roof. Violence against women in lesbian relationships are almost equally represented as in heterosexual relationships.

The most common perpetrators of violence against women by their intimate male partners, whether that violence occurs in the context of living together in a household, or during occasional sightings. In 96% of cases in heterosexual intimate relationships, the perpetrator is a man and the victim's wife, and therefore it is not clear why the priority given to the measures and activities aimed at combating violence against women and their consequences (6).

The definition of violence against women by the United Nations documents:

Violence against women is a manifestation of historically unequal relations of social power between men and women which have led to domination over and discrimination against women by men up to prevent the full advancement of women. Violence against women is one of the crucial social mechanisms by which women are forced into a subordinate position compared with men. Violence against women is an obstacle to the achievement of equality, development and the peace (7).

Violence against women in intimate relationships is the result of an imbalance of power between women and men (8).

Neurosis is a psychomatic phenomena occurred because of vegetative nervous system disorder caused by mental stimuli (9). Some authors consider psychoneuroses identical neuroses, while other believe there is a difference because neurosis have somatic origin, while psychoneurosis does not, also neurosis is disorder of somatic functions, that does not have mental content, while psychoneuroses do have, and also a shorter duration, on the other side, psychoneuroses last longer. The name neurosis was introduced by Cullen who wanted to indicate that it is general disorder of the nervous. The term included all disorders of nervous system that do not have migraine or physical lesions, an illness considered to be neurosis (10). Many experts consider to be more appropriate to say about different types of neuroses. The cause of neuroses generally lies in failure of an individual to satisfy certain motives, for him, very strong motives or to get rid of some conflict situation (10).

The clinical indicators of neuroticism (clinical assessment): badly or poorly organized personality, dependance, narrow interests, the lack of energy, abnormality before an illness, weak muscle tone, an isolation and the feeling of not belonging.

Self-assessment: the feeling of inferiority, anxiety or nervousness, tendency for an accident, avoidance and failure to report efforts, dissatisfaction, sensitivity, irritability and easy offensiveness. Constitutional characteristics: poor physical stamina and physical activity, inadequate body composition, poor vision in the dark or in twilight (10).

OBJECTIVE

The aim of the study was to determine the degree of correlation between domestic violince against women and neuroticism. Socio-demographics characzeristics were also compared.

METHODS

This research included 120 women from Novi Pazar and Sjenica, 60 women who were victims of domestic violence and 60 women who were not violence victims, age 18–65, average age was 39.12 (SD = 9.56). Respondents were of diffferent educational level, most of them had Associate Degree (61.67%). Criteria for testing were a) the respondent is not under 18, b) the respondent can write and read in serbian, c)the respondent experienced some form of abuse in the past year. Criteria for taking out of testing were a)the respondent has experienced at least one of the following events over the past year : traffic accidents, earthquake, flood, fire; b) The respondent has actual diagnosis of a psychotic disorder, c) the respondents has abused some of psychoactive substances.

Respondents were given the general neuroticism test, Cornell index (CI-N4). Cornell index is assigned to preliminary neoroticism diagnosis. It includes three scales: HY scale- elevated value on this scale indicates neorotic disorders ,such as psychosomatic, hysterical or conversion disorder; ALPHA scale- elevated value on this scale indicates anxiety, phobia, obsession, compulsion and depression; SIGMA scale- elevated value on this scale indicates aggressiveness of neurotic character. The test consist of 110 questions in which the respondent should respond with true (T) if she agree with the statement or false (N), if she disagrees. Cornell index can be applied individually and in groups, but you

can explain aforementioned scales only for individual testing, because the results are assessed on the basis of the total score, which is the sum of correct answers.

Retrospective study has been used. For statistical analysis we used the methods of descriptive statistics, t test and Spearman's correlation coefficient. Data processing was performed using SPSS 18.

RESULTS

Arithmetic mean of the degree of neuroticism of women who were violence victims is 78.89, for those who were not is 38.69. The difference is important (about 40).

In order to establish wheather there is a difference in neuroticism between the control and experimental groups, we used the t-test for independent samples, and the following results were obtained (Table 2):

Based on results (Table 2) we see that t-test is important ($t = 2.12$, $p = 0.039$). That there is a statistically significant difference depends on neurotiscm between patients who have suffered violence and those who are not at the level of 0.05 (with a risk of 5%). The results of the correlation between neuroticism and age of respondents victims of violence are shown in Table 3.

Based on the obtained results (Table 3) we may notice that between variables neuroticism and age there is a very low correlation (0.005), which was not statistically significant ($p > 0.05$).

By comparing the data on marital status and level of neuroticism, we came up with the following results shown in Table 4 and Table 5.

Table 1. *The significance of differences in neuroticism among respondents who were suffering violence and control group*

	respondents	N	Arithmetic mean	Standard deviation	Standard error of the arithmetic mean
Neuroticsm	women who have suffered violence	60	78.89	11.55	1.24
	women who have not suffered violence	60	38.69	5.36	0.93

Table 2. *The significance of differences in neuroticism among respondents who were suffering violence and control groups*

neuroticsm	F Levene's test	Significance	T	df	Significance
Equal variances assumed	2.474	0.121	2.112	62	0.039
The result of variances that are not expected			2.069	52.973	0.043

Table 3. *The significance of the correlation between the degree of neuroticism and age of the respondents the victims of violence*

		neuroticsm	age
neuroticsm	Pearson's correlation coefficient	1.000	0.005
	Significance		0.692
	N		60
age	Pearson's correlation coefficient		1.000
	Significance	0.692	
	N	60	

Table 4. *The significance of differences in neuroticism among respondents with different marital status (married-divorced)*

	Marital status	N	Arithmetic mean	Standard deviation	Standard error of arithmetic mean
The degree of neuroticism	married	35	79.16	7.59	1.00
	unmarried	25	65.70	7.90	1.15

From the obtained data (Table 4, Table 5) we see that between married an unmarried respondents, the victims of domestic violence, there is a statistically significant difference(at the level of 0.05 i.e. the risk is 5%) in the level of neuroticism. Married respondents have higher levels of neuroticism than the unmarried. Arithmetic mean neuroticism for married respondents is 79.16, while unmarried 65.70.

Married respondents have higher levels of neuroticism than the unmarried. Arithmetic mean neuroticism for married respondents is 79.16, while unmarried 65.70.

We also evaluated the degree of neuroticism in relation to the timeframe (expressed in years) during which the respondents suffered violence. Pearson coefficient results are shown in Table 6)

Pearson's correlation coefficient (Table 6) is 0.871, which means that the correlation is very high, and on the basis of significance, we conclude that the relationship between the degree of neuroticism and timeframe (expressed in years) during which the respondents suffered violence, it is also statistically significant, $p < 0.05$ ($p = 0.000$).

Namely, respondents with higher levels of neuroticism, who suffered the violence for much longer period of time than women with lower levels of neuroticism.

In assessing whether there is statistically significant difference in the degree neuroticism of patients, victims of violence, in relation to the level of qualifications, we obtained the results shown in Table 7 and Table 8.

The results (Table 7) shows that there are no large discrepancies in arithmetic mean of the degree of neu-

Table 5. *The significance of differences in neuroticism among respondents with different marital status (married-divorced)*

	F Levene's test	Significance	T	Df	Significance	The difference between the arithmetic mean	Standrad error of the arithmetic mean
The expected variances	0.427	0.515	2.277	103	0.025	3.45	1.52
The unexpected variances			2.267	96.795	0.026	3.45	1.52

Table 6. *The significance of the correlation between the degree of neuroticism and the timeframe in which the respondent suffered violence*

		The digree of neuroticism	Timeframe (expressed in years) during which the respondents suffered violence
The digree of neuroticism	Pearson's correlation coefficient	1.000	0.873
	Significance		0.000
	N		60
Timeframe (expressed in years) during which the respondents suffered violence	Pearson's correlation coefficient		1.000
	Significance	0.000	
	N	60	

Table 7. *Arithmetic means, standard deviations and standard errors (ar. Mid), of the degree of neuroticism of respondents with different levels of educational attainment*

	N	Arithmetic mean	Standard deviation	Standard error of the arithmetic deviation
Secondary school qualifications	14	75.21	8.59	2.30
Associate degree	37	75.62	7.92	1.30
University qualifications	9	79.45	6.85	1.06
Total	60	27.61	7.88	0.77

Table 8. *The significance of differences in the degree of neuroticism of respondents with different levels of educational attainment*

The degree of neuroticism	The square sum	Df — degree of freedom	Arithmetic mean of square	F	Statistical significance
Among grups	442.609	3	147.536	2.476	0.066
Within the groups	6018.381	101	59.588		
Total	6460.990	104			

roticism among different categories of level of educational attainment.

Based on the presented statistical analysis we can conclude that among the various categories of respondents (by level of education) there is no statistically significant difference in the degree of neuroticism $p > 0.05$ ($p = 0.066$).

DISCUSSION

The researches on this topic are scarce and there is not enough information so that this work can serve as an engine works on this or a similar topic. The results of this research show that people with experience of domestic violence have a higher degree of neuroticism than those who did not suffer violence. Avdibegović i Sinanović have undertaken researches on similar topic. The study was carried out in the Tuzla Canton region in the period from 2000 to 2002, and included 293 women aged 43 ± 9.6 years. Out of 283 women, 215 were psysically, psychologically, and sexually abused by their husbands. Among the abused, 107 (50.7%) experienced a combination of various forms of domestic violence. The frequency of domestic violence was high among psychiatric patients (78.3%). Victims of domestic violence had a significantly higher rate of general neuroticism, depression, somatization, sensitivity, obsessive-compulsive symptoms, anxiety, and paranoid tendency than women who were not abused. The prevalence of posttraumatic stress disorder (PTSD) symptoms according to the type of trauma was higher in women with the history of childhood abuse (8/11) and domestic violence (53/67) than inwomen who experienced war trauma (26/57) and the loss of loved ones (24/83). The majority of 104 psychiatric patients suffered from PTSD in comorbidity with depression (n = 45), followed by depression (n = 17), dissociative disorder (n = 13), psychotic disorder (n = 7), and borderline personality disorder with depression (n = 7). The intensity of psychological symptoms, depression, and Global Severity Index for Psychological Symptoms (GSI) were in significant positive correlation with the frequency of psychological ($r = 0.45$, $P < 0.001$), physical ($r = 0.43$, $P < 0.001$), and sexual abuse ($r = 0.37$, $P < 0.001$) (11).

CONCLUSION

It remains an open question, and it is necessary to longitudinally examine what is the role of violence against women in the emergence neurotic and other disorders. It is discovered that there is a statistically significant difference in neuroticism among respondents who were suffering some form of violence and those who have not.

Sažetak

KORELACIJA IZMEĐU PORODIČNOG NASILJA NAD ŽENAMA I NEUROTICIZMA

Numanovic S. Almedina,[1] Jovicic M. Milena[2]

1 Internacionalni univerzitet Novi Pazar, Novi Pazar, Srbija
2 Klinički centar Kragujevac, Klinika za psihijatriju, Kragujevac, Srbija

Cilj: Cilj studije je bio da se utvrdi stepen korelacije između porodičnog nasilja nad ženama i neuroticizma. Socio-demografske karakteristike su takođe poređene.

Metod: Istraživanje je obuhvatilo 120 žena iz Novog Pazara i Sjenice, 60 žena koje su bile žrtva porodičnog nasilja i 60 žena koje nisu bile žrtve nasilja. Stepen neuroticizma testiran je opštim testom za neuroticizam.

Rezultati: Postoji statistički značajna razlika između žena koje su bile žrtva nasilja i onih koje nisu, $t = 2,112$, $p = 0,039$. Aritmetička sredina stepena neuroticizma kod žena koje su bile žrtve porodičnog nasilja je

78,89, a kod onih koje nisu 38,69. Postoji statistički značajna razlika između udatih i neudatih žena koje su bile žrtve nasilja, kod udatih je veći stepen neuroticizma. Ispitanici koji su imali veći stepen neuroticizma su duži vremenski period patili od onih sa nižim stepenom neuroticizma, razlika je statistički značajna. Ne postoji statistički značajna razlika u stepenu neuroticizma među ispitanicima u odnosu na stručnu i profesionalnu kvalifikaciju.

Zaključak: Ovo ostaje otvoreno pitanje, i potrebno je dalje ispitati kakva je uloga nasilja nad ženama u nastanku neurotičnog i drugih poremećaja.

Ključne reči: nasilje nad ženama, neuroticizam, neuroza.

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Correspondence to /Autor za korespondenciju
Almedina Š. Numanović
ul. Vehba Kolašinca, 14
069 62 62 32
Internacionalni Univerzitet u Novom Pazaru

Milena M. Jovičić
Ul. Dragoljub Milovanović Bene
064 3848877
KC Kragujevac, Psihijatrijska klinika

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EARLY DIAGNOSIS OF CRANIOSYNOSTOSIS IN INFANTS AT PRIMARY HEALTH CARE

Skoric Jasmina

Children and Youth Health Care Center "Simo Miloseviæ", Belgrade, Serbia

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Abstract: Craniosynostosis or premature fusion of one or more cranial sutures in infants disturbs normal brain growth. This condition causes abnormal skull configuration, increased intracranial pressure, headache, strabismus, blurred vision, blindness, psychomotor retardation. The diagnosis of craniosynostosis is very simple. Pediatricians should routinely assess neurological status and measure head circumference and anterior fontanelle. When necessary, ultrasound of CNS, X-ray and cranial CT scan can be done. When it comes to this condition, early diagnosis and surgical intervention are of utmost importance. In this paper, we have presented a case on craniosynostosis in a female infant, discovered in the third month of life during systematic review that included measurement of head circumference, palpation of anterior fontanelle and cranial sutures. The child was referred to a neurosurgeon who performed the CT scan of endocranium and confirmed the initial diagnosis of craniosynostosis. With head circumference of 40 cm and fused anterior fontanelle, the surgery was timely performed at the sixth month of life due to early diagnosis.

Key words: premature closure of cranial sutures, infants, early diagnosis, surgical treatment.

INTRODUCTION

Craniosynostosis or premature fusion of cranial sutures in the infant period is a serious condition that disrupts brain growth and development due to limited endocranium (1). Clinical features depend on the number of fused sutures and duration of the disorder in question. Symptoms occur as a result of pressure on the brain tissue. The most common type of craniosynostosis represents the fusion of one suture, that is, the sagittal one (2). Craniosynostosis may be primary, i.e., present at birth or in the first months of life, and secondary which is more frequent, whereby it arises as a part of numerous other syndromes (3).

