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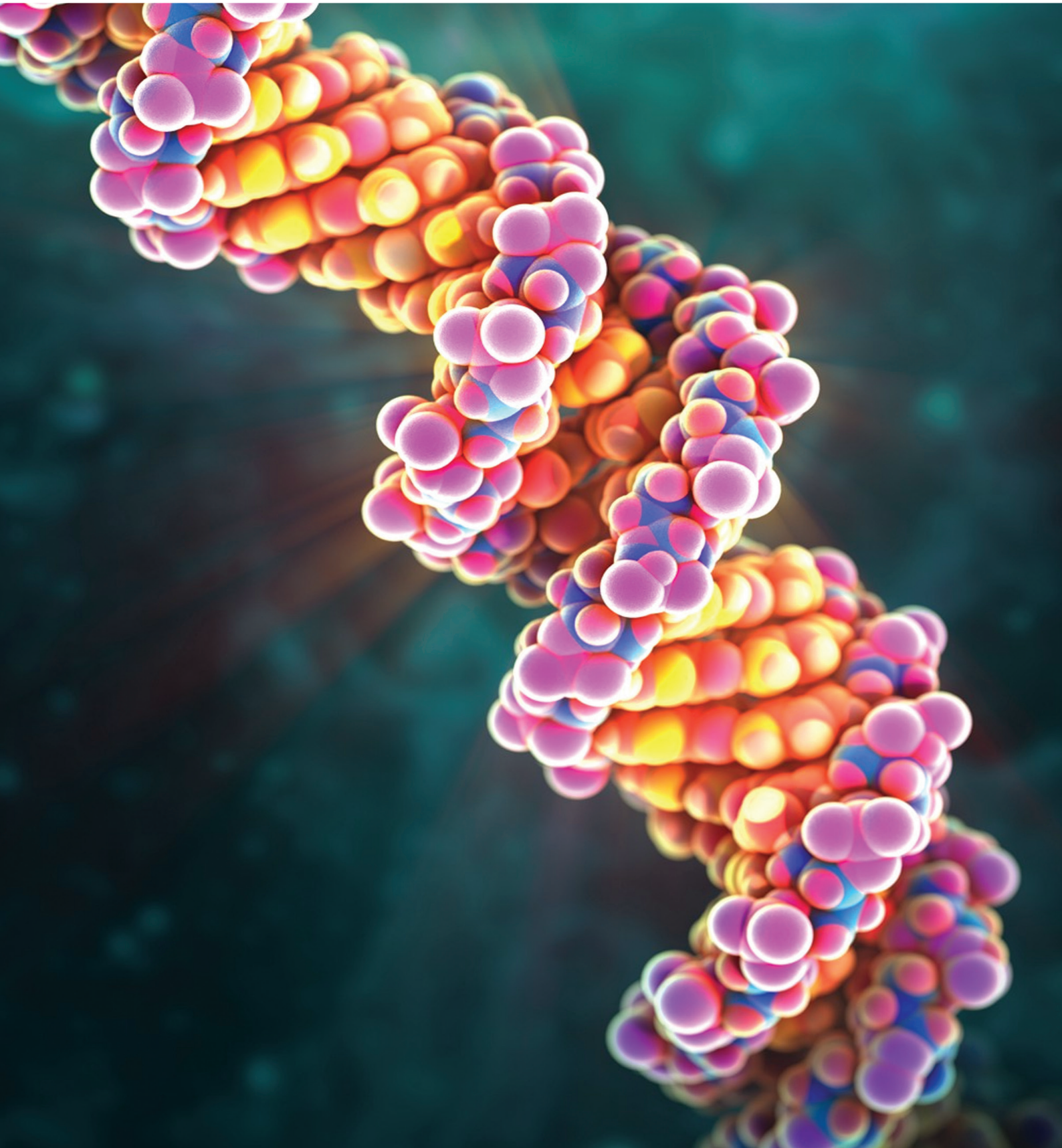

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Sadržaj / Table of Contents

Intensity of physical activity and basic metabolic and anthropometric parameters in patients with diabetes mellitus type 2 139
Edina Kuduzovic, Farid Ljuca, Selmira Brkic

Correlation between flexibility, and agility as it relates to anterior cruciate ligament injuries in University of Zululand female soccer and netball players 147
Gerrit J. Breukelman, Lourens Millard, Mbali R. Mohlakoana

Corelation of therapy response and toxic effects of chemotherapy in advanced lung cancer 153
Sefika Umihanic, Suvad Dedic, Sekib Umihanic

KoACT, a calcium-collagen chelate dietary supplement, increases bone mineral density and strength in an ovariectomized rat model of osteoporosis 158
Bianca Souza Bagatela, Ivan Pereira Lopes, Fernando Luiz Affonso Fonseca, David Feder, Jennifer Gu, Andrey Pereira Lopes

Influence of nutritional status, gender and intensity of physical activity to blood pressure and metabolic parameters in patients with diabetes mellitus type 2 162
Edina Kuduzovic, Kenana Ljuca, Faris F. Brkic

Role of Sensory Integration Therapy in Sensory Processing Disorder in Children with Autism Spectrum Disorder (ASD)
Sensory Integration and Autism Spectrum Disorder in South Africa
(Concise and Informative Article Title) 172
Chantell Gouws, Cornelia du Preez, Ranelda Dippenaar

Risk assesment of death according to bode index in chronic opstructive lung disease Prospective control study 180
Suvad Dedic, Samir Husic, Nurka Pranjic, Sefika Umihanic, Dzenan Halilovic, Mirnes Avdic, Mirza Coric

Biochemical and hematological study of the supplementation with ATAMg, a new source of N-acetyl-based organic magnesium, on bioavailability 187
Bianca Souza Bagatela, Ivan Pereira Lopes, Isabel Cruz do Amaral Pupo, Joao Carlos Lopes, Jennifer Gu, Andrey Pereira Lopes

Instructions for the authors 190

Intensity of physical activity and basic metabolic and anthropometric parameters in patients with diabetes mellitus type 2

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Abstract

We analyzed hundred patients with diabetes mellitus type 2 who were treated in Educational center of family medicine of Public Health Institution Tuzla. Diabetes is metabolic disease characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart and blood vessels.

The aim was to determine relationship among the basic metabolic parameters in blood (glucose, cholesterol, and triglycerides), arterial blood pressure and anthropometric parameters (weight, height, body mass index) and intensity of physical activities in patients with diabetes mellitus type 2. The intensity of physical activity was determined using the International Physical Activity Questionnaire.

It was found that more than 90% of adult patients with type 2 diabetes mellitus were overweight and had light intensity of physical activity. A variance analysis and chi-square test were used to determine the significance of differences in the arithmetic mean and in the frequency of observed variables among patients with diabetes mellitus type 2 with different intensity of physical activity. Results have shown that there are no statistically significant differences among analyzed variables (chi-square = 2.46; df = 4; p = 0.651).

Key words: diabetes mellitus type 2, intensity of physical activity, body mass index.

Introduction

Diabetes is metabolic disease characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially eyes, kidneys, nerves, heart and blood vessels (ADA, 2010). It is estimated there are approximately 20.8 million people with diabetes mellitus in the United States, which accounts for about 7.0% of the overall population, of which 90.0-95.0% suffer from type 2 diabetes (Polikandrioti and Dokoutsidou, 2009). Diabetes mellitus type 2 is one of the fastest growing health problems in the world. It is estimated that the prevalence of diabetes for all age groups around the world will increase from the current 2.8% to 4.4% in 2030. In the etiology of diabetes mellitus type 2, there are genetic and environmental factors of which the most important is physical inactivity and obesity (Hu et al., 2005). Most patients with type 2 diabetes are obese, and the global epidemic of obesity is evidence of a dramatic increase in incidence and prevalence of type 2 diabetes in the last 20 years (Eckel et al., 2011). Long-term physical activity of moderate or high intensity during free time can significantly contribute to health (Ischander et al., 2007). Physical activity and dietary programs are fundamental in the treatment and metabolic control of type 2 diabetes mellitus (Barreira et al., 2017). Physical activity in people with diabetes is one of the most important factors in the treatment and control of the disease. Moderate continuous body activity can be useful in day-to-day glucose regulation and may be a mechanism by which proper activity helps achieve improved long-term metabolic control (Radash et al., 2012). Physical activity reduces serious clinical complications and mortality risk in patients with type 2 diabetes mellitus (LaMonte et al., 2005). Many authors agree that it would be good to focus on education about the importance of physical activity (Ozdirenc et al., 2005).

Aim of this study was to determine correlation among intensity of physical activity with basic metabolic and anthropometric parameters in patients with diabetes mellitus type 2.

Patients and methods

This study included 100 patients aged between 40 and 84, 25 male and 75 female who were diagnosed with diabetes mellitus type 2. Patients were divided into 3 groups based on the intensity of physical activity. The first group is consisted of 69 subjects who engage in physical activity of light intensity, the second group of 23 subjects who engage in physical activity of moderate intensity, and the third group of 8 subjects who engage in intensive intensity physical activity. In this study we have examined the following variables: gender (GE), age (AGE), blood glucose level (BGL), cholesterol and (CHL), triglyceride (TGL), systolic blood pressure (SBP), diastolic blood pressure (DBP), body mass index in (BMI), and intensity of physical activity (IPHA).