Clinical findings include an abnormal skull configuration, reduced head circumference with fused anterior fontanelle or fontanelle with reduced dimensions, increased intracranial pressure, impaired vision or blindness due to pressure on the optic nerve, psychomotor development delay, whereas epileptic seizures and other disorders are rarely identified (4).

CASE PRESENTATION

The patient is a full term female infant, born on March the 6th, 2013, to mother who had not been pregnant before. The pregnancy was normal and supervised. Normal childbirth, BM of 2950 g, BL of 49 cm, head circumference of 33 cm (above third length percentile for her age class and sex) Apgar score 9. Family anamnesis is normal.

At the first systematic review on the ninth day of life, a spontaneously resolving mild degree of jaundice was noted, whereas the other findings were normal. At the second systematic review (2 months and 12 days of age), protrusion of the forehead in the midline, overlapping parietal bones, dimensions of anterior fontanelle 1 x 0.5 cm, folds in the occipital region of the scalp, head circumference of 36.5 cm (third length percentile) were identified. Neurological status was normal. Child was lively and attentive with no signs of psychomotor development delay. Other findings were normal.

The child was referred to a neurologist and neurosurgeon under the suspicion of craniosynostosis. CT revealed fusion of both lambdoid sutures with overlapping parietal and occipital bones. Brain parenchyma was of the proper volume and density with no focal changes. Subarachnoid space was very constricted in the occipital region. The head had occipital flattening. On the basis of clinical findings and CT scan results, the child was diagnosed with Craniosynostosis and referred to surgical treatment.

With the upcoming surgery, at the age of 4 months and 16 days, the attending pediatrician performed an examination. Neurological status was normal and the head circumference was 37.5 cm, which is below the third length percentile for her age class and sex.

After the sixth month of life, the following surgery was performed: Suturectomia suturae lamdoideae billateralis. The child was admitted to the hospital with fused anterior fontanelle and head circumference of 40 cm which is below the third length percentile. The postoperative course was uneventful and the child was discharged home in good general condition. A pediatrician performed four more check-ups at the Health Care Center. At the age of seven months, the head circumference was 40.5 cm, at the age of eight months was 41 cm, at the age of 10 months was 42 cm, at the age of 11 months was 42 cm, still below the third length percentile for her age class and sex — see percentile growth curve of the head (Figure 1). Neurological status and psychomotor development of the child were within normal limits for the whole time. Child was being taken to regular check-ups with the neurosurgeon.

DISCUSSION

Clinical features of craniosynostosis with the fusion of one suture, and especially with the fusion of multiple cranial sutures, are very serious and therefore pediatricians should strive for early diagnosis. Treatment depends on the timing of the diagnosis and which sutures are involved. While the timing of surgery is controversial, most doctors prefer to do surgery when the child is 3–6 months old. Older children (12–18 months) with a very mild deformity will probably not need surgery, while younger children with an obvious deformity that is moderate to severe will probably benefit from early surgery (5, 6). In my opinion, the diagnosis can be easily set at the level of primary health care during regular medical examinations within the first months of life, or up to one year at the latest. Ultrasound of CNS as a part of prenatal diagnostics enables us to examine the condition of cranial sutures, fontanelles and brain structures at the stage of intrauterine life (7, 8). As for postnatal diagnostics, regular measurement of head circumference and dimensions of anterior fontanelle, as well as palpation of the cranial sutures are simple diagnostic procedures. If the anterior fontanelle is still open, it would be advisable to perform an ultrasound of CNS due to increased intracranial pressure (9). Since changes in the retina might occur, it is desirable to do ophthalmologic examination, and possibly ENT screening (10). And finally, skull X-ray can be performed if necessary, as well as the CT scan of endocranium, as it was done in the case presented.

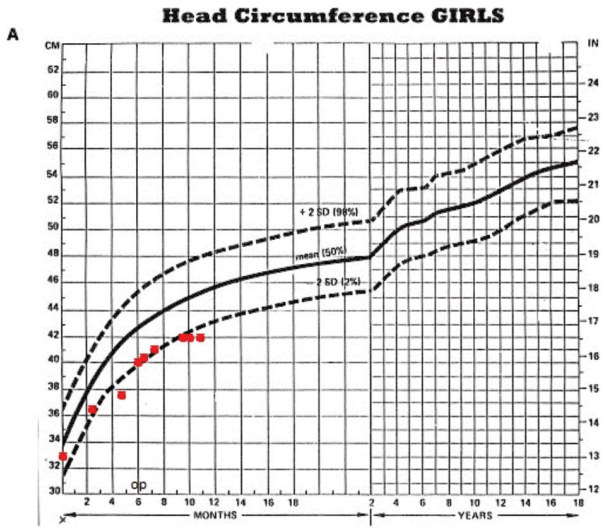

Figure 1. *Infant's Head Circumference for Age Percentile Growth Chart*

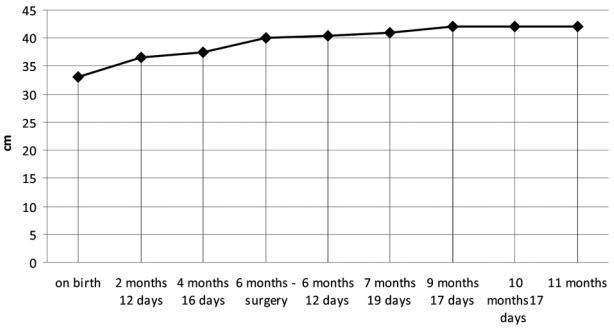

Figure 2. *Head circumference growth per months*

Although the head circumference is still below the third percentile for her age class and sex, there is an increase in head circumference by 3 cm, with the expectation of reaching its full size in time (Figure 2).

CONCLUSION

On the basis of the case presented, we may come to a conclusion that regular health pediatric examination is one of the key components in detecting anomalies such as craniosynostosis. In this case, the condition was diagnosed at the primary health care on the basis of clinical and physical findings, and was confirmed by additional testing such as the CT scan at the level of secondary health care. The time of diagnosis, in this case the third month of life, and early surgical procedure are of utmost importance, seeing how the anomaly is quite alarming, particularly when it comes to multiple cranial fusion.

Abbreviations

CT — computerized tomography
BM — body mass
BL — body length
CNS — Central Nervous System
P3 — third percentile
ENT — Otolaryngology

Sažetak

RANA DIJAGNOSTIKA KRANIOSINOSTOZE KOD ODOJČADI U PRIMARNOJ ZDRAVSTVENOJ ZAŠTITI

Skoric Jasmina

Dom zdravlja „Simo Milošević“, Služba za zdravstvenu zaštitu dece i omladine Čukarica, Beograd, Srbija

Kraniosinostoza ili prevremeno zatvaranje lobanjskih sutura kod odojčadi remeti normalan rast mozga. Ova anomalija uzrokuje abnormalnu konfiguraciju glave, povišeni intrakranijalni pritisak, glavobolje, strabizam, poremećaj vida, zastoj u psihomotornom razvoju. Dijagnostikovati kraniosinostozu je veoma jednostavno. Pedijatri bi trebalo rutinski da sprovode kontrole obima glave, neurološkog statusa, kao i merenje prednje fontanele. Ako je potrebno, takođe se može uraditi ultrazvuk CNS-a, rendgen snimak, kao i CT lobanje. Rana dijagnoza i hirurška intervencija su u ovom slučaju od najveće važnosti. Prikazan je slučaj kraniosinostoze kod ženskog odojčeta koja je otkivena u trećem mesecu života u toku sistematskog pregleda, merenjem obima glave, palpiranjem velike fontanele i lobanjskih šavova. Dete je upućeno na hospitalizaciju sa uputnom dijagnozom kraniosinostoza, koja je potvrđena pregledom od strane neurohirurga i CT-om endokranijuma. Zahvaljujući blagovremenoj dijagnozi, urađena je operacija sa navršenih šest meseci života deteta, sa obimom glave (OG) od 40 cm i zatvorenom velikom fontanelom.

Ključne reči: prevremeno zatvaranje lobanjskih sutura, odojče, rana dijagnoza, hirurška terapija.

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Correspondence to /Autor za korespondenciju
Jasmina Škorić, MD
Address: Poručnika Spasića i Mašere 53. Belgrade 11000
Phone No: +381637128664

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COCAINE CARDIOMYOPATHY — A CASE REPORT

Georgiev Antonio,[1] Zhivadinovik Julija[2]

[1] University Clinic for Cardiology, Medical Faculty, Skopje, University "Ss. Cyril and Metodius", R. Macedonia
[2] Institute of Anatomy, Medical Faculty, Skopje, University "Ss. Cyril and Metodius", R. Macedonia

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Abstract: Cocaine is the second most common illicit drug used and the most frequent cause of drug related deaths. The use of cocaine is associated with both, acute and chronic complications, that may involve any system, but the most common system affected is cardiovascular one. Cocaine cardiomyopathy may result from the use of cocaine.

This article presents a first case in Republic of Macedonia of 24-year-old male with reversible cocaine-related cardiomyopathy. Clinical presentation, laboratory, X-ray, ultrasound findings and treatment are reviewed.

Key words: cocaine, cocaine cardiomyopathy, diagnosis, treatment.

INTRODUCTION

Cocaine is the second most common illicit drug used and the most frequent cause of drug related deaths. In a retrospective of European study of 479 ACS patients younger than 50 years admitted to a critical care unit from 2001 to 2008, a total of 24 patients (5%) had admitted to recent cocaine abuse or tested positive on urine drug screening (1). In 2005, 2.4 million persons were actively using cocaine. The younger age groups of 18–25 are the most common users and it is estimated that 11% of the population has used it at some point (2). The 2008 National Survey on Drug Use and Health reported that approximately 36.8 million Americans aged 12 years and older (14.7% of Americans in that age group) had tried cocaine at least once (3). The trade with this illicit drug in Republic of Macedonia is prosecuted by law. Yet there are people who use this drug and have complications from it.

Cocaine acts as a powerful sympathomimetic agent. It blocks the presynaptic reuptake of norepinephrine and dopamine producing high level of these neurotransmitters at the postsynaptic receptors. It also may increase the release of catecholamines from central and peripheral stores. The sympathomimetic actions of cocaine, at cellular level, are mediated by stimulation of the α and β adrenergic receptors. Cocaine also interacts with the muscarinic receptors, and inhibits the reuptake of dopamine and seretonin by nerve endings (1).

Cocaine intoxication usually presents with symptoms of adrenergic excess. Hypertension, occasionally in the range of hypertensive crisis, may be present. Cerebral vascular accidents of either thrombotic or hemorrhagic origin are not uncommon. Acute delirium and mania may be present, particularly if other drugs were used concurrently (2).

The use of cocaine is associated with both acute and chronic complications that may involve any system, but the most common system affected is cardiovascular one (2–6). Cocain related complications include: cardiac (myocardial ischaemia, coronary artery spasm, myocardial infarction (MI), atherosclerosis, myocarditis, cardiomyopathy, arrhythmia, hypertension, and endocarditis); vascular (aortic dissection and rupture, vasculitis); gastrointestinal (mesenteric ischaemia or infarction, perforation); pulmonary (pulmonary oedema, pulmonary infarction, and haemoptysis); genitourinary and obstetric (renal and testicular infarction, abruptio placentae, spontaneous abortion, prematurity, and growth retardation); neurological (seizures, migraine, cerebral infarction, and intracranial hemorrhage); musculoskeletal and dermatological (rhabdomyolysis, skin ischemia, superficial and deep venous thrombosis, and thrombophlebitis (2–6).

CASE REPORT

We present a case of a twenty four years old male, with a history of inhaling vaporized cocaine, and marihuana for two years. The main complaints of patient were fatigue, labored respiration, especially at night, dyspnea, anxiety, increased heart rate and lost of appetite during last 2–3 months. The patient was conscious,

anxious, oriented to time, space and persons. Heart sounds were clear with systolic murmur. The ECG showed sinus tachycardia (HR > 100/min) (Figure 1) and about 0,5 mm upsloping ST segment depression in lateral leads. Blood pressure was elevated (150/105 mmHg). Laboratory analysis showed elevation of blood Urea (10.6 mmol/L), Creatinine (154 mmol/L), Na (149 mEq/L), K (4.2 mEq/L) and iron-deficiency anemia with Fe (7.1 mcg/dl). X-ray findings obtained enlarged heart silhouette (Figure 2). Echocardiographic evaluation showed left chamber dilatation with reduced global systolic function and ejection fraction (EF) 38%, designated mitral cusps with posterior cusp prolapsed, thin regurgitated flow and intraatrial septum tissue changes.

Preceding therapy Carvedilol and Acetylsalicylic acid was changed to heart failure — guideline-based heart failure therapy: Carvedilol, nonselective alfa/beta — adrenergic blocker (2 x 6,25 mg per day), Perindopril, ACE inhibitor (4 mg per day), Spironolactone, mineral corticoid receptor antagonist, MRA (25 mg per day), Thiazide diuretic (25 mg per day) and Acetylsalicylic acid (100 mg per day). Therapy for correction of anemic syndrome was recommended. Cocaine cessation was obligated.

Two months later, after cocaine cessation and treatment in specialized hospital, the patient didn't fill the symptoms from the first examination, but he was at bad physical condition. Laboratory findings were normalized: Urea 7.6 mmol/L; Creatinin 108 mmol/L; Na 139 mEq/L; K 4.2 mEq/L and Fe 16.2 mcg/dl. EKG showed sinus rhythm with HR 65/min. Blood pressure was 120/80 mm Hg. Dimensions of left ventricle were in referent values. Left ventricle function was slightly reduced with EF 49%, mitral cusps were designated with posterior cusp prolapsed and intraatrial septum tissue changes. The patient continued with the same therapy.

The patient abstained from cocaine use and five months later he didn't fill any of the symptoms from the first examination, and he was in good physical condition. Laboratory findings were in the ranges of referent values. Left and right ventricles function and dimensions were preserved. Left ventricle EF was 62%. The patient continued with medications: Nebivolol, cardioselective β1 — receptor blocker (2,5 mg per day) and Acetylsalicylic acid (100 mg per day).

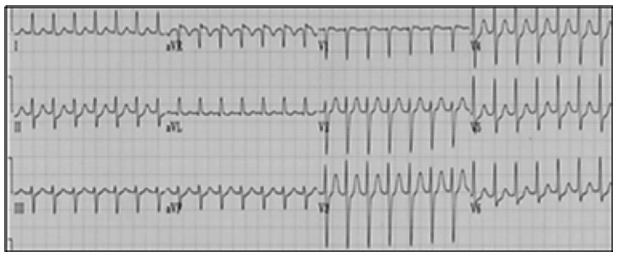

Figure 1. *ECG findings*

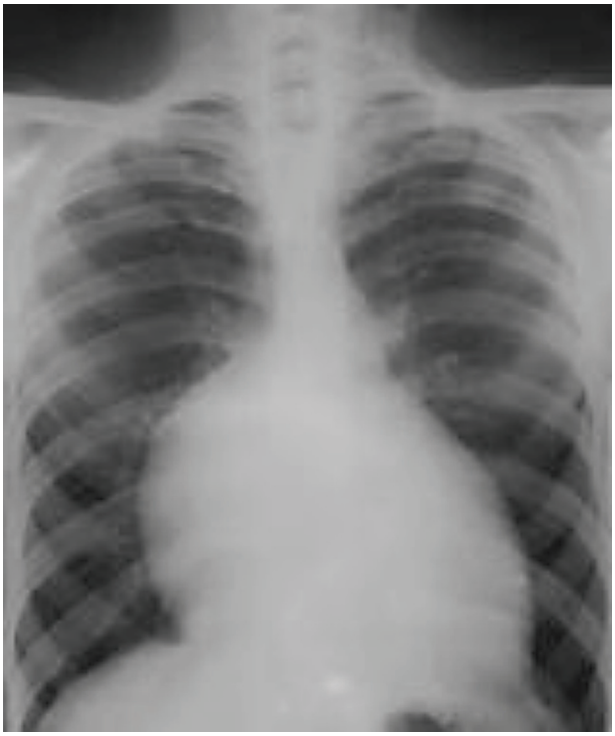

Figure 2. *X-ray findings of enlarged heart silhouette*

DISCUSSION

Cocaine users may have various symptoms referable to the cardiac system. Symptoms can include chest pain with or without myocardial ischemia or aortic dissection, hypertension with or without hypertensive crisis, cerebral ischemia, and hemorrhage. Patients also may present with acute myocardial decompensation with or without pulmonary edema and shock. In this case, shortness of breath and hypoperfusion dominate the clinical picture (1, 6, 7, 8).

Morbidity and mortality information associated with cocaine-related cardiomyopathy is commonly based on case reports (9, 10). Chokshi et al. were among the first authors to describe a reversible cocaine-related cardiomyopathy. The patient in their report, a 35-year-old woman, underwent endomyocardial biopsy that failed to reveal any necrosis, fibrosis, or inflammatory infiltrate (9).

While most cases of cocaine-related cardiomyopathy have proved to be reversible, others have resulted in permanent cardiac dysfunction or death. The symptoms of cocaine-related cardiomyopathy are the same as symptoms for other forms of congestive heart failure. The onset may be very sudden and of short duration. A cocaine-related etiology for cardiomyopathy should be suspected in any patient with a history of cocaine use, particularly binge use, and heart failure, wit-

hout another established etiology for the heart failure, such as coronary artery disease. If the clinical suspicion is high, the diagnosis of cocaine use should be investigated with a urine screen for cocaine and its metabolites. The typical patient with cocaine cardiomyopathy is a young male smoker who presents with signs of adrenergic excess (5, 10). With acute binge use of cocaine, the patient may present with acute congestive heart failure and pulmonary edema. Hypotension, rater than hypertension, may predominate, making the diagnosis and treatment more difficult. Cocaine-related cardiomyopathy presents more acutely than other types of congestive heart failure, and fewer findings of chronic congestive heart failure are present. Otherwise, the physical findings are similar. Diaphoresis, pallor, and acute dyspnea are present. Cardiogenic shock or evidence of cardiac ischemia also may be present.

The laboratory investigation of cardiomyopathy of any etiology generally shows abnormalities of electrolytes, usually anemia and compromised renal function, with elevation of blood urea nitrogen (BUN) and creatinine.

Cocaine usually is evident on a urine toxicology screen, because these cases almost always present immediately after use of the drug. Because individuals who use cocaine are predisposed to the development of endocarditis, consider blood cultures if the setting is at all appropriate.

In cases of cardiomyopathy, the chest radiograph usually shows evidence of cardiomegaly and congestive heart failure. Evidence of septic emboli may be present if endocarditis is present. The radiograph may be normal in many cases.

Echocardiographic evaluation shows chamber dilation and global dysfunction or regional wall motion abnormalities if myocardial infarction is present. Echocardiographic studies have shown that individuals who abuse cocaine have an increased left ventricular mass index with a higher tendency toward increased posterior wall thickness.

Cardiac catheterization usually shows normal coronary arteries or only minimal disease, even in the presence of myocardial infarction.

In cases of cardiomyopathy, the ECG is not specific but may show evidence of left ventricular hypertrophy and nonspecific ST-T wave changes. Arrhythmias also may be detected, and continuous monitoring may be advisable.

In autopsies of 40 patients, 31 of whom died cocaine-related deaths and 9 of whom were homicide victims with detectable blood cocaine levels, Virmani et al. found that 20% of the patients showed evidence of myocarditis on toxic screening tests (11). Tazelaar, in an autopsy study, reported contraction-based myocardial necrosis similar to that observed in pheochromocytoma (12).

In a case report by Robledo-Carmona, histologic findings of the left ventricular myocardium included sparse mononuclear infiltrates associated with degenerative changes, myocyte necrosis, and severe interstitial fibrosis (13).

Management

Associations of cardiologists don't have recommendations for concrete medicamentous treatment of cocaine cardiomyopathy (1). Management of these patients is similar to that of patients with other forms of dilated cardiomyopathy, although beta-blockers should be included in patients with cocaine-associated heart failure and benzodiazepines should be given in this setting to blunt adrenergic excess. If shock is present, inotropic agents and vasopressors are indicated. If evidence of ongoing ischemia is present, aggressive use of agents directed at relieving vasospasm (nitrates and calcium channel blocking drugs) are indicated. Endotracheal intubation may be necessary. If arrhythmias are present and are felt to be compromising the clinical situation, they should be treated aggressively. The use of beta-blocking drugs as single agents is contraindicated. For the purpose of these patients need to know and be used in medical practice cardiac magnetic resonance as a method that is quite useful for predicts reversibility of cocaine-induced ventricular dysfunction (1, 14, 15, 16).

John McMurray et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012 (17) recommend the following therapy:

An ACE inhibitor in addition to the beta-blocker is used for all patients with an EF ≤ 40% to reduce the risk of heart failure hospitalization and the risk of premature death. A beta-blocker in addition to an ACE inhibitor is used for all patient with an EF ≤ 40 % to reduce the risk of heart failure, hospitalization and the risk of premature death. An MRA is recommended for all patients with persisting symptoms and EF < 35%, despite treatment with ACE inhibitor and a beta-blocker to reduce the risk of heart failure hospitalization and the risk of premature death. It is good to mention that analysis of B-type natriuretic peptide (BNP) level can help monitor the presence of congestive heart failure. Also BNP is very helpful to monitor response to treatment.

In most of reported cases of cocaine-related cardiomyopathy, patients have shown significant improvement following the cessation of cocaine use. In some cases, patients have returned to normal cardiac func-

tion, but recurrence is reported if the patient relapses into cocaine use (5).

Efforts to assist the patient with their drug addiction should be a part of every treatment plan. Hospitalization for detoxification may be necessary, particularly if other drugs also are being abused. Outpatient treatment of drug dependence is strongly advised. Abstinence from cocaine use and long time follow up is mandatory.

CONCLUSION

This is the first publication of cocaine-related cardiomyopathy in our country. Physicians usually don't consider the possibility of cocaine use of their patients. Many cocaine users have little or no idea of the risks associated with its use. So, patients, health care workers and the public should be educated about the dangers and the considerable risks of cocaine use.

Abbreviations

ACE — Angiotensin converting enzyme
BNP — Natriuretic peptide
BUN — Blood urea nitrogen
ECG — Electrocardiography
EF — Ejection fraction
ESC — European Society of Cardiology
HR — Heart rate
MI — Myocardial infarction
MRA — Mineral corticoid receptor antagonist
ST — ECG between the end of the S wave (the J point) and the beginning of the T wave

Sažetak

KOKAINSKA KARDIOMIOPATIJA — PRIKAZ SLUČAJA

Georgiev Antonio,[1] Zhivadinovik Julija[2]

[1] Univerzitetska Klinika za kardiologiju, Univerzitet „Sv. Ćirilo i Metodije", Medicinski fakultet, Skoplje, R. Makedonija
[2] Institut za anatomiju, Univerzitet „Sv. Ćirilo i Metodije", Medicinski fakultet, Skoplje, R. Makedonija

Kokain je druga najčešća nezakonita droga koja se koristi i najčešći uzrok smrti zbog droge. Upotreba kokaina daje akutne i hronične komplikacije, koje mogu uključivati bilo koji sistem organa, najčešće kardiovaskularni sistem. Kardiomiopatija može biti izazvana konzumiranjem kokaina. Ovaj članak predstavlja slučaj dvadesetčetvorogodišnjeg muškarca s reverzibilnom kokainskom kardiomiopatijom, što predstavlja prvi takav u Republici Makedoniji. Nalazi kliničkog pregleda, laboratorijskih analiza, rendgengrafije srca i pluća, ultrazvuka srca i tretman su prikazani.

Ključne reči: kokain, kokainska kardiomiopatija, dijagnoza, lečenje.

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Correspondence to /Autor za korespondenciju
Georgiev Antonio
University Clinic for Cardiology
Vodnjanska bb
1000 Skopje, Republic of Macedonia
e-mail: antoniogeorgiev@yahoo.com
tel: 0038970 305114

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SENTINEL LYMPH NODE CONCEPT IN DIFFERENTIATED THYROID CANCER

Markovic Ivan, Dzodic Radan

Medical faculty University of Belgrade, Institute of oncology and radiology of Serbia, Belgrade, Serbia

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Abstract: **Introduction:** Differentiated thyroid carcinoma (DTC) account up to 90% of all thyroid malignacies, and represents the most common malignant tumors of endocrine system. The incidence of papillary thyroid carcinoma (PTC), especially small tumors is rapidly increasing during past three decades. At the time of diagnosis, the incidence of lymph node metastases (LNM) ranges from 80 to 90%. During the last 15 years, LNM were recognized as bad prognostic factor for both local-regional relapse (LRR) and cancer specific survival. There is general agreement that neck dissections are indicated in cases of clinically apparent LNM. The subject of the current controversy is the surgical treatment of occult LNM that remain unrecognized on preoperative diagnosis (cN0). The extent of operations of the lymph nodes ranges from "wait and see" so-called "Western school" principle substantiated the role of applying ablative I131therapy and frequency peroperative complications (recurrent laryngeal nerve injury and hypoparathyroidism), especially for less experienced teams to mutual prophylactic dissection of the central and lateral compartments so-called "Japanese school" due to the limited use of radioactive iodine therapy and significantly lower operating morbidity if dissetion was done during primary operation. Despite high prevalence of occult LNM, existing controversies regarding diagnosis, longterm prognostic impact and extent of lymph node surgery, motivated some authors to apply consept of sentinel lymph node biopsy (SLNb) in DTC, taking into account excellent results of SLN concept in breast cancer and skin melanoma. This review presents the summarized results of relevant studies and three meta-analysis of accuracy and applicability of SLN concept in patients with differentiated thyroid carcinoma.

Key words: Differentiated thyroid cancer, lymph node mestastases, sentinel lymph nodes.

INTRODUCTION

Thyroid cancer represents about 1.7% of all malignancies in humans. Survival of patients is favorable, but the disease and its treatment carries out morbidity and mortality (1). Differentiated thyroid carcinoma (DTC) account 90% of all thyroid malignancies and are the most common primary malignancy of the endocrine system, and their incidence is increasing.

Papillary thyroid carcinoma (PTC) metastasized to the regional lymph nodes in 30 to 80% of patients and up to 90% of children and adolescents. Metastasizes to the central (pretracheal and paratracheal, level VI), upper mediastinal (level VII) and lateral (supraclavicular, jugulocarotid, level II, III, IV and V) lymph nodes of the neck. Follicular thyroid carcinoma extremela rare metastasize to the lymph node, but often metastasize to distant organs such as the lungs and bones.

Lymph nodes in the neck are most commonly classified by the American Academy of Otolaryngology and the American Joint Committee on Cancer reccomendation. According to this classification, lymph nodes of the neck were divided into seven groups or levels (Figure 1).

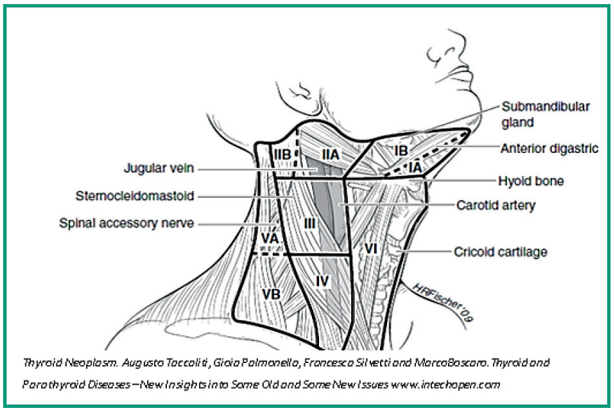

Figure 1. *Neck lymph node levels*

At the time of the first clinical presentation, 20 to 30% of patients with papillary thyroid carcinoma (PTC) has metastatic lymph nodes in the neck, and around 90% have micrometastases in lymph nodes (2, 3).

Although very common, lymph node metastasis (LNM) are just in recent 15 years recognized as a factor of poor cancer-specific outcome (4, 5). Despite the fact that lymph node metastases have a high prevalence, the patients with PTC have an excellent prognosis. In the past few decades, LNM were not considered a significant factor for overall survival of patients and were the subject of numerous controversies.

Finally, in the last two decades LNM are recognized as a negative prognostic factor for disease recurrence and cancer-specific survival, especially for older patients with large tumors and extra-thyroid extension (6, 7, 8).