Intensity of physical activity was classified by the International Physical Activity Questionnaire for a person aged between 15 and 69 years, which we use to discover the type of physical activity in their daily lives. Questionnaire has 27 questions separated on 5 parts: Physical activities at work or school, Physical activities in transport, Home activities, Recreation, sport and physical activities in free time and Time spent in seated position.

Intensity of physical activity was classified as:

Light (energy use of about 4 kcal/min; light walk-4 km/h, easy home chores-dust cleaning, small reparation, garden work, light playing with a child, caring for a child in a seated and upright position and light swimming.

Moderate (energy use of about 4-7 kcal/min; walking–brisk walking, bicycle riding, moderate home chores with home appliances, walls painting, playing with a child while walking or running, caring for a child–dressing, moderate swimming, moderate running.

Intensive (energy use of about over 7 kcal/min; walking–brisk walking up to the hill or with cargo, fast bicycle riding, heavy home chores such as moving furniture, carrying heavy objects, digging, intensive swimming, playing tennis, football, basketball, handball, field ball.

The statistical analysis was performed using the Statistical Package for Social Sciences (SPSS version 16.0). The basic statistic parameters that were being calculated were arithmetic mean, standard deviation, minimal and maximal results. In the statistical analysis, the mean values of numerical data were compared by analysis of variance, the qualitative data were analyzed using the chi-square test.

Results

According to level of intensity of physical activity, the majority of patients are engaged in physical activity of light intensity (69.0%), 23 with moderate intensity physical activity (23.0%) and 8 with intensive intensity physical activity (8.0%) (Figure 1).

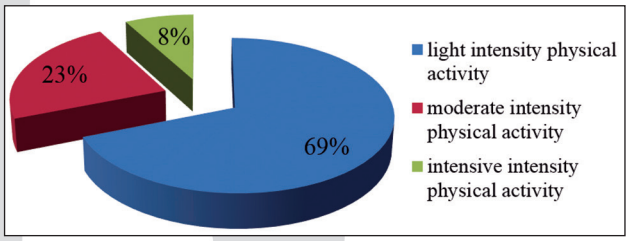

Figure 1. Distribution of patients with diabetes mellitus type 2 by intensity of physical activity (IPHA)

Figure 2 shows BMI mean values for the group of patients according to the intensity of physical activity. Patients with moderate physical activity had the highest mean BMI (32.09 kg/ m^2) and the lowest one was found in patients with intensive intensity physical activity (28.5 kg/m^2).

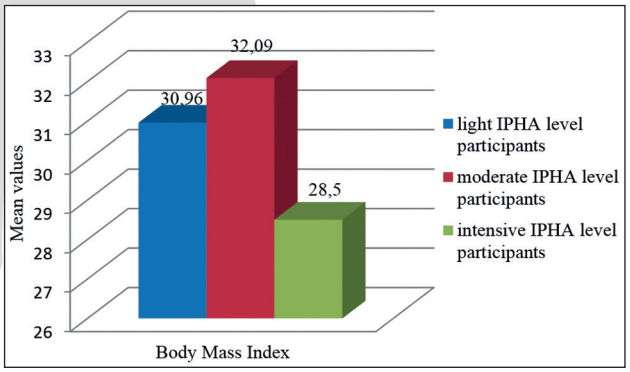

Figure 2. BMI in patients with diabetes mellitus type 2 according to IPHA

Figure 3. shows mean blood glucose level (GL), cholesterol (CHL) and triglyceride (TGL) in patients with diabetes mellitus type 2with different

level of intensity of physical activity. The highest mean blood glucose level was in patients with light intensity of physical activity (8.77 mmol/L) and the lowest one was in patients with intensive intensity of physical activity (7.76 mmol/L). The highest mean value of triglycerides blood level was in patients with moderate physical activity (2.32 mmol/L) and the lowest one was in patients with intensive intensity activity (1.75 mmol/L). Patients with moderate physical activity had the highest mean blood cholesterol level (5.40 mmol/L) and the lowest one was found in patients with light intensity of physical activity (5.24 mmol/L).

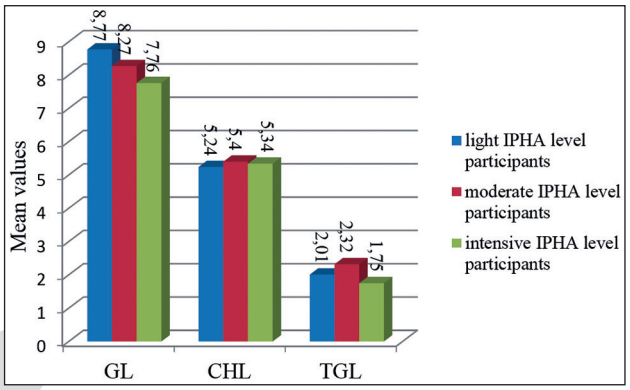

Figure 3. Blood glucose, cholesterol and triglycerides level in patients with diabetes mellitus type 2 according to IPHA

Table 1. Results of single-factor analysis of variance observed parameters in patients with diabetes mellitus type 2 with different intensity of physical activity

Variables	Source of variability	Sum of squares of deviations	Degrees of freedom	Average square deviation	F ratio	P value
AGE	Between groups	465,363	2	232,681	3,356	0,039*
	Within groups	6725,947	97	69,340		
	Total	7191,310	99			
BMI	Between groups	77,264	2	38,632	1,385	0,255
	Within groups	2704,696	97	27,883		
	Total	2781,960	99			
GL	Between groups	10,218	2	5,109	0,564	0,571
	Within groups	878,284	97	9,054		
	Total	888,502	99			
CHL	Between groups	0,445	2	0,222	0,203	0,817
	Within groups	106,508	97	1,098		
	Total	106,953	99			
TGL	Between groups	2,494	2	1,247	1,474	0,234
	Within groups	82,051	97	0,846		
	Total	84,545	99			
SBP	Between groups	583,832	2	291,916	1,019	0,365
	Within groups	27784,918	97	286,442		
	Total	28368,750	99			
DBP	Between groups	317,967	2	158,984	1,981	0,143
	Within groups	7784,783	97	80,255		
	Total	8102,750	99			
DD	Between groups	471,917	2	235,958	3,045	0,052
	Within groups	7517,043	97	77,495		
	Total	7988,960	99			

AGE-years; BMI-body mass index; GL-glucose (mmol/l); CHL-cholesterol (mmol/l); TGL-triglycerides (mmol/l); SBP-systolic blood pressure; DBP-diastolic blood pressure; DD-duration of diabetes (years)

The mean values of systolic blood pressure (SBP) and diastolic blood pressure (DBP) in patients with diabetes mellitus with different level of physical activity are shown in Figure 4. The highest mean SBP was measured in patients with light intensity physical activity (135.87 mm Hg) and the smallest one was in patients with intensive intensity physical activity (130.62 mmHg). The highest median value of DBP was measured in subjects with light intensity physical activity (82.83 mmHg) and the smallest one was in subjects with moderate physical activity (76.70 mmHg).

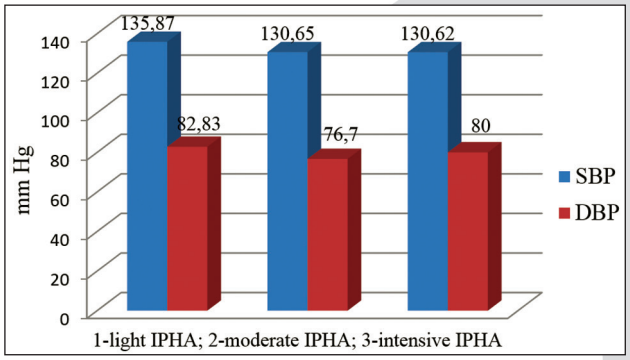

Figure 4. Systolic and diastolic blood pressure in patients with diabetes mellitus according to IPHA

A variance analysis and chi-square test were used to determine the significance of differences in the arithmetic mean and in the frequency of observed variables among patients with diabetes mellitus type 2 with different intensity of physical activity. Results have shown that there are no statistically significant differences among analyzed variables, except age (chi-square = 2.46; df = 4; p = 0.651) (Table 1).