Impact of LNM to disease recurrence is certainly less controversial. The existence of LNM significantly increases the rate of locoregional recurrence. Moreover, recurrence or rest of tumor in the neck after apparently curative surgery remains a major cause of morbidity and represents a significant therapeutic challenge for clinicians (9). Despite the best efforts of therapy, 10 to 30% of patients with DTC develop locoregional recurrence after the initial surgery, causing an increase in morbidity. Numerous studies have shown that relapses are the most common in lymph nodes. Therefore, surgery is a key therapeutic modality in the treatment of DTC. Total or near total thyroidectomy is standard in the treatment of primary thyroid carcinoma. Therapeutic dissection of central or lateral neck compartments is indicated in patients with clinically suspected or cytologically or histologically proven lymph node metastases (10).

The procedure with occult LNM, which are radiologically undetectable (clinically N0, cN0) is still controversial, considering the high prevalence of histologically proven micrometastases in prophylactic dissections.

American Thyroid Association (ATA) in its most recent review (2009) recommends prophylactic central neck dissection (CND) in cN0 and advanced tumors (T3 and T4). ATA also admits that avoiding the central dissection in the case of smaller tumors, "may increase the risk of locoregional recurrence, but in total can be safer in the hands of unexperienced surgeon" because of higher rates of morbidity (recurrent laryngeal nerve injury and hypoparathyroidism) when working together with total thyroidectomy (2 , 11).

In Europe and the United States prophylactic lateral neck dissection is not routinely done because of the role of ablative radioactive iodine therapy (2, 12).

On the other hand, some European authors, especially some Japanese say that the prophylactic lateral neck dissection improves prognosis. According to recently published reccomendations of Japanese Association of thyroid surgeons and the Japanese Association of Endocrine Surgeons, CND in papillary thyroid cancer is standard, and prophylactic modified radical neck dissection (MRND) is routinely applied in most centers dealing with endocrine surgery in Japan (6, 7, 13, 14).

Current controversies in the surgical approach and prognostic significance of lymph node metastases, as well as the limitations of preoperative diagnosis and adjuvant therapy, has led some authors to apply the concept of sentinel lymph nodes (SLN) in patients with DTC.

SENTINEL LYMPH NODES — HISTORICAL REVIEW

Sentinel lymph node is the first lymph node/s in the corresponding lymph drainage area that receives afferent lymphatic drainage of malignant tumors. Gould and colleagues, from Washington Hospital Center, in 1960, were the first to use the term sentinel lymph node of nearest lymph node within parotidectomy for cancer of the parotid gland (15).

The concept of SLN and its predictive value in the staging of regional spread of malignant tumors, is most commonly associated with Ramon Cabanas, South African surgeon, and his pioneering work (1977) on lymphatic drainage using vital dye injection in 100 patients with carcinoma of the penis (16).

Although Cabanas first demonstrated the usefulness of this concept, many authors in the last 100 years have investigated and documented the concept of sentinel lymph nodes in different malignat tumors.

THE CONCEPT OF SENTINEL LYMPH NODES

The assumption is that the existence or absence of metastasis in the SLN expected to reflect the status of the regional lymph nodes.

The primary objectives of this procedure are to achieve reliable detection of LNM in clinically unaffected lymph nodes and thus avoid unnecessary dissection and its complications and to provide optimal and timely selective surgical treatment.

The secondary objectives are optimal planning of adjuvant therapy and potentially reducing the risk of locoregional relapse.

The concept of SLN has become a standard in the detection of occult LNM in case of early breast cancer and skin melanoma. The effectiveness of the method was confirmed by its inclusion in the UICC TNM classification of malignant tumors (17, 18, 19, 20).

Pioneering study of Kelemen and coworkers (1998) on SLN for thyroid nodules inducted a series of studies that have shown that SLN biopsy may be appropriate procedure in assessment of lymph node status in patients with differentiated thyroid cancer (21).

The concept involves mapping, detection and surical biopsy and their frozen-section and standard hi - stopathologic analysis. The choice of markers (vital colors and/or nanocolloid), skills and experience of the surgeon in detecting (learning curve), the experience and knowledge of the pathologist in the processing of SLN are of key importance. The ratio of positive (malignant) and negative (benign) SLN presents the findings of sensitivity (Se), specificity (Sp), positive (PPV) and negative predictive value (NPV). On the basis of these findings overall accuracy of the method is calculated.

RESULTS OF SLN BIOPSY FOR DIFFERENTIATED THYROID CANCER — REVIEW OF LITERATURE

By 2012, three meta-analysis were published investigating the SLN techniques, the use of different markers and the results of methods accuracy of all relevant studies.

The first meta-analysis published by Raijmakers (2008), included 14 studies, of which in 10 were used the vital dye, and in four radiocolloid (Tc99m). The rate of SLN detection (identification rate, IR) in studies with vital dye was 83%, and 96% in four studies with radiocolloid. The data on the sensitivity of the method were available in six of the 10 studies with a vital dye, and only one of the four studies with radiocolloid in which only a percentage of false negative results was available. Sensitivity in studies with vital dye was 87.3% (79 to 93%) with a rate of false negative results of 12.7%, versus 11.3% in the only study with radiocolloid. Histologically SLN somewhat questionable because several studies have included patients with benign thyroid tumors. Percentage of thyroid malignancy in seven studies ranged from 33 to 98%, while in other studies, all patients had thyroid cancer. As a conclusion, with the real limitation, according to the detection of SLN in thyroid cancer is possible and potentially useful, but there is a need for new and more numerous prospective studies (22) (Figure 2).

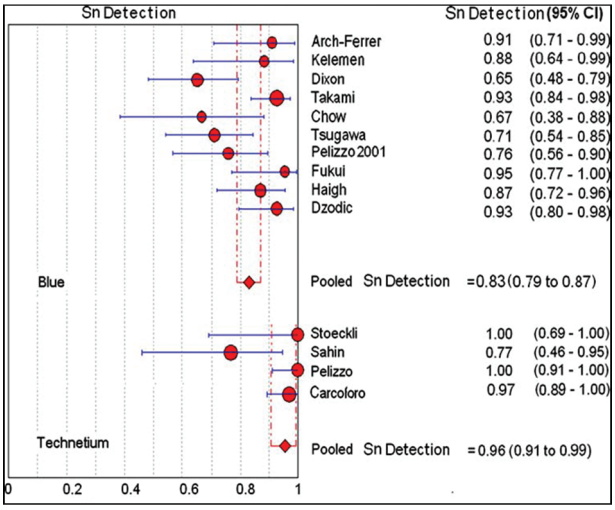

Figure 2. *Detection rate of SLN in Raijmakers's meta-analysis*

Source: *Raijmakers P. G. H. M., Paul M. A., Lips P. Sentinel node detection in patients with thyroid carcinoma: A meta-analysis. World J Surg (2008)*

The second meta-analysis by Balasubramanian and Harrison (2011) cover 24 relevant original studies on the role of SLN biopsy in thyroid cancer published until February 2010. In 17 studies vital dye was used as a marker, in four radiocolloid, while in the two studies, the combination of these two markers was used. Detection rate (IR) was 83.7%, 98.4% and 96% successively.

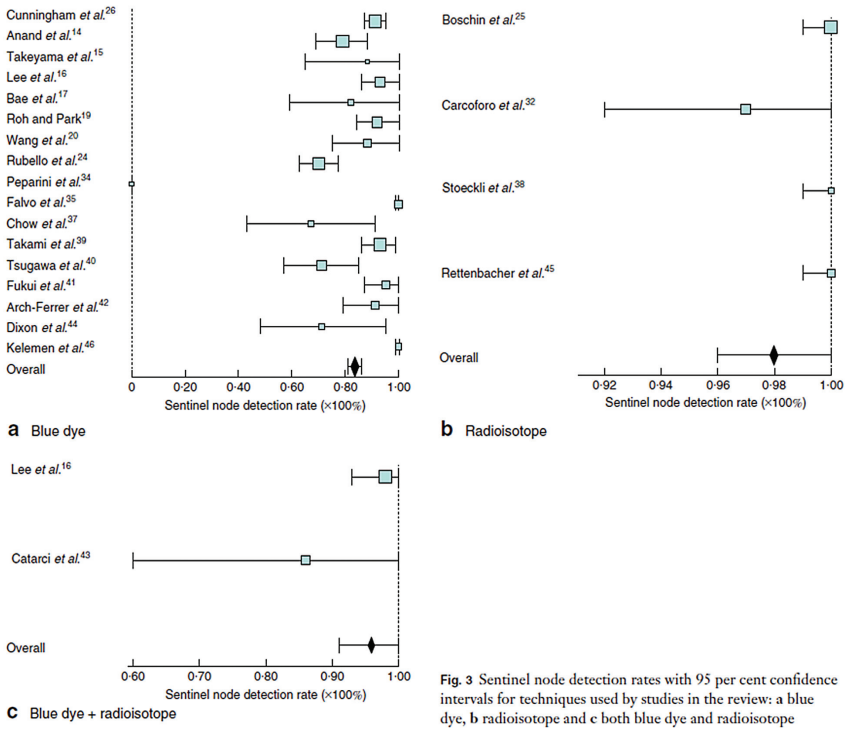

Fig. 3 Sentinel node detection rates with 95 per cent confidence intervals for techniques used by studies in the review: a blue dye, b radioisotope and c both blue dye and radioisotope

Figure 3. *Detection rate of SLN in Balasubramanian's meta-analysis*

Table 3 Results of studies using the blue dye technique of sentinel node biopsy in papillary thyroid cancer

Reference	No. of PTCs	SN identified	Positive SN	Negative SN	Sensitivity (%)	Specificity (%)	Accuracy (%)	False-negative rate (%)
Cunningham *et al.*[26]	211	192 (91·0)	71	121	NA	NA	NA	NA
Anand *et al.*[14]	70	55 (79)	14	41	100	100	100	0
Takeyama *et al.*[15]	8	7 (88)	3	4	75	100	86	25
Lee *et al.*[16]	54	50 (93)	19	31	NA*	NA*	NA*	NA*
Bae *et al.*[17]	11	9 (82)	5	4	83	100	89	25
Roh and Park[19]	50	46 (92)	14	32	78	100	91	13
Wang *et al.*[20]	25	22 (88)	19	3	100	100	100	0
Rubello *et al.*[24]	153	107 (69·9)	36	71	100	100	100	0
Peparini *et al.*[34]	8	0 (0)	—	—	NA	NA	NA	NA
Falvo *et al.*[35]	18	18 (100)	12	6	100	100	100	0
Dzodic *et al.*[36]	34	?†	?†	?†	NA†	NA†	NA†	NA†
Chow *et al.*[37]	15	10 (67)	7	3	87	100	90	33
Takami *et al.*[39]	68	63 (93)	35	28	87	100	92	18
Tsugawa *et al.*[40]	38	27 (71)	16	11	84	100	89	27
Fukui *et al.*[41]	22	21 (95)	7	14	78	100	90	14
Arch-Ferrer *et al.*[42]	22	20 (91)	17	3	100	100	100	0
Dixon *et al.*[44]	14	10 (71)	6	4	NA	NA	NA	NA
Kelemen *et al.*[46]	11	11 (100)	5	6	NA	NA	NA	NA
Total	832	668 of 798 (83·7)	286	382	91·6 (12 studies)	100 (12 studies)	95·8 (12 studies)	7·7 (12 studies)

Values in parentheses are percentages. Positive and negative sentinel node (SN) refers to the presence and absence of metastases in the SN on the basis of the final histology report (includes micrometastases on immunohistochemistry, where applicable). PTC, papillary thyroid cancer; NA, not applicable (routine dissection not done), except *could not be calculated as diagnostic accuracy figures were reported as a fraction of the total number of patients and not the number of patients with an identified SN, and †numbers not reported as study examined SNs in lateral compartment only.

Table 4 Results of studies using the radioisotope technique of sentinel node biopsy in thyroid cancer

Reference	No. of PTCs	SN identified	Positive SN	Negative SN	Sensitivity (%)	Specificity (%)	Accuracy (%)	False-negative rate (%)
Boschin *et al.*[25]	65	65 (100)	34	31	NA	NA	NA	NA
Carcoforo *et al.*[32]	59	57 (97)	14	43	67	100	88	16
Stoeckli *et al.*[38]	1	1 (100)	1	0	NA	NA	NA	NA
Rettenbacher *et al.*[45]	4	4 (100)	2	2	NA	NA	NA	NA
Total	129	127 (98·4)	51	76	67 (1 study)	100 (1 study)	88 (1 study)	16 (1 study)

Table 5 Results of studies using both blue dye and radioisotope techniques of sentinel node biopsy in thyroid cancer

Reference	No. of PTCs	SN identified	Positive SN	Negative SN	Sensitivity (%)	Specificity (%)	Accuracy (%)	False-negative rate (%)
Lee *et al.*[16]	43	42 (98)	21	21	NA	NA	NA	NA
Catarci *et al.*[43]	7	6 (86)	4	2	100	100	100	0
Total	50	48 (96)	25	23	100 (1 study)	100 (1 study)	100 (1 study)	0 (1 study)

Figure 4. *Results of studies with different markers used in Balasubramanianžs meta-analysis*

Source: *Balasubramanian S, Harrison B Systematic review and meta-analysis of sentinel node biopsy in thyroid cancer. Br J Surg (2011)*

Analysis of sensitivity, specificity and overall accuracy of the method was possible in 12 studies with a vital stain, and only by one study with radiocolloid and combined method. The percentage of false negatives was successively 7.7%, 16% and 0%. Lymph node metastasis in the SLN were observed in 42.9% of patients, whereas in eight studies, which is used for additional immunohistochemical analysis, micrometastases verified in another 14.8% of patients. Balasubramanian and Harrison concluded that SLNb method has high expectation and with its implementation can be avoided prophylactic dissection in almost 57% of patients with thyroid cancer and clinically negative lymph nodes (23) (Figures 3 and 4).

Finally, the third meta-analysis by Kaczka and associates (2012) included 25 studies, which according to the techniques of marking and detection of SLN was divided into three groups. The first group of 18 study used the vital dye, in the second group of four studies, radiocolloid was used, and in the third group the two studies used a combined technique. SLN detection rate in patients was 83.1% in the first group, 98.8% in the second group and 97.8% in the third group. In two studies of the third group, Catarci have shown better result of detection with radiocolloid relative to the vital dye (83.3% versus 50%), while Lee showed a better IR with vital dye (93% versus 88.4%) (24, 25, 26).

This meta-analysis showed the advantage in IR of peritumoural injection of the vital dye compared to intratumoural application (92.2% to 71.8%). It also showed a better detection rate of SLN using methylene blue (Methylene blue), compared to isosulfan blue (Isosulfan blue) and patent blue (Patent blue) — (91.9% versus 86.1% and 68.3%). There were no differences in the rate of detection of intratumoral and peritu-

Table IV. *Methodology and results of studies in which only the blue dye technique was used*
Tabela IV. *Metodologia i wyniki badań, w których zastosowano jedynie metodę barwnikową*

No.	Study and year	Detection technique	Tracer volume and dose	Injectionsite	No of pts	No. of malignant pts	No. of pts with detected SLNs	No. of malignant pts with detected SLNs	No. of malignant pts with detected and metastatic SLNs
1.	Kelemen et al. 1998 [35]	1% Isosulfan blue dye	0.1–0.8 mL, average 0.5 mL	Intratumoural	17	12	15	12	5
2.	Dixon et al 2000 [40]	1% Isosulfan blue dye dye	0.1–0.8 mL, average 0.7 mL	Intratumoural	40	15	26	11	7
3.	Arch-Ferrer et al. 2001 [41]	1% Isosulfan blue dye	0.5 mL	Intratumoural	22	22	20	20	12
4.	Pelizzo et al. 2001 [42]	0.5% Patent Blue V	0.5 mL	Intratumoural	29	29	22	22	4
5.	Fukui et al. 2001 [43]	2% Methylene blue	0.1 mL 4 quadrant	Intratumoural	22	22	21	21	7
6.	Tsugawa et al. 2001 [44]	1% Patent blue dye	0.2–0.5 mL	Directly in the thyroid mass	38	38	27	27	16
7.	Takami et al. 2003 [45]	Isosulfan blue dye	0.3 mL	Peritumoural	68	68	63	63	35
8.	Chow et al. 2004 [46]	2.5% Patent Blue V	0.5–1 mL	Intratumoural	15	15	10	10	7
9.	Peparini et al. 2006 [47]	2.5% Patent blue V	0.1–1.2 mL mean 0.5	5 — intratumoural 3 — peritumoural	8	8	0	0	0
10.	Rubello et al. 2006 [48]	0.5% Patent blue V	0.25 mL for 1 cm diameter	Intratumoural	153	153	107	107	36
11.	Dzodic et al. 2006 [49]	1% Methylene blue dye	0.2 mL	Peritumoural	40	40	37	37	9
12.	Abdalla et al. 2006 [50]	1% Isosulfan blue dye	0.5–1 mL	Intratumoural	30	0	18	0	0
13.	Roh et al. 2008 [51]	2% Methylene blue	0.2 mL	Peritumoural	50	50	46	46	18
14.	Wang et al. 2008 [52]	2% Methylene blue	0.5 mL	Peritumoural	25	25	22	22	19
15.	Bae et al. 2009 [50]	2% Methylene blue	0.5 mL	Intratumoural and surrounding parenchyma	11	11	9	9	5
16.	Takeyama et al. 2009 [53]	1% Isosulfan blue dye	0.1 mL 4 quadrant	Peritumoural	37	12	32	11	4
17.	Anand et al. 2009 [54]	1% Methylene blue	0.2–0.3 mL	Peritumoural	75*	75	70	70	15
18.	Cunningham et al. 2010 [55]	1% Isosulfan blue dye	0.5–2 mL	Intratumoural	211	211	192	192	71

*Sentinel lymph node biopsy in patients with benign lesions was not analysed

Figure 5. *Methodology and results of studies in which only blue dye was used in Kaczka's meta-analysis*

Source: *Kaczka K, Celnik A, Luks B, Jasion J, Pomorski L. Sentinel lymph node biopsy techniques in thyroid pathologies — a meta-analysis. Endokrynol Pol. (2012)*

moural applications of radiocollodi. Lymph node metastasis in the SLN were detected successively in 40.8%, 39.9% and 52.1% of cases (24) (Figure 5).

Disparity of histopathological findings of primary thyroid tumor, involvement of benign tumors and cancers with different biological behavior, relatively few studies have been undertaken a complete surgical exploration of central and lateral neck compartmments and the lack of data on the statistical reliability of the testing methods, represent real constraints.

In the experimental study of Li and associates in laboratory rabbits, the advantage of methylene blue staining in speed, depth of penetration and persistence of staining compared to other vital colors have been shown (27).

Thevarajah and associates in the review paper analyzed the side effects and allergic reactions to the use of vital blue dye in the detection of SLN in breast cancer in the period from 1985 to 2002. They concluded that isosulfan blue cause significant allergic reactions, even life-threatening. Therefore, the use of methylene blue strongly recommended as an equally effective and safe alternative in the detection SLN (28).

The results of previous prospective study by Dzodic and associates (2006) are included in all three meta-analysis. Also, by 2011, our concept SLN biopsy in the lateral compartment was only published in the relevant literature. We used a 1% solution of methylene blue as peritumoral injection in 40 patients with thyroid cancer in the period from 2001 to 2004. Lymph node metastases in the lateral neck compartment were histologically confirmed in 22.5% of patients with clinically unaffected lymph nodes (cN0). SLN detection rate was 92.5%, sensitivity 77.7%, specificity 100%, positive predictive value of 100%, negative predictive value 94%, while the overall accuracy of the method was 95% (29).

Unlike other studies that were based on the identification of the SLN biopsy in the central neck compartment, in this study the path of the vital dye was followed to the lymph nodes in lateral compartment with the idea to check them histologically in the case of metastases and perform selective lateral neck dissection.

During 2011, two studies that have analyzed rezltate SLNb lateral neck compartment were published. Ikeda presented the results of detection SLNb with Indocyanin green peritumoral application in 12 patients with PTC. The rate of detection was 100% as well as sensitivity, specificity and overall accuracy of the method. Lymph node metastases in the lateral compartment were confirmed in 50% of patients preoperatively staged as cN0 (30).

Lee and associates were included 94 patients with PTC, which had undergone SLN detection in the lateral compartment with intratumoral application of radiocolloid (Tc99m), preoperative lymphoscintigraphy and intraoperative hand held gamma probe. Detection rate was 63.8%. The study included patients with PTC larger than 1 cm in diameter or evident central metastases. Lymph node metastases in the lateral compartment were confirmed in 31.7% of cN0 patients. Approximately 93% of SLN was located in the ipsilateral compartment in the level III and IV, 4.6% in level II and 2.3% in the third level. The sensitivity and accuracy of the method were not tested in this study (31).

CONCLUSIONS AND PERSPECTIVES

Based on the three meta-analysis it could be concluded that SLN biopsy is a safe and feasible, with high reliability in predicting occult lymph node metastases in differentiated thyroid carcinoma. Using vital dye is cheap and does not require technical equipment. The sensitivity of the method is increasing, while the complementary immunohistochemical and molecular techniques evolve. SLNb for thyroid cancer may prove practical use in precise staging of cervical lymph node status, detection LNM outside the central compartment, the selection of patients who will benefit with adequate and timely selective neck dissection and optimize application of ablative radioiodine therapy.

Currently, there is no direct evidence that SLNb could associated with long-term prognosis in terms of locoregional relapse and survival of patients with thyroid cancer.

Controlled prospective clinical studies on a larger number of patients and longer follow-up period will determine the clinical significance of occult LNM and their early detection method SLNb in patients with thyroid cancer.

The authors have no conflict of interests.

Abbreviations:

TC — Differentiated thyroid carcinoma
PTC — Papillary thyroid carcinoma
UICC — Union International Against Cancer
LNM — Lymph node metastases
ATA — American Thyroid Association
CND — Central neck dissection
MRND — Modified radical neck dissection
SLN — Sentinel lymph node
SLNB — Sentinel lymph node biopsy

Sažetak

KONCEPT STRAŽARSKIH LIMFNIH NODUSA KOD DIFERENTOVANOG TIROIDNOG KARCINOMA

Marković Ivan, Džodić Radan

Medicinski fakultet Univerziteta u Beogradu, Institut za onkologiju i radiologiju Srbije, Beograd, Srbija

Diferentovani tiroidni karcinomi (DTK) čine do 90% svih tiroidnih maligniteta i najčešći su primarni maligniteti endokrinog sistema. Njihova učestalost je u značajnom porastu u poslednje tri decenije, a posebno malih papilarnih tiroidnih karcinoma (PTK). U vreme dijagnoze, učestalost limfonodalnih metastaza (LNM) iznosi od 80 do 90%. U poslednjih 15 godina, LNM su prepoznate kao loš prognostički faktor za pojavu lokoregionalnog relapsa bolesti (LRR) i kancer-specifičnog preživljavanja. Postoji generalna saglasnost da su disekcije vrata indikovane kod klinički suspektnih LNM. Predmet aktuelnih kontroverzi predstavlja hirurški postupak sa okultnim LNM koje preoperativnom dijagnostikom ostaju neprepoznate (cN0). Opseg operacije na limfnim nodusima kreće se od teorije „sačekati i videti“ takozvane „zapadne škole“ argumentovane ulogom primene ablativne terapije J131 i učestalošću peroperativnih komplikacija (povrede povratnog laringealnog nerva i hipoparatireoidizma) posebno kod manje iskusnih timova, do obostranih profilaktičkih disekcija centralne i lateralne regije vrata takozvane „japanske škole“ zbog ograničene upotrebe radioaktivnog joda u terapijske svrhe kao i značajno manjeg operativnog morbiditeta ukoliko se disekcija uradi u primarnom aktu. Uprkos visokoj prevalenci okultnih LNM, postojeće kontroverze u dijagnostici, dugoročnom prognostičkom značaju i opsegu operacija na limfnim nodusima, motivisale su neke autore da koncept provere stražarskih limfnih nodusa (SLN) primene kod pacijenata sa DTK, imajući u vidu odlične rezultate kod karcinoma dojke i melanoma kože. U ovom pregledu prikazani su sumirani rezultati relevantnih studija i tri meta analize pouzdanosti i primenljivosti konecpta SLN kod pacijenata sa diferentovanim tiroidnim karcinomom.

Ključne reči: Diferentovani tiroidni karcinom, limfonodalne metastaze, stražarski limfni nodusi.

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Corresponding author/ Autor za korespondenciju
Ivan Markovic, MD, PhD,
Medical faculty University of Belgrade,
Institute of oncology and radiology of Serbia
Pasterova 14
11000 Belgrade
Serbia
Tel: +381637792716
Fax: +381112685300

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SYSTEMIC DISORDERS AFFECTING DENTAL PATHOLOGY

Knezevic R. Milan,[1] Andjelic S. Gordana,[2] Knezevic M. Milena[3]

[1] FEBOMFS, University Las Palmas, Spain
[2] Institute for Medical Research, Military Medical Academy, Belgrade, Serbia
[3] Medical School, University Las Palmas, Spain

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Abstract: A retrospective overview of systemic disorders which might be associated with dental pathology is made. They are grouped as follows: (a) congenital dental developmental disorders, (b) chromosomal anomalies, (c) radiations, (d) immune disorders, (e) intoxications, (f) neurological alterations, (g) gastrointestinal diseases, (h) osteodystrophy and associated conditions, (i) skin diseases, (j) metabolic and endocrine disorders, (k) craniofacial malformation syndromes and other congenital general malformations. The associated dental pathology is described in each case.

Key words: Dental diseases, Symptoms, Systemic disease, Retrospective overview.

INTRODUCTION

Dental pathology may be divided into five etiological groups /1/ infections (e.g., caries) /2/, traumatisms /3/, disorders resulting from dental wear (e.g., attrition, erosion, and abrasion) /4/, pathologic formations /5/ and dental developmental disorders — the latter usually being associated to other extra oral clinical manifestations that may or may not form part of a common syndrome.

Many diseases and pathological conditions, involving practically all human apparatuses and systems, exhibit associated dental pathology or manifestations. The present study reviews those systemic disorders that may associate dental pathology, grouped as shown below. The grouping of such systemic diseases into categories is complicated; however, since group overlapping inevitably occurs. On reviewing the etiologies of dental disorders, no uniform classification criteria are to be found among the different authors who have addressed the subject. As an example, in the case of morphology — structural dental enamel defects, Neville et al. (1) propose an exhaustive classification comprising trauma to developing tissues, the ingestion of chemical substances, chromosomal anomalies, infections, hereditary diseases, malnutrition, metabolic alterations and neurological disorders. In contrast, Wright (2) describes only three etiological groups: metabolic diseases, syndromic hereditary disorders and nonsyndromic hereditary disorders (e.g., amelo génesis imperfecta and other enamel developmental disorders). As commented above, the classification or grouping of the different diseases poses difficultness — particularly when referring to congenital disorders. In this context, it is accepted that in addition to the etiological factors associated to the dental anomalies described below, other underlying factors — probably genetic, related to tooth development and individual resistance to disease — are also implicated (3).

CONGENITAL ALTERATIONS OF TOOTH DEVELOPMENT

In this first group of dental disorders associated to systemic pathology, mention should be made of taurodontism, characterized by the presence of large pulp chambers that can occupy the entire root. This dental condition is associated to the trichodentoosseous (TDO) syndrome, hypohidronic ectodermal dysplasia and Klinefelter's syndrome (4). All pacients with TDO syndrome present this malformation (5); in contrast, it is only observed in certain hypo maturate variants of amelogenesis imperfecta (6). This marked association between both entities suggests the existence of a genetic determining characteristic referred to as idiopathic dental fluorosis (4). On the other hand, 28.9% of paents with oligodontia suffer taurodontism of one or more, lower molars, with greatly diminished length of the mandibular cuspids and first molars in women (7). In turn, the hypoplastic form of amelogenesis imperfecta can manifest in combination with multiple unerupted teeth, hypercementosis and different root malformati-

ons (8). In animals - specifically, in mice with transgenic cystic fibrosis (9) — anomalies have been observed in the form of soft whitish-blue enamel together with enamel of normal thickness and structure; ameloblasts that rapidly degenerate after the secretory phase, and enamel crystals of granular appearance and low molecular weight.

In the case of odontodysplasia associated to ectodermal dysplasia, clinical manifestations such as hypodontia and hypoplastic enamel appear (10).

Dentinogenesis imperfecta associated to osteogenesis imperfecta constitutes a structural anomaly affecting only the dentine. The teeth appear normal, though their development is abnormal (11); alterations in dentine formation occur in such cases (12). In experimental studies in rats, cyclosporine A has been shown to affect dentine formation, with alterations in the amount of secondary dentine appositioning and the generation of globular dental structures; the pulp is also affected in such situations (13).