Discussion

The number of people with diabetes is constantly increasing in line with population development, aging, urbanization and increasing prevalence of obesity and physical inactivity (Wild et al., 2004). In our study were 75.0% of females and 25.0% of men. These are the expected results because women are more likely to suffer from DM, (Banković et al., 2011) about 61.0%. In this study, 8.0% of subjects were with normal body weight, 31.0% with excess body weight and 61.0% with obesity. This number of obese persons increased to 53.0% in 2009 (Kuduzović et al., 2009a). The average BMI for women was 31.51 kg/m² and for men 29.56 kg/m². These data are similar to those published by Paul et al. (2012). In the research by Huffman et al. (2012) has been established that sedentary habits are a risk factor for diabetes. People suffering from this disease should avoid sedentary habits such as watching TV. It was concluded that people with type 2 diabetes are more than 4 hours a day in front of the TV compared to healthy people. And in our research, the average time spent in resting and watching TV is 3.9 hours a day. The emergence of metabolic syndrome in developed countries with excessive nutrition and inadequate body activity has reached epidemic proportions. In Type 2 diabetic metabolic syndrome there is a presence in 50.0% to 80.0% of cases. In the research by Kuzmanić et al., (2008) in patients with diabetes mellitus type 2 average BMI was 30.02 ± 3.01 kg / m², the mean systolic blood pressure was 139.91 ± 11.92 and the diastolic 81.85 ± 7.62 mmHg. The average serum total cholesterol concentration was 5.77 ± 0.99 and triglyceride 2.29 ± 1.07 mmol /L. In our research it has been found similar values of metabolic parameters. The mean systolic blood pressure was 134.25 ± 16.92 and the diastolic 81.65 ± 9.05 mm Hg. The total serum cholesterol concentration was 5.29 ± 1.04 and triglyceride 2.06 ± 0.92 mmol/L. For the control of diabetes mellitus in addition to regular pharmacotherapy, it is necessary to individually adapt nutritional therapy, education and increase of physical activity (Nikolić, 2008). Type 2 diabetes mellitus (T2DM) has reached epidemic proportions worldwide, as a result of population growth and aging, urbanization, and increasing prevalence of obesity and physical inactivity. T2DM is associated with an adverse cardiometabolic profile including hypertension, dyslipidemia, and obesity. Along with pharmacological treatment, lifestyle modifications including diet, weight management and exercise are important features of the management of T2DM. Physical Activity (Resistance, or Aerobic Exercise, or both) has been shown to improve the control of glycaemia along with other cardiovascular risk factors such as hypertension and obesity and is associated with reduced morbidity and mortality in T2DM patients (Dahjio et al., 2016). The American College of Sports Medicine and the American

Association for Diabetes recommend at least 150 minutes per week of moderate or high intensity physical activity. There are two types of exercises (endurance exercises and strength exercises); of those, endurance exercises or aerobic exercises are recommended. These include the participation of several muscle groups to improve cardiorespiratory function. These activities include running, swimming and cycling (Roden, 2012). In our case, it is sufficient to mention that only one of patients is riding a bicycle and that we do not talk about other activities. Most people with diabetes type 2 encounter difficulties in adapting to a structured exercise program, and improvement can only be achieved with adequate multidisciplinary care and continuous physical activity, but under strict personal supervision (Praet and Loon, 2008).

In our study using a variance analysis and chi-square test were used to determine the significance of differences in the arithmetic mean and in the frequency of observed variables among patients with diabetes mellitus type 2 with different intensity of physical activity. Results have shown that there are no statistically significant differences among analyzed variables (chi-square = 2.46; df = 4; p = 0.651).The reson of this is most probably small number of patients included in this study.

Individuals with prediabetes and type 2 diabetes are recommended to engage in at least 150 min/week of moderate to vigorous intensity physical activity. Moderate intensity physical activity corresponds to repeated aerobic movement of large muscle groups such as walking, cycling, jogging and swimming. These recommendations are based on rigorous evidence. Yet, only a small proportion of the population with type 2 diabetes meets this recommendation. Reducing time in sedentary behavior and increasing time in light intensity physical activity (standing, stepping and slow walking) during the day is suggested as a first part of a stepped approach in increasing physical activity (Rossen et al., 2017). It has long been established that exercise is powerful medicine for those with type 2 diabetes mellitus (T2DM), such that it should represent a priority in the treatment and management of that condition. Published guidelines for aerobic exercise in those with T2DM recommend only moderate intensity, due to the elevated risk of untoward outcomes with more vigorous exercise in persons with chronic disease (Buresh and Berg, 2017). The American Diabetes Association nutrition and lifestyle recommendations for prediabetes and type 2 diabetes focus on losing 7% of body weight and increasing physical activity to at least 150min per week. This emphasis is largely based on results of the Diabetes Prevention Program (DPP) and Look AHEAD (Action for Health in Diabetes) clinical trials. DPP demonstrated that a lifestyle intervention aimed at 7% weight loss and 150 min of activity per week reduced diabetes incidence by 58% after 2.8 years of follow-up and resulted in sustained improvements in hemoglobin A1c, blood pressure and lipid levels (Delahanty, 2017). Both continuous and interval aerobic exercise, in a same intensity, are effective for glycemic and pressure acute reductions in individuals with type 2 diabetes. For patients with greater risk of hypertension, Santiago et all believes that the interval method is safer (Santiago et al., 2017). Randomized trials have shown that physical activity alone or in conjunction with dietary changes can reduce the incidence of type 2 diabetes. However, the intensity of activity required remains unclear because the independent role of moderately intense activities has not been directly examined in these trials. Observational studies have consistently reported an inverse association between physical activity and type 2 diabetes, but most of these studies focused on vigorous activities or physical activity of various intensities combined (Jeon et al., 2007). Exercise is typically one of the first management strategies advised for patients newly diagnosed with type 2 diabetes. Together with diet and behavior modification, exercise is an essential component of all diabetes and obesity prevention and lifestyle intervention programs. Exercise training, whether aerobic or resistance training or a combination, facilitates improved glucose regulation (Kirwan et al., 2017). Exercise (physical activity that is planned and structured) seems to promote additional benefits on glycemic control and cardiovascular risk factors compared to daily life physical activity. The effects of regular exercise programs developed according to international exercise recommendations (combined aerobic and resistance exercise) for patients with type 2 diabetes on glycemic control and cardiovascular risk factors are very well established. However,

the majority of intervention studies have developed exercise programs, with expensive equipment such as ergometers for aerobic exercise (treadmills, stationary bikes, rowing machines, steppers and ellipticals) and resistance machines for resistance exercise. Accessing these material resours represents an elevated economic cost in a population already burdened with high health expenditures due to diabetes and related comorbidities treatments. Therefore, these types of facilities are not accessible to most of patients with type 2 diabetes, especially in community settings such as in primary health care and elderly institutions (Mendes et al., 2017). The most appropriate exercise program for people with type 2 diabetes is not yet established, due to the lack of evidence suggesting the most favorable type, intensity or duration of the activity. In the future, within this area, it is necessary to explore the physiological and practical uses of the exercise itself and to work on the creation of individually tailored programs in order to improve general health (O'Hagan et al., 2013). Physical activity and exercise should be recommended and prescribed to all individuals with diabetes as part of management of glycemic control and overall health. Specific recommendations and precautions will vary by the type of diabetes, age, activity done and presence of diabetes-related health complications. Recommendations should be tailored to meet the specific needs of each individual. In addition to engaging in regular physical activity, all adults should be encouraged to decrease the total amount of daily sedentary time and to break up sitting time with frequent bouts of activity. Finally, behavior-change strategies can be used to promote the adoption and maintenance of lifetime physical activity (Colberg et al., 2016). Patient education programs, such as the nationwide DIAfit program, a program in Switzerland to promote regular exercise in patients with type 2 diabetes, should increase recruitment among low educational level (EL) patients and adapt the program's content to cover their needs with the aim to reduce morbidity and mortality. The finding of a strong and independent relationship between EL and different physical fitness measures in patients with type 2 diabetes is clinically relevant. For example, the difference between low and high EL in aerobic fitness was 46% (Allet et al., 2016). Both aerobic and strength exercises can help the metabolic control in patients with type 2 diabetes, even without significant changes in anthropometry over the 20 weeks of training. However, this period was sufficient to cause changes in hemoglobin A1c values and the estimated average glucose, which are important parameters in controlling diabetes, thus signaling an important consequence of adhering to an exercise routine for type 2 diabetic patients. Diabetics that are physically active and/or present good aerobic conditioning feature better prognosis than those who are inactive and/or those with low aerobic conditioning. Both aerobic and strength exercises can increase insulin action, improve the lipid profile, glycemic levels, blood pressure (BP), decrease the risk of cardiovascular diseases, lower body weight, reduction of mortality, prevent complications related to DM and improve the life quality of diabetics when performed continuously. These factors make the inclusion of physical activity a fundamental element of a diabetic's treatment (de Lade et al., 2016). Structured exercise, consisting of aerobic training, resistance training or a combination of aerobic and resistance exercise training for at least 12 weeks is associated with improved glycemic control in type 2 diabetic patients. Structured weekly exercise of more than 150 minutes per week was associated with greater declines in HbA1c to a larger degree than physical activity advice. Physical activity advice is beneficial only if associated with dietary recommendations (Umpierre et al., 2011).