CHROMOSOMAL ANOMALIES

Turner's syndrome involves morphological and volumetric dental alterations, with root abnormalities in lower molars and premolars, and reductions in size; the coronal portions of the incisors, canines and premolars are also affected (14), and the mesio-distal diameters are reduced (except in the upper canines) along with the vestibule lingual diameter of some teeth only (15). In Down syndrome the frequency of agenesis is 10 times greater than in the general population, with a higher incidence in males than in females. In order of descending frequency, agenesis affects the maxillary central incisors, the maxillary lateral incisors, the maxillary second premolars, and the mandibular second premolars (16). Microdontia is also observed. Another trisomy-involving chromosome 16 , is also associated to dental alterations. In this sense, decreases in the size of different dental organs have been documented in mice, together with the appearance of hypoplasias (17).

In one case of triple X syndrome the congenital absence of teeth was reported, with the presence of only one maxillary central incisor in both the deciduous and permanent dentition (18). Internals with a 45, XO karyotype, reductions in cuspid surface can be observed, along with decreases in volumenn -as reflectedby shortened mesiodistal and vestibulolingual diameters (19). Taurodontism has also been described (20). In Klinefelter's syndrome (males 47, XXY), important increments in enamel (but not of dentine) have been reported — in contrast to what is seen internals (21). As regards the gnostic condition 45, X/46, XX, 43% of the mandibular premolars have two roots — the proportion being approximately the same as internals with a 45, X karyotype (22).

RADIATIONS

Radiotherapy for head and neck cancer produces symptoms such as mucositis, oral dryness and taste alterations (23). A consequence of xerostomia is the increased risk of caries, which in these patients tend to be rapidly evolving, extensive and located in non-habitual zones (24). In children receiving radio-and chemotherapy, the number of dental anomalies has been found to increase (25).

INTOXICATIONS

Dental pathology associated to drug ingestion is diverse (26). As regards the production of caries, three groups of drugs can be cited: (a) those containing saccharose as excipient; (b) drugs that depress salivation and there-fore reduce the action of salivary caryoprophylactic agents in general (ie., buffer systems, dilution effect, etc.) — including tricyclic antidepressants, antipsychotic drugs, antihistamines, medication for arthritis, analgesics, diuretics, muscle relaxants, antiarrhythmic drugs, anticonvulsive agents, antidiarrhea formulations, antihypertensive drugs, medication for Parkinson's disease, antispasmodic drugs, anorexigenic agents; and (c) lithium-containing drugs. Drug intoxications can also cause dental discoloration, e.g., topical tin fluoride and systemically administered flours, chlorhexidine (though in this concrete case the dental plaque rather than the actual dental structure is stained), tetracyclines and ciprofloxacin. Regarding morpho-structural alterations of teeth, phenytoin should be mentioned, as it produces shortening, resorption and increased cement deposisitioning turn; local anesthetics are cytotoxic for tooth enamel and can interfere with amelogenesis when introduced under pressure into deciduous tooth ligaments. Additionaly, they may cause enamel hypoplasias in permanent dentition. Lastly, doxapram has been reported to induce the pre-mature appearance of dental germs (27).

GASTROINTESTINAL DISEASES

One of the most frequent dental alterations is erosion associated to gastrointestinal disorders. An example of this is provided by voluntary regurgitation (28), where the acid gastric contents attack the dental surface, causing progressive dental erosion (wear). In such situations the patient suffers marked dental hard tissue loss in the anterior group, and even in the palatine (lingual) surfaces of the premolars — to the point of exposing the pulp chambers. These alterations may in turn

be associated to dental discoloration. Similar effects are observed in patients with gastro esophageal reflux, where continuous exposure to low pH values leads to irreversible loss of dental substance once the salivary buffering capacity has been overcome (29, 30).

Patients with celiac disease have been found to suffer an increased incidence of amelogenesis imperfecta and other enamel developmental defects (31). In turn, Gardner's syndrome involves dental anomalies associated to maxillary osteomas.

OSTEODYSTROPHY AND ASSOCIATED CONDITIONS

In two siblings with dwarfism, severe microcephaly has been observed in association with generalizad microdontia (32). The appearance of dental dyschromia (gray-yellowish teeth) has also been described, probably as a residue of connective tissue alterations — in one case associated to osteopenia, fetal hydrops and communicating hydrocephalus (33). In three patients in whom retarded growth was associated to hypotonus and hypotrophy, microdontia with extensive diastases were recorded (34).

In the Hallermann-Streiff syndrome, generalized (though sometimes occasional) microdontia can be observed (35), as well as hypodontia, persistent deciduous dentition, enamel developmental defects, late dental development, mandibular hypoplasia, and caries (36). A typical feature of this syndrome is the proximity of the lower molar root apexes to the inferior mandibular mar-gin (37). Ehlers-Danlos mucopolysaccharidosis (type VII syndrome) involves the appearance of microdontia with yellowish discoloration ofthe teeth, and caries. Radiologicaly, marked dentinal opacity is observed (38). In turn, Ehlers-Danlos syndrome type I may present imperfect dentinogenesis (particularly of the mandibular incisors), alterations in root size, and occasionally also root hypoplasia or aplasia. Histologically, giant root canals are observed, with pulp calcifications and vascular inclusions (39). In the Winchester syndrome — another example of mucopolysaccharidosis — a clinical case has been reported involving the presence of supernumerary teeth together with unerupted teeth, irregularly spaced teeth and caries (40).

This extensive group of syndromes also comprises the following disorders: infiltrating congenital lipomatosis, with unilateral coronal enlargement or ma-crodontia, anomalous root formation and chronic periodontitis (41); tumor al calcinosis, where in addition to microdontia and dental structural wear the dental alterations may also involve the root and dental pulp, with the formation of short and bulbous roots, taurodontism ofthe first molars, pulp calcifications and partial pulp obliteration (42); and pyknodysostosis, where in one documen-ted case sharpened teeth with narrow pulp chambers were observed, together with enamel and root developmental alterations, malocclusion and caries (8).

Dwarfism associated to Grebe chondrodysplasia involves permanent dentition hypodontia along with diminished dental volume; additional findings include delayed formation and eruption of retained deciduous teeth. The jaws are hypoplastic (42). The Russell-Silver syndrome is in turn quite similar as regards the dental manifestations, with hypodontia, microdontia, delayed eruption, an arched palate, and crowding (39, 41); in another case reported in the literature, additional findings comprised the presence of double teeth in the deciduous dentition (40, 41). This form of dwarfism also manifests in the facial region, with an inverted orientation of the labial commissures.

CONCLUSION

The oral cavity is an important, very specific anatomical location with a significant role in many critical physiologic processes, such as digestion, respiration, and speech. It is also unique for the presence of exposed hard tissue surrounded by mucosa. Diseases of the tissues of the oral cavity can be categorized in the various groups: viral, hormonal, fungal, bacterial, dermatological, pharmaceutical, systemic disease, non-cancerous growths, psychiatric disorders, cancer and genetics. The primary and most important factor contributing to oral disease is tobacco use. However, other factors such as: alcohol beverage use, bad oral hygiene, diabetes and other medical conditions affecting the immune system, medications, stress and genetics can all play a role. The mouth is frequently involved in conditions that affect the skin or other multiorgan diseases. In many instances, oral involvement precedes the appearance of other symptoms or lesions at other locations.

Sažetak

SISTEMSKE BOLESTI KOJE UTIČU NA ZUBNU PATOLOGIJU

Knezevic R. Milan,[1] Andjelic S. Gordana,[2] Knezevic M. Milena[3]

[1] FEBOMFS, University Las Palmas, Spain
[2] Institute for Medical Research, Military Medical Academy, Belgrade, Serbia
[3] Medical School, University Las Palmas, Spain

Prikazan je retrospektivni pregled sistemskih poremećaja koji mogu biti povezani sa zubnom patologijom. Oni su grupisani na sledeći način: (a) kongenitalni dentalni razvojni poremećaji, (b) anomalije hromozoma, (c) zračenja, (d) poremećaji imunskog sistema, (e) trovanja, (f) neurološki poremećaji, (g) gastrointestinalne bolesti, (h) osteodistrofija i slični poremećaji, (i) kožna oboljenja, (j) metabolički poremećaji i endokrine bolesti, (k) kraniofacijalni sindromi i udružene kongenitalne malformacije. Za svaki slučaj je ponaosob data udružena dentalna patologija.

Ključne reči: bolesti zuba, simptomi, sistemske bolesti, retrospektivni pregled.

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Correspondence to /Autor za korespondenciju
Prof. dr Knezevic R. Milan
FEBOMFS, University Las Palmas, Spain
Email makmilk1@gmail.com

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ETHNICITY AND TYPE 2 DIABETES IN ASIAN INDIAN MIGRANTS IN AUCKLAND, NEW ZEALAND

Jowitt Ljiljana

University of Auckland, Department of Surgery, Auckland, New Zealand

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Abstract: *T*he aim of this review was to present ethnic differences in body size and body composition in Asian Indian migrants in New Zealand, associated with metabolic syndrome and type 2 diabetes, through the comparison with other ethnic groups in New Zealand. International databases including *PubMed* and *Google scholar* were consulted, as well as the websites of the *World Health Organization* and *International Diabetes Federation*. About 74 studies out of 128 publications were selected to ensure relevance to the topic of the review. Seven research projects were presented for the body size and body composition of Asian Indian migrants in New Zealand. The prevalence of type 2 diabetes of 8.6% in Asian Indians in New Zealand is still higher than in their homeland, owing to their ethnicity, genetic predisposition, sedentary lifestyle and altered nutrition, and other psychosocial factors related to migration and living conditions like stress at work and depression. For the same body mass index, in comparison with people of other ethnic groups in New Zealand Asian Indians had more total body fat, higher percent body fat, more central fat, less lean mass and appendicular skeletal muscle mass. Central obesity was associated with insulin resistance and low grade systemic inflammation. Considering the evidence that type 2 diabetes develops ten years earlier in Asian Indians than in other populations, further studies are warranted to shed some light on the still incompletely understood metabolic syndrome and "thin-fat" Indian phenotype.

Key words: ethnicity, Asian Indian migrants, body composition, insulin resistance, metabolic syndrome.

INTRODUCTION

Asia has become the major epicenter of a diabetes epidemic, and accounts for 60% of the world"s diabetic population (1). The number of people with diabetes in the region of South Asia is estimated to increase to 120.9 million by 2030 (2). Estimates based on population growth, ageing, and rate of urbanization in Asia show that by the year 2030 India as the largest country in the region will have about 79.4 million people with diabetes. Studies from India showed higher prevalence rates in urban areas compared to rural settings, a finding that has been partly attributed to the adoption of a „Western" lifestyle as in the case of migrant South Asians. Rapid economic development, urbanization, and changes in nutritional status, have led to an explosive increase in prevalence of type 2 diabetes. South Asians who migrated to westernized countries have about four times higher prevalence of diabetes than those living in urban India (3). Factors which contributed to increase in higher prevalence of type 2 diabetes in Asian Indian migrants include ethnicity, genetic predisposition, change in diet and lifestyle, and other psychosocial factors mostly depression and stress at work place related to migration and living conditions (4, 5). From a diet rich in pulses and cereals, which contain large amounts of fruits and vegetables, Asian Indian migrants have changed to a diet high in sugars and saturated and total fats, low in fruits, vegetables and fibre (6).

The prevalence of type 2 diabetes in Indian diaspora was the highest in the United Kingdom (11–33%) followed by Norway (14–28%), United States (18%), Singapore (12.8%) and Canada (10%), whereas the prevalence in native South Asians of Pakistan, India and Bangladesh is 7.6, 7.1, and 6.1% respectively (7). The prevalence of type 2 diabetes of 8.6% in Asian Indians in New Zealand is still higher than in their country of origin.

The number of Asian Indians who migrated to New Zealand, has grown from the 2001 census to 2006 census, from 61, 803 to 104,583 respectively making them, after the Chinese ethnic group, the second largest Asian ethnic group in New Zealand. Between the two censuses, the population in New Zealand has grown by

6.4%, with a 40% increase in the Asian populations (8). About 26% of the New Zealand Asian population comprises Asian Indians. In 2013 the Asian Indian ethnic group was the second largest Asian ethnic group, with 155,178 people (32.9 percent of the Asian ethnic group, up from 29.5 percent in 2006) (9).

Comprehensive epidemiological data about the prevalence of type 2 diabetes were obtained in South Auckland between 1991 and 1995, where a household survey of 100,000 residents was undertaken, recorded a highest prevalence of diabetes of 8.6% in Asian Indians in the 40–49 age groups (10). Between the two New Zealand Health Surveys (NZHSs), in the 2002–03 and 2006–07, a significant rise in obesity from 44% to 55% respectively was recorded in Asian Indians, as well as the highest prevalence of diabetes and coronary heart disease (CHD) (11). A recent HbA1c (glycated haemoglobin (A1c)) screening in South Auckland for undiagnosed diabetes of 50,819 volunteers aged 20+ recorded particularly high rates of HbA1c in Asian Indians (12).

In spite of their population growth, Asian ethnic groups have been largely neglected by New Zealand health and research policies (13), although the research on health issues in Asian Indian migrants has been developed in the recent years.

The aim of this review was to present ethnic differences in body size and body composition in Asian Indian migrants in New Zealand associated with metabolic syndrome and type 2 diabetes, through the comparison with other ethnic groups in New Zealand Presented studies were part of the current health research carried out in Asian Indian migrants at AUT University and University of Auckland, New Zealand. In this review, the name Asian Indians is used to define the ethnic group of South Asian Indians, who migrated to New Zealand from Indian subcontinent, Sri-Lanka, Pakistan, and Bangladesh.

International databases including *PubMed* and *Google scholar* were consulted in a search using the terms “South Asians”, “Asian Indians”, “Asian Indian migrants”, “central obesity”, “metabolic syndrome”, “insulin resistance”, and “body composition”, “obesity”, and their combinations. The websites of the *World Health Organization* and *International Diabetes Federation* were also consulted. The searches provided 128 publications from which 74 were selected and assessed to ensure their relevance to the main topic of the review. Seven research projects, out of 74, were separately presented in terms of body composition and body size relevant to “thin-fat” phenotype of Asian Indian migrants in New Zealand. Manual search was employed to allocate these studies from the database of the AUT University, published by the researchers at the Faculty of Health and Environmental Sciences.

Participants in these studies were clinically healthy, although the most of the participants were overweight, and had no knowledge of presence of the metabolic syndrome. Recruitment of participants for these studies was from the urban Auckland areas, by personal contact, advertisement or through existing networks of recruiters.

Pathogenesis of type 2 diabetes

The healthy pancreatic β cell is capable of adapting to changes in insulin action (14). Any decrease in adaptation of the â pancreatic cells to insulin levels, leads to impaired glucose tolerance (IGT), and impaired fasting glucose (IFG) or type 2 diabetes. Impaired pancreatic insulin secretion has been reported in all type 2 diabetic patients in all ethnic groups. Decreased insulin secretion and IFG cause acceleration of endogenous glucose production or hyperglycemia. Increased endogenous glucose production and hepatic insulin resistance represent the driving force for hyperglycemia in type 2 diabetes. The process of conversion from an insulin resistant state to type 2 diabetes is dependent on a relative deficit in â cell insulin secretion capacity. However, type 2 diabetes cannot develop as long as β cell secretory capacity matches the degree of insulin resistance (15).

The role of adipokines in metabolic syndrome and type 2 diabetes

Besides storing fat for excess energy, adipose tissue is an endocrine organ which produces and releases molecules commonly referred to as adipokines (16). Most adipokines in obesity form an important part of an “adipo-insular” axis, dysregulaton which may support β-cell failure and development of type 2 diabetes (17).

Research studies suggest that the adipokines, adiponectin and leptin, regulate functional β cell mass, and are crucial for protection against the development of metabolic syndrome and diabetes (18, 19). Adiponectin is a key regulator of insulin sensitivity and tissue inflammation, with predominant action in the liver, skeletal muscles, and vasculature (20). Prominent roles of adiponectin are to improve hepatic insulin sensitivity, increase fuel oxidation, and reduce vascular inflammation. Circulating levels of adiponectin are inversely proportional to body fat content.

Adipokine leptin plays a major role in regulation of energy intake and energy expenditure, and its levels increase in response to accumulation of long-chain free fatty acids (21). In obesity, leptin resistance causes insulin resistance, hepatic steatosis, type 2 diabetes, and

cardiac dysfunction (22). Circulating plasma levels of free fatty acids (FFAs), ceramides and glucose, promote serine phosphorylation of insulin receptor substrate (IRS-1) present in the skeletal muscle tissue; tumor necrosis factor α (TNF-α), promotes serine/threonine phosphorylation of the insulin receptor and IRS-1 (23). Serine-phosphorylated IRS-1 inhibits insulin receptor tyrosine kinase activity, which inhibits downstream insulin signaling. Defective insulin signaling in both the skeletal muscle tissue and fat tissue seems to play a role in development of type 2 diabetes (24, 25).

Inflammatory cytokine interleukin -6 (IL-6) is produced by adipocytes which may also be responsive to IL-6, owing to the presence of IL-6 receptors in the membrane of abdominal subcutaneous adipocytes (26). It was also observed that IL-6 expression was increased 15 fold in the fat tissue of insulin resistant people, which indicated IL-6 induced insulin resistance in fat cells by which it was produced (27). Insulin resistance leads to increased fat mass and BMI. It was suggested that the IL-6- 174C allele from the common functional gene variant IL-6-174GC, is associated with higher BMI in people with type 2 diabetes, and a role for this gene is in mediating inflammatory insulin resistance (28).

The plasma levels of interleukin -6 (IL-6) increase in obesity, and in combination with other cytokines has cytotoxic effects on β-cells causing β-cells apoptosis, and synergizes with interleukin -1 (IL-1) in this respect (29). The interleukin-1 (IL-1) family of ligands and receptors is primarily associated with acute and chronic inflammation, where IL-1β causes local and systemic inflammatory conditions called autoinflammatory diseases (30, 31). The type of inflammation associated with type 2 diabetes is mediated by IL-1β. A sensitive marker for systemic inflammation is the acute-phase C-reactive protein (CRP) (32, 33). Higher plasma concentrations of CRP suggest a state of low-grade systemic inflammation in obese and/or insulin resistant people.

Excessive insulin resistance and metabolic syndrome in Asian Indians

Apparently, both insulin resistance and reduced insulin secretion are involved in the pathogenesis of type 2 diabetes, and the predominant mechanism seems to be different in various ethnic groups. Excessive insulin resistance in Asian Indian migrants appears to be the predominant mechanism for the excessive prevalence of diabetes in this population (34).

Genetic predisposition, central obesity, and unfavorable lifestyle, including unhealthy diet, sedentary lifestyle, and other psycho-social factors related to migration and living conditions were associated with the prevalence of type 2 diabetes in Asian Indian migrants However, lifestyle changes associated with the process of urbanization/westernization might largely explain an ongoing increase in the prevalence of type 2 diabetes in Asian Indian migrants. Apparently, environmental factors certainly play a major role in diabetes epidemics, which occurs on a background of genetic susceptibility (35).

Asian Indians have different body phenotype from Europeans (36). The major differences are in high body fat, high truncal, subcutaneous and intra-abdominal fat, and low muscle mass. Biochemical parameters include hyperinsulinemia, hyperglycemia, dyslipidemia, hyperleptinemia, low levels of adiponectin and high levels of CRP, procoagulant state and endothelial dysfunction.

Owing to lean appearance and lower mean BMI, central obesity in Asian Indians cannot be clinically observed (37). Central obesity plays a significant role in pathogenesis of insulin resistance and is associated with increased risk of diabetes, hypertension, dyslipidemias and atherosclerosis, and represents the corner-stone of the metabolic syndrome (38). Centrally obese people have the most severe insulin resistance and low plasma levels of cytokine adiponectin, as is commonly seen in Asian Indians (39). Low adiponectin concentrations in Asian Indians with impaired glucose tolerance, are predictive of prospective diabetes. Apparently, high percent of total body fat, central obesity, insulin resistance, hyperinsulinaemia, and low muscle mass, predispose Asian Indians to the development of the metabolic syndrome (40). Moreover, about 25% of the urban Indian population of obese or non-obese adults has non-alcoholic fatty liver disease (NAFLD) with significantly higher insulin resistance than those without NAFLD (41). A proton magnetic resonance spectroscopy study of enzymes involved in gluconeogenesis pathway showed elevated gluconeogenesis in non-diabetic, non-obese Indian people with NAFLD. This finding indicates increased risk for the development of type 2 diabetes in later life.

An explanation proposed by Barker as “thrifty phenotype” hypothesis, ascribes the epidemic of type 2 diabetes to an unfavorable intrauterine environment (42). Fetal under-nutrition leads to altered metabolic programming in resource-poor developing countries like India (43, 44). An abundance of food supply may lead to increased velocity of weight gain during childhood and catch-up obesity in low-birth weight Indian babies, which has been reported to be important for adult-onset hyperglycemia and cardiovascular risk factors (45).

Intrauterine growth and development of Indian babies is completed before birth, and is the result of or-

chestrated gene expression influenced by the mother (46). Indian mothers are small and thought to be chronically malnourished, with iron, vitamin, and nutrient deficiencies. One third of Indian babies are born with low birth weight (LBW < 2,5 kg). In comparison with European babies, Indian "thin-fat" babies were lighter and smaller, with the smallest abdominal circumference and mid-arm circumference, while the most preserved measurement was the subscapular skinfold thickness, even in the lightest babies (47). The sub-scapular skinfold in Indian babies is better preserved than the triceps skinfold, suggesting a tendency in Indians to central adiposity, even during intrauterine development. It seems that the relatively thin and centrally fat phenotype of Indian adults originates in intrauterine life (48).

The possibility exists that observed abnormalities might have genetic causes (49). It has been reported that a possible role in regulation of insulin receptor signaling is attributed to ectonucleotide pyrophosphatase phosphodiesterase 1 (ENPP1), a widely expressed class II transmembrane glycoprotein, which could interact with the insulin receptor and decrease insulin-induced tyrosine phosphorylation of its intra-cytoplasmic domain (50, 51). Possibly, this physical interaction occurs on the cell surface between gene ENPP1 and the insulin receptor, preventing insulin-induced conformational changes of the extracellular receptor alpha subunit. This failure prevents beta subunit autophosphorylation and tyrosine-kinase activity, which switches off insulin signaling. A reported gene variant ENPP1 121Q, appears to contribute to the excessive insulin resistance and type 2 diabetes in Asian Indian migrants living in Dallas and South Asians in Chennai, and might provide an important genetic marker to identify Asian Indian people at risk with type 2 diabetes (52).

The D1057 D genotype of insulin receptor substrate -2 (IRS-2) gene, makes Asian Indians susceptible to type 2 diabetes by interacting with obesity (53). Similarly, the peroxisome proliferator activated receptor-co-activator-1 α (PGC-1) gene polymorphism Thr394Thr (G-A) is associated with type 2 diabetes among Asian Indians, and with total, central, and subcutaneous body fat (54, 55).

Vitamin D deficiency and insulin resistance in Asian Indians

The association between vitamin D deficiency and insulin resistance is still incompletely understood in Asian Indians. Serum concentrations of vitamin D are largely determined by food intake and ultraviolet exposure in sunny India (56). Prevalent social and cultural practices in India preclude exposure to sunshine. The problem of vitamin D deficiency worsens in women during pregnancy and has important consequences for the newborn, including fetal hypovitaminosis D, neonatal rickets, tetany, and infantile rickets which is associated with infection of the lower respiratory tract, zand is the leading cause of infant mortality (57, 58). Vitamin D has more targets such as heart, stomach, brain, liver, skin, pancreatic β cells, thyroid, parathyroid and adrenal glands and immune cells which contain the nuclear vitamin D receptor (VDR) and the enzyme 1 α-hydroxylase which facilitates conversion of vitamin D into its active form in kidneys (59, 60). This finding indicates actions of vitamin D other than calcium homeostasis and bone metabolism. The presence of the VDR in pancreatic β cells supports the findings that vitamin D affects insulin secretion and/or insulin sensitivity through the insulin receptor gene. In Asian Indian migrants vitamin D deficiency is further associated with elevated parathyroid hormone (PTH). When serum 25-xydroxyvitamin D (25OHD) falls below 15 ng/mL, PTH levels rise sharply (61). Low levels of vitamin D correlate positively with BMD and/or increased markers of bone catabolism when compared with Caucasians (62). In cultured fibroblasts derived from two groups of participants (Asian Indians and Caucasians) an enzyme 25OHD-24-hydroxylase activity (in vitro) was higher in Asian Indians, which raised concerns about increased catabolism of serum vitamin D. Further, skin capacity for vitamin D synthesis seems to be substantial in both ethnic groups, Asian Indians and Caucasians. Serum vitamin D was measured after exposure to UV-radiation (63). To achieve a given level of vitamin D production, Asian Indians needed over twice as much UV-B exposure when compared to Caucasians. However, suboptimal production of vitamin D in Asian Indians might be the result of conjoined effects of possible catabolism of serum vitamin D and dark skin pigmentation which has been found to decrease skin synthesis of vitamin D because longer exposure to UV radiation is needed. In addition, Asian Indian migrants in sunny Auckland have very low BMC and BMD, which might be related to low serum concentrations of vitamin D, which further is associated with insulin resistance.

HEALTH RESEARCH IN ASIAN INDIAN MIGRANTS AT AUT UNIVERSITY

Research studies present ethnic differences in body size and body composition in Asian Indian migrants in NZ

The study by *Rush et al.*, (64) provided comparative analysis of the body composition of European, Maori, Pacific Island, and Asian Indian peoples in urban

Auckland, New Zealand. The method used in this study included anthropometric measurements (height, weight, and BMI kg/m^2) and the whole body composition (fat mass, fat-free soft tissue and bone mineral content (BMC)) was assessed by DEXA. Fat — free mass was calculated as the sum of fat-free soft tissue and BMC. Percentage of body fat (%BF) was calculated as 100 x FM/DEXA weight. This was the first study which made direct comparison between Polynesian and Asian Indian peoples in New Zealand, the two ethnic groups considered to lie at opposite ends of the spectrum in terms of their body size and body composition. At a fixed percentage of body fat corresponding to BMI of 30 kg/m^2 for Pacific Island people BMI values were up to 5 units higher and for Asian Indians up to 6 units lower, a span of 11 BMI units. For the same BMI, body fat in Pacific men and women was 25% and 38% respectively, while in Asian Indian men and women percent body fat was 37% and 47%, respectively. Therefore, Asian Indian people have more total body fat (TBF) than Pacific people, more central fat, less lean mass and appendicular skeletal muscle mass (APSMM), and less bone mineral content (BMC) than other participants in the study of different ethnicities. Use of universal BMI cut-off points underestimate risks associated with the levels of obesity in Polynesian and Asian Indian ethnic groups, although it does show a need for ethnic specific BMI cutoffs for people of both ethnicities. The BMI cutoff point for observed metabolic risk in different Asian populations should be between 22 kg/m^2 and 25 kg/m^2, and for high risk the range from 26 kg/m^2 to 31 kg/m^2 is appropriate (65). It was also observed that with increasing age, body fat in Asian Indian people showed a shift in the fat body distribution to the abdominal area which shows their tendency for the development of central obesity and consequently insulin resistance, while in people of other ethnicities in the study increase in abdominal fat was coupled with increase in total body fat.

The aim of the study by *Rush et al.*, (66) was to characterize ethnic differences in the relationships between total body fatness and body size and body fat distribution in women from five ethnic groups in New Zealand and South Africa (SA). The objective of the study was to investigate differences in body composition, especially the relationship between BMI kg/m^2 and %BF among female participants. The study participants were 721 women aged 18–60 years from five ethnic groups in New Zealand (173 European, 76 Maori, 84 Pacific, and 93 Asian Indian) and South Africa (SA 201 black and 94 European). The method used included anthropometry (measurements of height, weight, waist and hip circumference), and TBF, central and peripheral body fat, BMC and ASMM were derived from dual X-ray absorptiometry in the Department of Surgery, University of Auckland, New Zealand and the Department of Human Biology, University of Cape Town in South Africa. BMI was derived from height and weight. It was reported that for the same BMI of 30 kg/m^2, the Pacific women had the lowest body fat (~38%BF) while Asian Indian women had the greatest body fat content (~48%BF). Pacific women had the highest levels of fat free mass (FFM) and APSMM, while Asian Indian women had the lowest FFM and APSMM. More importantly, New Zealand Asian Indian women had the greatest central fat mass, followed by the NZ Maori, NZ European and NZ Pacific women who had the least. Also, DEXA derived peripheral or appendicular fat mass (AFM) was the highest in SA black women and Asian Indian women, which can be explained by their greater total body fatness. In addition, the whole body BMC was lower in Asian Indian women followed by Pacific and Maori women. This finding suggests that vitamin D deficiency in Asian Indians in New Zealand is associated with impaired glucose tolerance in the population under a high risk of developing type 2 diabetes.