References

1. *Allet L, Giet O, Barral J, Junod N, Durrer D, Amati F, et al. Educational Level Is Related to Physical Fitness in Patients with Type 2 Diabetes - A Cross-Sectional Study. PloS one 12, 2016; 11(10): e0164176. doi: 10.1371/journal.pone.0164176. eCollection 2016.*

2. *American Diabetes Association Diagnosis and Classification of Diabetes Mellitus. Diabetes Care, 2010; Volume 33, Supplement 1: 562-569.*

3. *Banković V, Simonović Lj, Šarac B, Cekić Stanković V. Diabetes Mellitus: Najčešća bolest starijeg doba? Drugi kongres doktora medicine Republike Srpske. Banja Vrućica, Teslić, 2011; str. 3.*

4. *Barreira E, Novo A, Vaz JA, Pereira A. Dietary program and physical activity impact on biochemical markers in patients with type 2 diabetes: A systematic review. Aten Primaria. 2017 Oct 21. pii: S0212-6567(17)30152-X. doi:10.1016/j.aprim.2017.06.012. [Epub ahead of print] PubMed PMID: 29061310.*

5. *Buresh R, Berg K. Exercise for the management of Type 2 Diabetes Mellitus. Factors to consider with current guidelines. J Sports Med Phys Fitness. 2017 Apr 28. doi: 10.23736/S0022-4707.17.06969-9. [Epub ahead of print] PubMed PMID: 28462566.*

6. *Colberg RS, Sigal RJ, Yardley JE, Ridell MC, Dunstan DW, Dempsey PC, et al. Physical Activity/ Exercise and Diabetes: A Position Statement of the American Diabetes Association. Diabetes Care, 2016; 39: 2065-2079.*

7. *Dahjio Y, Noubiap JJ, Azabji-Kenfack M, Essouma M, Loni GE, Onana AE, et al. Impact of a 12-week aerobic exercise training program on anthropometric and metabolic parameters of a group of type 2 diabetes Cameroonian women aged ≥50 years. Ann Transl Med, 2016; 4(19): 364.*

8. *de Lade CG, Marins JC, Lima LM, de Carvalho CJ, Teixeira RB, Albuquerque MR, et al. Effects of different exercise programs and minimal detectable changes in hemoglobin A1c in patients with type 2 diabetes. DiabetolMetabSyndr. 2016 Feb 16; 8: 13. doi: 10.1186/s13098-016-0123-y. eCollection 2016.*

9. *Delahanty LM. Weight loss in the prevention and treatment of diabetes. Prev Med. 2017 Jul 28. pii: S0091-7435(17)30269-4. doi: 10.1016/j.ypmed.2017.07.022. [Epub ahead of print] PubMed PMID: 28757449.*

10. *Eckel R, Kahn S, Ferrannini E, Goldfine A, Nathan D, Schwartz M, et al. Obesity and Type 2 Diabetes: What Can Be Unified and What Needs to Be Individualized? Diabetes Care, 2011; 34: 1424-1430.*

11. *Hu Gang, Lakka TA, Barengo NC, Tuomilehto J. Physical activity, Physical Fitness, and Risk of Type 2 Diabetes Mellitus. Metabolic Syndrome and Related Disorders, 2005; 3(1): 35-44.*

12. *Huffman GF, Vaccaro AJ, Exebio CJ, Zarini GG, Katz T, Dixon Z. Television Watching, Diet Quality, and Physical Activity and Diabetes among Three Ethnicities in the United States. Journal of Environmental and Public Health. Hindawi Publishing Corporation, Vol. 2012. Article ID 191465.*

13. *Ischander M, Zaldivar FJr, Eliakim A, Nussbaum E, Dunton G, Leu SY, et al. Physical activity, growth, and inflammatory mediators in BMI-matched female adolescents. Medicine & Science in Sports & Exercise, 2007; 39(7): 1131-8.*

14. *Kirvan JP, Sacks J, Nieuwoudt S. The essential role of exercise in the management of type 2 diabetes. Cleveland Clinic Journal of Medicine 2017 July; 84 (suppl 1): S15-S21.*

15. *Kuduzović E, Nuhbegović S, Ljuca F, Imamović S. Indeks tjelesne mase u oboljelih od dijabetes melitusa tip 2. Defektologija, 2009; 15 a (1): 1-7.*

16. *Kuzmanić M, Vrdoljak D, Rumboldt M, Petrić D. Metabolički sindrom u dijabetičara tipa 2. Med Jad, 2008; 38(1-2): 13-22.*

17. *LaMonte MJ, Blair SN, Church TS. Physical activity and diabetes prevention. J. Appl. Physiol. 2005; 99: 1205-1213.*

18. *Mendes R, Sousa N, Reis MV, Themudo-Barata LJ. Implementing Low-Cost, Community-Based Exercise Programs for Middle-Aged and Older Patients with Type 2 Diabetes: What Are the Benefits for Glycemic Control and Cardiovascular Risk?Int. J. Environ. Res. Public Health 2017, 14, 1057; doi:10.3390/ijerph14091057.*

19. *Nikolić M. Dijetetika. Wus Austria, Medicinski fakultet, Niš, 2008; 142-150.*

20. *O'Hagan C, De Vito G, Boreham CA. Exercise prescription in the treatment of type 2 diabetes mellitus: current practices, existing guidelines and future directions. Sports Med. 2013; 43(1): 39-49.*

21. *Ozdirenc M, Ozcan A, Akin F, Gelecek N. Physical fitness in rural children compared with urban children in Turkey. Pediatrics International 2005; 47: 26-31.*

22. *Paul S, Thomas G, Majeed A, Khunti K, Klein K. Women develop type 2 diabetes at a higher body mass index than man. Diabetologia, 2012; DOI 10.1007/s00125-012-2496-2.*

23. *Polikandrioti M, Dokoutsidou H. The role of exercise and nutrition in type 2 diabetes mellitus management. Health Science Journal 2009; 3(4): 216-221.*

24. *Praet SFE, van Loon LJC. Exercise: the brittle cornerstone of type 2 diabetes treatment. Diabetologia, 2008; 51: 398-401.*

25. *Radaš J, Furjan-Mandić G, Ružić L. Razlike u tjelesnoj aktivnosti između muškaraca i žena oboljelih od diabetes mellitusa. Hrvat. Športskomed. Vjesn; 2012; 27: 24-27.*

26. *Roden M. Exercise in type 2 diabetes: to resist or to endure? Diabetologia, 2012; DOI 10.1007/s00125-012-2513-5.*

27. *Rossen J, Buman MP, Johansson U-B, Yngve A, Ainsworth B, Brismar K, Hagstromer M. Reallocating bouted sedentary time to non-boutedsedentary time, light activity andmoderate-vigorous physical activity in adultswith prediabetes and type 2 diabetes. PLOS ONE | https://doi.org/10.1371/journal.pone.0181053 July 28, 2017.*

28. *Santiago É, Delevatti RS, Bracht CG, Netto N, Lisboa SC, Vieira AF, Costa RR, Hübner A, Fossati MA, Kruel LFM. Acute glycemic and pressure responses ofcontinuous and interval aerobic exercise in patients with type 2 diabetes. ClinExpHypertens. 2017 Jul 24; 1-7. doi: 10.1080/10641963.2017.1339075. [Epubahead of print] PubMed PMID: 28737464.*

29. *Umpierre D, Ribeiro PAB, Kramer CK, Letao CB, Zucatti ATN, Azevedo MJ, et al. Physical Activity Advice Only or Structured Exercise Training and Association with HbA1c Levels in Type 2 Diabetes. JAMA, 2011; Vol. 305: No.17.*

30. *Wild S, Roglic G, Green A, Sicree R, King H. Global Prevalence of Diabetes. Estimates for the year 2000 and projections for 2030. Diabetes Care, 2004; 27: 1047-1053.*

31. *Jeon YC, Lokken PR, Hu BF, Van Dam MR. Physical Activity of Moderate Intensity and Risk of Type 2 Diabetes. Diabetes Care, 2007; Volume 30: Number 3.*

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Correlation between flexibility, and agility as it relates to anterior cruciate ligament injuries in University of Zululand female soccer and netball players

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Abstract

Introduction: In competitive sports, anterior cruciate ligament (ACL) injuries are amongst some of the most common injuries in both male and female athletes. ACL injuries were found to be the highest in women (3.1% vs 1.9%) in men. There has been a growing number of incidents of injury, mainly in female athletes.

Methodology: There were (N=30) participants recruited in this study of which were female athletes aged between 18 – 30 years older from uThungulu district located in KZN (South Africa). Participants were assigned into two groups, 1st group (n=15) was a netball team (NetG) and 2nd group (n=15) was the soccer team (SocG). The programme which was given to the teams was part of their existing training and skill focus programme which they followed for over two weeks. Each team had 1hr: 30m each day to execute the programme.

Results: NetG showed a significance difference (p = 0,001) on the Illinois Agility test; whereas the SocG had a significance difference (p = 0,000) in the sit and reach test.

Discussion: With a higher weight mass, netball is more prevalence to ACL injuries than soccer. Even though BMI is a modifiable factor that can either present as a risk factor to ACL injury or an opportunity to prevent ACL injury occurrence.

Conclusion: The study shows that several variables were predisposing factors which increase a higher prevalence of ACL injuries, more especially were a higher BMI. Netball has a higher prevalence of ACL injuries compared to soccer.

Key words: ACL; Competitive sports; BMI; Injury

Introduction

In competitive sports, anterior cruciate ligament (ACL) injuries are amongst some of the most common injuries in both male and female athletes (Miller, Herniman, Ricard, Cheatham & Micheal, 2006; Roozen, 2008). The National Collegiate Athletic Association Surveillance System conducted a study on 16 different sports (8 women's & 8 men's), college and university athletes over a period of 16 years. ACL injuries were found to be the highest in women (3.1% vs 1.9%) than in men (Hootman, Dick, & Agel, 2007). There has been a growing number of incidents of injury, mainly in female athletes. Knee injuries is seen as the most common injury site, specifically injuries to the ACL ligament (Pollard, Davis, & Hamill, 2004). (McAlindon, 1999) and (Holtke, Steinacker and Steur, 2005), discovered that female athletes were about 4-10 times more prone to ACL injuries in comparison to their male counterparts.

Netball is known to be one of the most physically demanding sports, which involve great demands of strength, speed as well as flexibility and fitness. With great participation numbers, and the demands put on players, there is a high risk of injury occurrence during participation (McManus, Stevenson & Finch, 2005). Soccer is considered one of the most popular sports, with about 22% of women contributing to the world's soccer athletes (Mandelbaum & Putukian, 1999). Over the past two decades, female soccer athletes experienced an incredible progress and evolution with successions of participations events organized by the Federation International Football Association (FIFA) and the Olympics. Growing number of incidents of injuries have been occurring mainly in female soccer athletes (Dvorak, Junge, Dermon & Schwellnus, 2011); (Dvorak, Junge & Grimm, 2007).

Sports such as netball and soccer require manoeuvres such as pivoting and jumping which is a concern to sports athletes in relation to ACL injuries (Garrick & Requa, 2001). An increase in ligamentous knee injury rates has been seen in female athletes, particularly in relation to the ACL ligament, in comparison to male athletes, when participating in related activities. There is a noticeable gap when non-contact injuries are being isolated (Arendt, Agel, & Dick, 1995).

Some researchers have speculated as to the reason for there being such a large amount of ACL injuries in female athletes, specifically those which don't occur from straight-contact, however researchers are still eluded by the ACL mechanism injury occurrence (Griffin, Agel, Albohm, 2000). Sports like soccer and netball showed that there is a higher ACL tear rate in female athletes due to fast stopping, changing of direction and cutting, with only about 30% of all injuries occurring due straight-contact with other players or objects (Griffin, Agel & Albohm, 2000). Force generated by the trunk and hip towards the knee were observed through different gender patterns motions and positions. It's important to note that pattern motions, and hip position influence loads, knee position and stiffness (Van Ingen, Bobbert & Rozendal, 1987).

Coordinated muscle activation is the largest and most single contributor in producing motion, stability of position and developing of movements of any joint in a body segment (Van Ingen, Bobbert, & Rozendal, (1987). Lower muscle activation is prevalent in females in relation to their gluteus medius and hamstring muscles (Van Ingen, Bobbert & Rozendal, 1987); Bobbert & van Zandwijk, 1999). Women have weak hip extensors which necessitates the use of the illiopsoas muscle for trunks control over the hip, and their knee alteration is due to their upright landing from a jump (Putnam, 1993). Minimum quadriceps and hamstring activation is due to the minimum activation of the hip muscles. The monoartucular muscles (glutei) stabilizes and facilitates the bilateral muscles (quadriceps and hamstring) (Van Ingen, Bobbert & Rozendal, 1987); Bobbert & van Zandwijk, 1999).

The peak load bearing capacity is changed by the minimized activation, this decreases activation and alters optimal load-bearing capacity. Females show a significantly shorter duration of gluteus medius activation instance, or load-absorbing phase when executing a cutting manoeuvre. This results in higher loads per unit of body weight in anteroposterior and varus/valgus directions. In addition, the peak loads are reached. The above mentioned factors may be the reason why women are more prevalent to ACL injuries than their male counterparts (Van Ingen, Bobbert & Rozendal, 1987); Bobbert & van Zandwijk, 1999). The aim of the study is to investigate the correlation that exists between flexibility, and agility as it relates to ACL injuries in University female soccer and netball players.

Methods

Description and Selection of Participants: There were (N=30) participants recruited in this study of which were female athletes aged between 18 – 30 years older from uThungulu district located in KZN (South Africa). Participants were assigned into two groups, 1st group (n = 15) was a netball team (NetG) and 2nd group (n = 15) was the soccer team (SocG).

Description of Procedures: Prior to participation, all participants were required to give written informed consent to participate in the study and all participants were informed of their right to discontinue the study at any point. Following informed consent, eligibility was determined using defined study inclusion and exclusion criteria.

Assessment: The 1st tests recorded were non-running measures (1. anthropometry measurements - *Body Mass*: A Detector 02 scale was used to determine the participant's body mass, as described by the ACSM (2010). *Stature*: The protocol, as described by the ACSM (2010). *BMI*: described by the ACSM (2010). *Fat Percentage*: A Lange skinfold calliper was used to determine the fat percentage of the participants as described by the ACSM (2010). *Waist and hip circumference*: The measuring tape was used to measure the waist and hip circumference according to the protocol as described by the ACSM (2010). *Sit and Reach*: the protocol described by the ACSM (2010) 2. Resting measurements - *Resting Blood Pressure*: ALPK2 aneroid sphygmomanometer was used to determine arterial blood pressure described by the ACSM (2010). *Resting Heart Rate*: Follow the described protocol by the ACSM (2010) and

Week 1 & Week 2	SocG (1hr: 30) session	NetG (1hr: 30) session	Exercises
Day 1	Conditioning	Conditioning	Squads / stair climb Sit ups / Burpees Walking lunges Horizontal & vertical jumps
Day2	Cardiorespiratory exercise	Cardiorespiratory exercise	Indoor Cycling
Day3	Skill / ball technique	Skill / ball technique	Sports-specific skills, drills and techniques.
Day4	Flexibility Agility speed	Flexibility Agility Speed	Stretch, short sprints, coordinated running drills.
Day5	Skill / ball technique	Skill / ball technique	Sports-specific skills, drills and techniques

Statistical Analysis: Results are expressed as means. Data were also processed using one-way analysis of variance (ANOVA), with a subsequent independent t-test. A p-value of ≤0.05 was considered statistically significant.

2nd tests were running measures (Edgren side step Test (ESST); T-test and Illinois' Agility test (IAT).

Data collection procedure: The administration order of these tests were consist of two phases. Phase 1 being the non-running tests, and phase 2 were running tests. A water station was provided for hydration purposes. Athletes were briefed and tests were demonstrated a day prior to the actual test. Phase 1 (non-running measures), consists of anthropometric & sit and reach test; Phase 2 (running measures) Edgren Side Step Test (ESST), T-Test, and Illinois Agility Test (IAT) were implemented. Athletes were randomly selected, and were assigned two score keepers of whom were concurrently observing and individually recording test results. Score keeper 1 read the written instructions, whiles the second score keeper was walking and demonstrating the tests to athletes to make sure the athlete understood the instructions and have witnessed the pattern and movement of the tests. Athletes were not given any form of external motivation to perform the tests, thus it did not influence results. Individual results were recorded by two score keeper through the entire testing and their score were blinded from each other. A one-minute resting period between each trail was given to players and their best scores were recorded.

Intervention: The programme which was given to the teams was part of their existing training and skill focus programme which they followed for over two weeks. Each team had 1hr:30m each day to execute the programme. Researcher observed the training sessions without being influential to any team.

Results

Of the initial 30 participants who were eligible to participate in the study, 24 participants (NetG: n=9, SocG: n=15) completed the study and were included in the final analysis. Six participants were excluded from the analysis in the study as they were unable to be tested throughout the 2 weeks. There were significant ($p>0.05$) differences found in the SocG for Sit & reach (Table 1) and in the NetG for IAT (Table 2).

Discussion

This study is conducted based on the prevalence of ACL injuries between netball and Soccer players, as they are prone to ACL injuries (Miller, Herniman, Ricard, Cheatham & Micheal, 2006; Roozen, 2008). According to (Griffin, Agel & Albohm, 2000) both netball and soccer are sports which include activities such as jumping, cutting, sudden change of directions, acceleration and deceleration. Because of the higher weight mass, ACL injuries can also be caused by stress due to valgus movements, whereas the ligaments are provided with a posterior protective force which is produced by the hamstring (Draganich & Vahey, 1990).