The study by *Rush et al.*, (67) recruited a total of 114 healthy male volunteers (64 European, 31 Pacific Island, and 19 Asian Indian) aged 17–30 years. Height and weight were measured, BMI was calculated, while %BF, FFM, BMC, bone mineral density (BMD), abdominal fat, thigh fat, and APSMM were obtained from total body DEXA scans. For the fixed BMI, Asian Indian men had significantly more body fat than Pacific Island and European men. These ethnic differences were explained by differences in body build and muscularity in particular. Compared with European men of similar weight and height, Asian Indian men had significantly less skeletal muscle mass, while Pacific Island men had significantly more. Examination of body fat distribution has shown that Asian Indian men have more central fat than European or Pacific Island men. BMC and BMD were lower in Asian Indian than in European and Pacific Island men.

The levels of body fatness, physical activity, and nutritional behavior in 52 Asian Indian men and 62 Asian Indian women, aged 44–91 years (mean 67,5 ± 7.6ys) in the study by *Kolt et al.*, (68). The study draws attention to the different levels of fatness in Asian Indian men and women. The measurements of the BF by the bioelectrical impedance (BIA) have ranged from 13.2% to 58.8% (mean = 41.1, SD = 9.1) for both of the sexes. Asian Indian men (34.6%, SD = 6.8) had significantly less body fat than their female (45.7%, SD = 6.8) counterparts. Cutoff points of greater than 25% body fat for Asian Indian men, and 30% body fat for Asian Indian women, put them under the increased risk of

type 2 diabetes and CHD associated with excess body fat. The use of WC ethnic specific cutoff points in Asian Indian men and women (greater than 90 cm for men and 80 cm for women), have shown that 82% of men and 90% of women had significantly high levels of central obesity, which predispose them to insulin resistance and risk of type 2 diabetes.

Ethnic differences in body size and body composition in Asian Indian children in NZ

The study by *Duncan et al.*, (69), investigated demographic and lifestyle risk factors for excess body fatness in a multiethnic group of 1229 healthy children aged 5–11 years, which consisted of 46.8% European, 33.1% Polynesian, 15.9% Asian, and 4.1% from other ethnicities. The Asian group comprised of Asian Indian children (38.3%), Chinese (21.9%), and Korean (13.8%), Filipino (9.7%), Sri Lankan (4.1%), and other Asian (12.2%) children. The study draws attention to the body composition of Asian Indian children, which in this study is presented only through the %BF, measured using hand-to-foot BIA. Over-fat children were defined as those with a %BF ≥ 25% (boys) and %BF ≥ 30% (girls). Asian children had more excess body fat than European children. Asian Indian and Sri Lankan children comprised the majority of Asian children (42.4%), who at the age of eight had more fat tissue than their European counterparts of the same age, which already put them under the high risk of developing insulin resistance in adolescence or later life.

Genetics and/or lifestyle changes

Living predominantly sedentary lifestyle with low level of physical activity, predispose Asian Indian population in New Zealand to type 2 diabetes and CHD. It appears that early intervention programs are more successful when initiated at an early stage of metabolic syndrome. It is well known that metabolic syndrome is not a diagnosis (70). It is rather a pre-morbid condition that can be reversed at an early stage. The impact of a group diet and physical activity on body composition, lipid profile and insulin resistance in Asian Indian migrants was assessed in the study by *Rush et al.*, (71). Study participants were Asian Indian men and women (aged ? 50 y), recruited from urban Auckland. Anthropometric measures of obesity for total body (BMI) and central fat (WC), and fasting blood tests for serum glucose, insulin and lipids, and blood pressure, were obtained one month prior to the commencement of the intervention program, and were repeated after a five-month period, following the intervention of altered diet and exercise. Significant decrease in body weight, total and central body fat, resulted in decrease in blood pressure in Asian Indian men, while these changes were not significant in women. Lipid profiles in both men and women improved, such as increased blood level of high density lipoprotein (HDL), decreased low density lipoprotein (LDL), and total cholesterol/HDL ratio, without changes in serum glucose, insulin resistance and triglycerides. Apparently, the intervention program was a good indicator that change was possible but limited. However, in the early stages of the disease, insulin resistance is compensated by an increase in pancreatic β- cell mass and function, that often delays diagnosis of type 2 diabetes for a period of years (72).

The role of inflammation in metabolic syndrome

The relationships between markers of insulin resistance and inflammation, resting energy expenditure (REE), and body composition were examined by professor *Rush et al.*, (73). The participants in the study were 79 (38F, 41M; age 30–49 years) healthy adult Asian Indian migrants from urban Auckland. Total and regional body composition, including regional FM and ASMM were determined by DEXA. Beta-cell function (HOMA B %) (74) and insulin sensitivity (HOMA S %) were derived, using homeostatic model assessment. The REE was measured using indirect calorimetry, and fasting blood samples were taken for the measurement of serum glucose, insulin, and cytokines interleukin (IL)-6, tumour necrosis factor (TNF)-α, and CRP. The association of inflammation and metabolic syndrome is particularly relevant to Asian Indians, owing to their high propensity to insulin resistance and central obesity. Apparently, Asian Indian men had more central body fat distribution than women, and their REE rate was highly associated with plasma circulating cytokine IL-6 concentrations. Further, in both sexes IL-6 concentrations were associated positively with % BF and insulin resistance, and inversely with APSMM and insulin sensitivity. The study showed that the relationship between body fat distribution and insulin sensitivity were strongly sex dependent, where male Asian Indians had a greater propensity for the development of the metabolic syndrome than their female counterparts.

CONCLUSION

The research projects which were presented have recognized the major ethnic characteristics of the typical “thin-fat” Indian phenotype in the population at high risk for development of the metabolic syndrome and type 2 diabetes. In comparison with other ethnic groups in New Zealand Asian Indians had more total

Table1. *Summary of findings in selected studies*

Study	Findings
Rush et al., 2009 "Body size, body composition and fat distribution: comparative analysis of European, Maori, Pacific Island and Asian Indian adults"	Participants: 933 (454 men and 479 women) of European, Maori, Pacific Island, and Asian Indian ethnicity, aged 17–80 years ✓ For the same BMI Asian Indian men and women (37% and 47% respectively) have more total body fat than Pacific men and women (25% and 35% respectively). ✓ Asian Indian people have more central fat, less lean mass and ASMM, and less BMC than other participants in the study ✓ With increasing age, body fat in Indian people showed a shift in the body fat distribution to the abdominal area (increase in central fat and insulin resistance)
Rush et al., 2007 "BMI, fat and muscle differences in urban women of five ethnicities from two countries"	Participants:173NZ European, 76 Maori, 84 Pacific, 93 Asian Indian, and South African (201 South African black and 94 South African white) women, aged 18–60years ✓ For the same BMI of 30 kg/m^2 Asian Indian women had the greatest body fat content (~48%BF) while Pacific Island women had the least (~38%BF) ✓ Asian Indian women had the lowest FFM and ASMM AFM was the highest in South African and Asian Indian women (general fatness) ✓ Asian Indian women had the greatest central fat mass followed by Maori, NZ European, and Pacific Island women ✓ The whole body BMC was lower in Asian Indian women followed by Pacific and Maori women. Low BMC indicates vitamin D deficiency and its association with insulin resistance
Rush et al., 2004 "Body size, body composition and fat distribution: a comparison of young New Zealand men of European, Pacific Island and Asian Indian ethnicities"	Participants: 64 Europeans, 31 Pacific Island, and 19 Asian Indian healthy men, aged 17–30 years ✓ For the fixed BMI Asian Indian men had significantly more body fat than Pacific Island and European men ✓ Asian Indian men when compared with their European counterparts had significantly less skeletal muscle mass, while Pacific Island men had significantly more ✓ Asian Indian men had more central fat than European or Pacific Island men ✓ BMC and BMD were lower in Asian Indian men than in European and Pacific Island people
Kolt et al., 2007 "Body fatness, physical activity, and nutritional behaviors in Asian Indian immigrants to New Zealand"	Participants:52 Asian Indian men and 62 Asian Indian women, aged 44–91 years ✓ The %BF have ranged from 13.2% to 58.8% for both of the sexes ✓ About 82% of Asian Indian men(25% BF) and 90% of women (30%BF) had significantly high levels of central fat which predisposed them to high risk of type 2 diabetes
Duncan et al., 2008 "Risk factors foe excess body fatness in New Zealand children"	Participants: 1229 healthy children aged 5–11 years ✓ Over-fat children were defined as those with $ 25%BF ✓ Asian Indian and Sri Lankan children at the age of eight had more fat tissue than their European counterparts at the same age

Continued on the next page

Rush et al., 2007 "Reduction of abdominal fat and chronic disease factors by lifestyle change in migrant Asian Indians older than 50 years"	Participants: 41 Asian Indians (21 men and 20 women) aged > 50 years ✓ Decrease in body weight, total and central body fat, and decrease in blood pressure ✓ Lipid profiles in both Asian men and women improved (HDL, LDL, and total cholesterol/HDL ratio. ✓ Serum glucose, insulin resistance and triglycerides have not changed ✓ Asian Indian men had higher â cell function (HOMA-B%) and lower ✓ Insulin sensitivity (HOMA-S%)
Rush et al., 2007 "Interleukin-6, tumor necrosis factor-alpha and insulin relationships to body composition, metabolism and resting energy expenditure in a migrant Asian Indian population"	Participants: 79 healthy Asian Indians (38 women and 41 men), aged 30–49 years ✓ Asian Indian men had more central body fat than women ✓ Interleukin-6 was associated with REE in Asian Indian men ✓ In both sexes interleukin-6 was positively associated with: %BF and insulin resistance and inversely associated with ASMM and insulin sensitivity ✓ Asian Indian men have a greater propensity for the development of the metabolic syndrome than their female counterparts

body fat, percent body fat, and central fat, less lean mass and appendicular skeletal muscle mass. Higher plasma circulating levels of inflammatory marker CRP indicated the state of low-grade systemic inflammation in obese and insulin resistant people. CRP reflected higher plasma circulating levels of inflammatory cytokine IL-6 in Asian Indian men and women, which were accompanied by an increase in %BF and insulin resistance. It has been notified that male Asian Indians have a greater propensity for the development of the metabolic syndrome than their female counterparts, owing to the presence of more central fat. BMC and BMD were the lowest in Asian Indian migrants, which might be associated with low serum concentrations of vitamin D, which is further associated with insulin resistance. Further research is warranted to clarify metabolic syndrome and associated comorbidities in Asian Indians.

Abbreviations

AFM — appendicular fat mass
APSMM — appendicular skeletal muscle mass
BMI — body mass index
CRP — C-reactive protein
FFM — fat free mass
HbA1c — glycated haemoglobin (A1c)
HOMA B % — beta cell function
HOMA S % — insulin sensitivity
IL-6 — interleukin-6
IL-1 — interleukin-1
IRS-1 — insulin receptor substrate-1
NAFLD — non-alcoholic fatty liver disease
REE — resting energy expenditure
TBF — total body fat
TNF-α — tumour necrosis factor alpha

Sažetak

ETNIČKA PRIPADNOST I DIABETES TIP 2 KOD AZIJSKIH INDIJSKIH MIGRANATA U OKLANDU, NOVI ZELAND

Jowitt Ljiljana

University of Auckland, Department of Surgery, Auckland, New Zealand

Cilj ovog revijalnog rada je bio da se prikažu etničke razlike u veličini i sastavu tela kod Azijskih Indijskih migranata na Novom Zelandu, u vezi sa metaboličkim sindromom i tip 2 dijabetesom, kroz poređenja sa drugim etničkim grupama na Novom Zelandu. Međunarodne baze podataka, uključujući i PubMed i Google Scholar su konsultovani, kao i sajtovi Svetske Zdravstvene Organizacije i Međunarodne Dijabetes Federacije. Oko 74 studija od 128 publikacija su izabrane kao relevantne za temu revijalnog rada. Sedam istraživačkih projekata su prikazali veličinu i sastav tela u Azijskih Indijskih migranata na Novom Zelandu.

Prevalenca tipa 2 dijabetesa od 8,6% kod Azijskih Indusa na Novom Zelandu je još uvek veća nego u njihovoj domovini, zbog njihove etničke pripadnosti, genetske predispozicije, sedelačkog načina života i izmenjene ishrane, i drugih psihosocijalnih faktora koji su vezani za migracije i uslove života kao i stres na radnom mestu i depresiju. Za isti indeks telesne mase, u poređenju sa ljudima iz drugih etničkih grupa na Novom Zelandu, Azijski Indusi imaju više ukupne telesne masti, veci procenat masti u telu, više centralne masti, manje mišićne mase i skeletne mišićne mase. Centralna gojaznost je povezana sa insulinskom rezistencijom i niskim stepenom sistemske inflamacije. S obzirom na dokaze da se tip 2 dijabetesa razvija deset godina ranije u Azijskih Indusa nego u drugim populacijama, dalja istraživanja su neophodna da se razjasni još uvek nekompletno shvaćen metabolički sindrom i „tanki–debeli“ indijski fenotip.

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Correspondence to /Autor za korespondenciju
MD Ljiljana Jowitt MA
Faculty of Health and Environmental Sciences
Interprofessional Health Studies
North Shore Campus, AF 416
90 Akoranga Drive, North Shore Campus,
Auckland 0627
New Zealand
Work phone number: +649 921999 x 8096;
Work fax number: +649 9219721
Mobile phone number: +649226515962
Email address: ljowitt@aut.ac.nz

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(za Sanamed)
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Latković Z. Tumori očnih kapaka. U: Litričin O i sar. Tumori oka. 1. izd. Beograd: Zavod za udžbenike i nastavna sredstva, 1998: 18–23.

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Ul. Palih boraca 52, 36300 Novi Pazar
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