A quick change of movement in planned events adds to the voluntary patterns of movements (Griffin, Agel & Albohm, 2000) were seen in netball players, it is clear that during the game on both teams, there will be forces which develop within the tendon of the patella creating an anterior directed shear force on the proximal side of the tibia

Table 1. Weight, BMI, Hip Circumference, Waist Circumference, Waist to Hip Ratio, Fat% and Sit and Reach following a 2-week physical activity programme

	Groups	Pre-test	Post test	P-value	% Difference
Weight	NetG	74,27	72,22	0,697	↓ 2,77
	SocG	56,80	55,31	0,524	↓ 2,63
BMI	NetG	26,94	26,20	0,725_	↓ 2,75
	SocG	21,95	21,48	0,588	↓2,15
Hip Circumference	NetG	110,22	108,55	0,700	↓ 1,52
	SocG	97,32	96,00	0,598	↓ 1,36
Waist Circumference	NetG	78,88	77,22	0,654	↓ 2,11
	SocG	70,32	68,74	0,437	↓ 2,25
W H R	NetG	0,71	0,70	0,795	↓ 1,41
	SocG	0,71	0,71	0,814	0
Fat %	NetG	23,18	21,53	0,458_	↓ 7,12
	SocG	20,79	19,44	0,362	↓ 6,50
Sit & reach	NetG	49,22	54,77	0,232	↑ 11,27
	SocG	52,13	56,26	0,000*	↑ 7,92

***Significant at p≤0.05**

Values are means and percentage differences

Weight: Kg: kilograms; Hip Circumference: cm: Centimetre; Waist Circumference: cm: Centimetre; Fat %: percentage; Sit & reach: cm: Centimetre

Table 2. T test, ESST and IAT following a 2-week physical activity programme

	Groups	Pre-test	Post test	P-value	% Difference
T test	NetG	13,56	12,73	0,404	↓ 6,13
	SocG	13,27	13,24	0,946	↓ 0,23
ESST	NetG	4,91	4,20	0,140	↓ 14,47
	SocG	3,57	3,69	0,288	↑ 3,36
IAT	NetG	22,12	19,75	0,001*	↓ 10,72
	SocG	18,38	18,99	0,534	↓ 3,31

***Significant at p≤0.05**

Values are means and percentage differences

T test: s: seconds; ESST: s: seconds; IAT: s: seconds

from landing on ground from a jump which then results in ACL strain (Renstrom, Ljungqvist, Arendt, Beynnon, Fukubayashi, Garrett, Georgoulis, Hewett, Johnson, Krosshaug, Mandelbaum, Micheli, Myklebust, Roos, Roos, Schamasch, Shultz, Werner, & Wojtys, 2008). This statement supports the findings that with a higher weight mass, netball is more prevalence to ACL injuries than soccer.

Even though BMI is a modifiable factor that can either present as a risk factor to ACL injury or an opportunity to prevent ACL injury occurrence. BMI (Table I) can be related to the increase chances of ACL injury occurrence when considering posterior tibial slope (PTS) (Hewett, Lindenfeld, Riccobene, & Noyes, 1996). Which this statement supports our finding that netball is more prevalence to ACL injuries as compared to soccer. Yet again, it is unclear that higher BMI is due to the high fat body mass or maybe a higher lean body mass or perhaps the combination of the two masses have such effects on ACL injury when related to PTS since BMI is an overall of weight but does not specify exactly where that weight is located on the body Hewett, Lindenfeld, Riccobene, & Noyes, 1996). At the same time, we find that these factors BMI, weight and body mass (lean) may be complicated in determining the accuracy to ACL injury prevalence (Hudek, Schmutz, Regenfelder, Fuchs & Koch, 2009).

NetG showed a significance difference (p=0,001) on the Illinois Agility test, which theoretically will

place a high axil load on the tibiofemoral joint which will form tension on the ACL during relative extension. In theory, BMI would place great axial load onto the tibiofemoral joint, increasing ACL tension in relative extension. Conflicting studies exist with some showing a significant increase in BMI associated with ACL and others show no significance (Brown, Yu, Kirkendall & Garrett, 2005); (Evans, Kilcoyne, Dickens, Rue, Giuliani, Gwinn, & Wilckens, 2012); (Knapik, Sharp, Canham-Chervak, Hauret, Patton, & Jones, 2001); Ostenberg & Ross, 2000).

Weight, BMI and fat % play an important role in sports participations and injury occurrence, more especially when netball and soccer includes these kind of variation movements such cutting, dribbling, sudden change of direction, stopping and acceleration. There is an influence of these factors on both teams, a more obvious of ACL injury occurrence on NetG (Griffin, Agel & Albohm, 2000; Garrick & Requa, 2001). Flexibility is an important component which is needed by both teams, as this will enable quick reaction time and respond to any uncertain directional change or stopping and acceleration or turning with a foot planted and pivoting. Table I. Indicates that SocG had a significance difference (p = 0,000) with the sit and reach test.

This showed that with a lesser flexibility from the netball as compared to soccer, the netball has indeed a higher prevalence of ACL injuries (McManus, Stevenson & Finch, 2005). It's important to note that pattern motions, and hip position influence loads, knee position and stiffness (Van Ingen, Bobbert & Rozendal, 1987). Other studies reported that women have weak hip extensors which necessitates the use of the illiopsoas muscle for trunks control over the hip, and their knee alteration is due to their upright landing from a jump (Putnam, 1993).

Conclusion

The study shows that several variables were predisposing factors which increase a higher prevalence of ACL injuries, more especially where a higher BMI (which will have an influence in the increase of lateral PTS on ACL injuries) in NetG as compared to SocG. An increase in lateral PTS Middle cartilage slope (MCS) was associated with an increased risk of an ACL tear, irrespective of BMI. We can only conclude from the results which were recorded that netball will have a higher prevalence of ACL injuries as compared to soccer, but also in mind with other variable (PTS, MCS) from other researchers.

References

1. *American College of Sports Medicine. Guidelines for exercise testing and prescription – 8th ed. Philadelphia: Lippincot Williams and Wilkins. 2010; 46–233.*
2. *Arendt EA, Agel J, Dick R. Knee injury patterns among men and women in collegiate basketball and soccer. American Journal of Sports Medicine, 1995; 23: 694-701.*
3. *Brown CN, Yu B, Kirkendall DT, Garrett WE. Effects of increased body mass index on lower extremity motion patterns in a stop-jump task. Journal of Athletic Training, 2005; 42: 26 - 51.*
4. *Draganich LF, Vahey JW. An in vitro study of anterior cruciate ligament strain induces by quadriceps and hamstring forces. Journal of Orthopedic Research, 1990; 8: 57-63.*
5. *Dvorak J, Junge A, Grimm K. Commentary on "Medical report from the 2006 FIFA World Cup Germany". British Journal of Sports Medicine, 2007; 41: 581-581.*
6. *Dvorak J, Junge A, Dermon W, Schwellnus M. Injuries and illnesses of football players during the 2010 FIFA World Cup. Britain Journal Sports Medicine, 2011; 4-5.*
7. *Evans KN, Kilcoyne KG, Dickens JF, Rue J, Giuliani J, Gwinn D, et al. Predisposing risk factors for noncontact ACL injuries in military subjects. Knee Surgery Sports Traumatol Arthroscopy, 2012; 20: 1554-1559.*
8. *Garrick JG, Requa RK. Anterior cruciate ligament injuries in men and women: how common are they? Prevention of Noncontact ACL Injuries, 2001; 1: 1-9.*
9. *Griffin LY, Agel J, Albohm MJ. Noncontact anterior cruciate ligament injuries: risk factors and prevention strategies. American Academy of Orthoprdic Surgery, 2000; 8: 141-150.*
10. *Hewett TE, Lindenfeld TN, Riccobene JV, Noyes FR. The effect of neuromuscular training on the incidence of knee injury in female athletes. A prospective study. American Journal Sports Medicine, 1996; 27: 699-706.*

11. *Holtke V, Steinacker T, Steuer M. Injuries and overload-damages at players of the German lady-soccer-national-team. Sportverletz Sportschaden, 2005; 19: 33-36.*

12. *Hootman JM, Dick R, Agel J. Epidemiology of collegiate injuries for 15 sports: summary and recommendations for injury prevention initiatives. Journal of Athletic Training, 2007; 42(3): 11- 19.*

13. *Hudek R, Schmutz S, Regenfelder F, Fuchs B, Koch PP. Novel measurement technique of the tibial slope on conventional MRI. Clinical Orthopedic Relat Res, 2009; 467: 2066-2072.*

14. *Knapik JJ, Sharp MA, Canham-Chervak M, Hauret K, Patton JF, Jones RH. Risk factors for training related injuries among men and women in basic combat training. Medicine Science Sports Exercise, 2001; 33: 946-954.*

15. *Mandelbaum B, Putukian M. In Medical concern and specification in female soccer players. Science and Sports, 1999; 14(2): 54-60.*

16. *McAlindon R. ACL injuries in women. Hughston sport medicine foundation, 1999; 11(1): 1-5.*

17. *McManus A, Stevenson RM, Finch FC. Incidence and risk factors for injury in non-elite netball. Curtin University of Technology, Division of Health Sciences. Perth: Division of Health Science, 2005.*

18. *Miller M, Herniman J, Ricard M, Cheatham C, Michael T. The effects of a 6-week plyometric training program on agility. Journal of Sports Science Medicine, 2006; 3(4): 59-65.*

19. *Ostenberg A, Roos H. Injury risk factors in female European football: A prospective study of 123 players during one season. Scand Journal Medicine Science Sports, 2000; 10: 279-285.*

20. *Pollard CD, Davis IM, Hamill J. Influence of gender on hip and knee mechanics during a randomly cued cutting manoeuver. Clinical Biomechanics, 2004; 19: 1022-1031.*

21. *Putnam C. Sequential motions of body segments in striking and throwing skills: descriptions and explanations. Journal of Biomechanics, 1993; 26: 125-135.*

22. *Renstrom P, Ljungqvist A, Arendt E, Beynnon B, Fukubayashi T, Garrett T, et al. Non-contact ACL injuries in female athletes: an International. Britain Jornal Sports Medicine, 2008; 394-412.*

23. *Roozen M. Action-reaction: Illinois Agility Test. Journal of NSCA Perfom Training, 2008; 42: 394-412.*

24. *Van Ingen SG, Bobbert M, Rozendal R. The unique action of biarticular muscles in complex moements. Journal of Anatomy, 1987; 155: 1-5.*

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Corelation of therapy response and toxic effects of chemotherapy in advanced lung cancer

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Abstract

Introduction: Lung cancer remains the leading cause of cancer incidence and mortality, with 2.1 million new lung cancer cases and 1.8 million deaths predicted in 2018.

Methods: This prospective study included patients in stages IIIb or IV of NSCLC, with ECOG ≤ 2. First group contained 30 patients treated with cisplatin-etopozid, second group were treated with cisplatin-gemcitabin. Monitoring of toxical side effects and response to chemotherapyST.

Results: In the patients that had undertaken the PE protocol it was noted that progression positively corelates with variables: loss of body mass >5%, rash, mucositis, alopetio, high toxicity, while in the PG protocol, progression corelates with variables: rash, toxic death, high toxicity, renal toxicity.

Conclusion: The research results showed that PG protocol had better treatment effects in developed NSCLC.

Key words: Advanced Lung Cancer. Chemotherapy. Side effects. Response.

Introduction

Lung carcinoma is the leading disease of incidence and mortality from all cancers. About 2.1 million people suffered and 1.8 million deaths in 2018, representing 1 out of 5 cancer patients (18.4%). Only 19% of patients with a diagnosis of lung cancer will survive for 5 years or more, but diagnosed at an early stage in the five-year survival scenario dramatically improves (1).

For both sexes, lung cancer is the most commonly diagnosed cancer (11.6% of the total number of cases) and the leading cause of cancer deaths (18.4% of total cancer mortality). By sex, lung cancer is the most commonly diagnosed cancer and the leading cause of cancer death in men, followed by prostate cancer and colorectal cancer. Among women, breast cancer is the most commonly diagnosed cancer and the leading cause of cancer death, followed by colon cancer and lung cancer (2).

Four decades of clinical research demonstrate the effectiveness of chemotherapy in lung cancer patients. Chemotherapeutic agents can improve the symptoms of lung cancer, prolong life in most lung cancer patients, and improve its cure for people with locoregional disease in combination with surgery or radiation.

The efficacy of chemotherapy has been improved in patients with EGFR mutant and ALK-positive lung cancer and can "save" individuals whose oncogene cancer has become resistant to targeted agents. As immunotherapies become part of the therapeutic weapon for lung cancer, chemotherapeutic agents have the ability to modulate the immune system to boost the effectiveness of the immune control inhibitor. Even in this period of personalized medicine and targeted therapies, chemotherapeutic agents remain essential components in the treatment of cancer.

Platinum doublets based chemotherapy should be considered in patients in an inoperable phase of the disease in the absence of driver mutations if the patient has ECOG PS 0-2 and without significant comorbidities. The benefits of chemotherapy versus best supportive care (BSC) are reflected in a 23% reduction in the risk of death, a prolonged 1-year survival of 9% and an improvement in the quality of life of QoL, regardless of age, gender, histology (3,4,5).

Based on meta-analysis from 2006; a statistically important one year decrease of death risk had been proved, for around 22% of the ones treated with platinum-based chemotherapy, without the unwanted toxicity induction, so the platinum based combinations are recommended to all the patients without contraindications on platinum compounds (6).

Methods

This prospective study included 60 patients in stages IIIb or IV of NSCLC, with ECOG ≤ 2. The patients were divided in two groups. First group contained 30 patients treated with chemotherapeutic protocol using cisplatin-etopozid (PE), and the same number of patients in the second group were treated with cisplatin-gemcitabin (PG). Monitoring of toxical side eff ects after each cycle of chemotherapy was based on anamnesis, clinical examination, parameters of blood (7) (level of hemoglobin, leukocyte, erythrocyte, neutrophils, and platelet count), parameters of renal function (levels of urea and creatinine) parameters of liver function (levels of alanine aminotransferase–ALT, and aspartate aminotransferase–AST), according to „Common Terminology criteria for adverse events"(8). Response to chemotherapy was defined in concordance with RECIST (Response Evaluation Criteria in Solid Tumors) as: complete response (CR), partial response (PR), progressive disease (PD), stationary disease (SD) (9). Data analysis was per formed using SPSS software, version 15 (SPSS, Inc., Chicago, IL).

Results

The study included 60 respondents, 30 treated PE protocols and the same number of patients treated with PG protocol. The whole sample was dominated by: male sex 53/60 (88%), planocellular carcinoma 31/60 (51%) and IIIB stage of disease 32/60 (53%). Table 4 shows the sex structure, the pathohistological diagnosis, the stage of the disease, and the presence of comorbidity observed in 31 subjects (51%). The average age of patients in the PE protocol was 62.13 ± 6.3, while in the PG protocol this value was 56.67 ± 6.01.

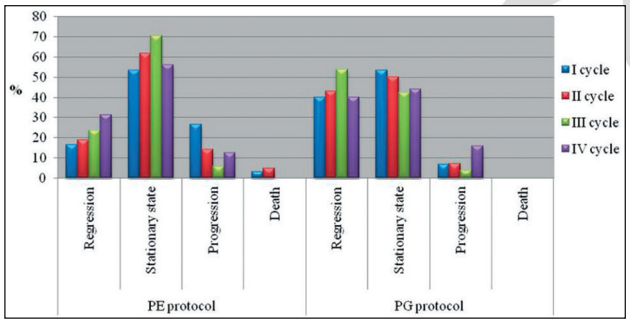

Figure 1. Chemotherapy response rate for both protocol

Figure 1 presents response rate after administration of chemotherapy for both protocols. After the first cycle of chemotherapy using PE protocol, 8 patients had progression of disease and there was one case of toxic death. Forth cycle of chemotherapy using PE protocol was prescribed in 16 patients, and after administration of chemotherapy 2 patients had progression of disease. Following the f rst cycle of chemotherapy using PG protocol 2 patients had progression of disease. Twenty-f ve patients were assigned to receive forth cycle of chemotherapy using PG protocol, and after administration of chemotherapy there were 4 cases with progression of disease.

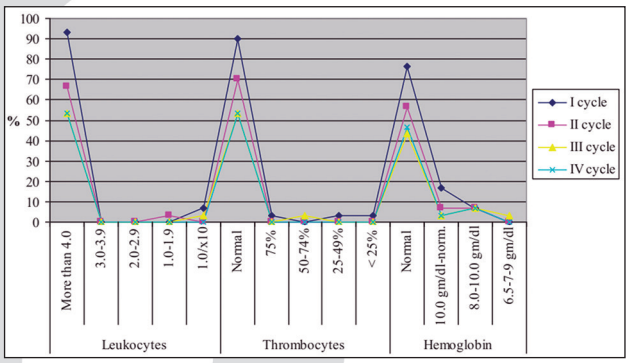

Figure 2. Incidence of hematological toxical effects in patients treated according to PE protocol

Figure 2 shows the incidence of chemotherapy-induced hematological toxicities in patients treated according to PE protocol. After the first cycle of chemotherapy 6,7% of patients experienced grade IV leukopenia, grade V thrombocytopenia was found in one patient, and five patients experienced grade I anemia. Following forth cycle of chemotherapy normal platelet count was recorded in 16 patients, and normal level of hemoglobin was found in 14 patients.

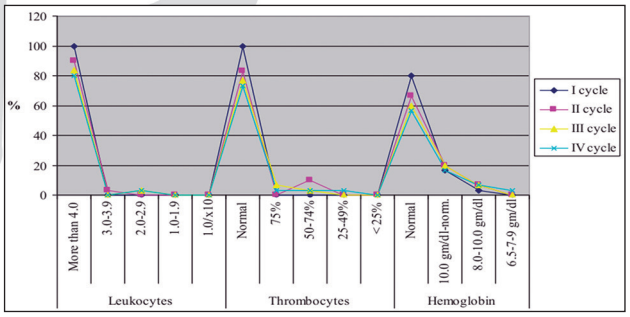

Figure 3. Incidence of hematlological toxical effects in patients treated according to PG protocol

Incidence of chemotherapy-induced hematological toxicities treated according to PG protocol are

summarized in Figure 3. With the exception of lower values of hemoglobin found in 5 patients, there was no other hematological toxicities after the f rst cycle of chemotherapy. After 4 cycles of chemotherapy grade 2 leukopenia occurred in one patient, whereas normal platelet count was recorded in 22 patients, and normal level of hemoglobin was found in 17 patients.

The relationship between therapeutic responses and toxic effects in PE protocol (N = 30) was tested by calculating the Spearman coefficient of correlation of ranks. Table 1 presents the results of statistically significant relationships, and given the nature of the data and the method of encoding the variables, and based on the signs of the correlation coefficient, it can be noticed that progression correlates positively with the indicated toxic effects, while the stationary state and regression with these toxic effects negatively correlate. It is noticeable that most of these connections belong to medium and high intensity.

The relationship of therapeutic response variables and toxic effects in the PG protocol (N = 30) was also determined by the Spearman coefficient of correlation. The results presented in Table 2 show a lower number of statistically significant links than the PE protocol. In cases of existing statistical links, the strength of the correlation belongs to the medium strong and high correlation. Considering the method of encoding the variables, it is noted that progression is positive, and regression negatively correlates with toxic effects.

Table 2. Correlation of therapeutic responses and toxic effects in the PG protocol

Correlation rang		Progression	Regression
Rash	ρ	,37(*)	-,22
	p	,05	,23
Mucositis	ρ	,35	-,37(*)
	p	,06	,05
Toxic death	ρ	,42(*)	-,33
	p	,02	,08
High toxicity	ρ	,50(**)	-,37(*)
	p	,005	,05
Renal toxicity	ρ	,50(**)	-,37(*)
	p	,005	,05
Hepatal toxicity	ρ	,50(**)	-,37(*)
	p	,005	,05

** correlation is significant on level 0,05;*
*** correlation is significant on level 0,01*

Table 1. Corelation of therapy responses and toxic effects in PE protocol

Correlation rang		Progression	Stationary	Regression
Body weight	ρ	,43(*)	-,61(**)	-,35
	p	,02	,000	,06
Bleeding	ρ	,35	-,55(**)	-,46(**)
	p	,06	,002	,01
Rash	ρ	,37(*)	-,59(**)	-,44(*)
	p	,04	,001	,02
Mucositis	ρ	,36(*)	-,59(**)	-,44(*)
	p	,05	,001	,02
Alopetia	ρ	,36(*)	-,60(**)	-,34
	p	,050	,000	,065
Toxic death	ρ	,39(*)	-,61(**)	-,44(*)
	p	,03	,000	,02
High toxicity	ρ	,37(*)	-,59(**)	-,44(*)
	p	,04	,001	,02
ECOG	ρ	,25	-,37(*)	-,039
	p	,18	,05	,84
Renal toxicity	ρ	,48(**)	-,60(**)	-,42(*)
	p	,007	,000	,02
Hepatal toxicity	ρ	,48(**)	-,60(**)	-,42(*)
	p	,007	,000	,02
Spirometry	ρ	,24	-,43(*)	-,35
	p	,19	,02	,06

** correlation is significant on level 0,05; ** correlation is significant on level 0,01*

Discussion

Chemotherapy is accompanied by various complications and unwanted toxic effects. The acceptability of a therapeutic protocol is measured by the achieved therapeutic effects in relation to its toxicity. The toxicity of chemotherapy depends on several factors: the type of cytostatics, drug dosage, protocol of administration, the mode of administration, and the predisposing factors of the patient. Table 1 presents the results of statistically significant relationships, given the nature of the data and the method of encoding the variables, and on the basis of the signs of the correlation coefficient it can be noticed that progression correlates positively with variables: loss of body weight> 5%, rash, mucositis, alopecia, high toxicity, renal and hepatic toxicity. Stationary state and regression with these toxic effects negatively correlates. It is noticeable that most of these connections belong to medium and high intensity.

By examining the individual values of toxic effects in all cycles and their distribution in all therapeutic responses, the strength of the link shows that the absence of progression follows the absence of toxic effects, while in the stationary state and regression the situation is reversed.

Given the course of treatment and insight into the results of all subjects individually, it has been found that patients most often appear in the stationary state, then regression, and that, if they are not immediately after chemotherapy in progression, they move from the stationary state to the state of progression. Also, the occurrence of toxic effects in the stationary state and regression is higher, but they occur instantaneously and sporadically, they are related to chemotherapy with a tendency of gradual abscess with the departure of treatment. In the case of progression, patients are excluded from further monitoring, but on the basis of the gradual absence of toxic effects through the stationary condition, the assumption that a greater presence of progression would not induce the occurrence of a greater number of toxic effects.

The results presented in Table 2 show a lower number of statistically significant links, compared to the PE protocol, and that toxic effects do not correlate with the stationary state. Progression correlates with variables: rash, toxic death, high toxicity, renal and hepatic toxicity. Negative correlation was recorded between regression and variables: mucositis, high toxicity, renal and hepatic toxicity. In cases of established statistical links the strength of the correlation belongs to a medium strong and high connection. Considering the method of encoding variables, it is noted that progression positively correlates, and regression negatively correlates with toxic effects.

This type of correlation means that in the absence of progression there is a pronounced absence of toxic effects, while in regression the situation is reversed, the greater the presence of regression implies an increase in the absence of toxic effects. The conclusions of the obtained results are the same as in the PE protocol.

For the prevention of chemotherapy-induced toxicity, the correct time interval and dosing is important, as confirmed by Rosia et al. (10). They followed the toxicity of the combination of gemcitabine and cisplatin. They concluded that for the safety and low toxicity of chemotherapy, proper schedule and dosing is important, especially in elderly patients and patients with co-morbidity. This research was also supported by Fonta et al., (11). Their goal was to investigate the efficacy of accelerated dosing of cisplatin and etoposide, where one group of patients received chemotherapy on the 21st day, and the second on the 28th day. They concluded that the administration of chemotherapy on the 21st day is not correlated with significant improvements in the rate of good response or survival and can not be recommended as a treatment of choice.

Pignon et al. study, (12) monitored the effect of chemotherapy based on cisplatin administered after surgery. Researchers have shown that patients with a better ECOG performance status give a more favorable response to treatment with cisplatin chemotherapy with etoposide or vinca alkaloid, which partly agrees with our results. There was a significant improvement in patient survival and there was no significant difference between the chemotherapeutic response in relation to gender, age, pathohistological findings, type of surgery, planned radiotherapy, or the planned total dose with cisplatin.

Mohani et al. (13) investigated the effect of chemotherapy on the incidence of cough, dyspnoea, chest pain, fever, anorexia, weight loss, and the improvement in hemoglobin and albumin levels.

The results showed that there was no significant improvement in lung function, nutritional status or quality of life (QOL) after treatment. The authors concluded, which would be our conclusion, that the treatment of NSCLC must include a strategy to improve various aspects of quality of life, nutritional status and pulmonary reserve in order to achieve a comprehensive benefit

Conclusion

Few diseases have engendered as much nihilism as lung cancer. In particular, the role of chemotherapy has frequently been denigrated as toxic and ineffective. However, over the past 50 years remarkable progress has been seen in the treatment of the most common type of lung cancer, non–small cell lung cancer (NSCLC). Platinum-based chemotherapy is clearly established and have demonstrated unequivocal benefit, both in terms of increasing cure rates in adjuvant and multimodality settings in lower stages of disease and enhancing quality and length of life in advanced disease.

References

1. *Malvezzi M, Carioli G, Bertuccio P. European cancer mortality predictions for the year 2017, with focus on lung cancer. Ann Oncol 2017; 28: 1117–23.*

2. *Bray F, Ferlay J, Soerjomataram I, Siegel LR, Torre AL, Ahmedin DVM. GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. Global cancer statistics 2018.*

3. *Non-small Cell Lung Cancer Collaborative Group. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. BMJ 1995; 311: 899–909.*

4. *NSCLC Meta-Analyses Collaborative Group. Chemotherapy in addition to supportive care improves survival in advanced non-small-cell lung cancer: a systematic review and meta-analysis of individual patient data from 16 randomized controlled trials. J Clin Oncol 2008; 26: 4617–25.*

5. *Non-Small Cell Lung Cancer Collaborative Group. Chemotherapy and supportive care versus supportive care alone for advanced non-small cell lung cancer. Cochrane Database Syst Rev 2010; CD007309.*

6. *Pujol JL, Barlesi F, Daures JP. Should chemotherapy combinations for advanced non-small cell lung cancer be platinum-based? A metaanalysis of phase III randomized trials. Lung Cancer. 2006; 51: 335–45.*

7. *Crawford J, Dale DC, Lyman GH. Chemotherapy-induced neutropenia. Risks, consequences and new directions for its management. Cancer. 2004; 100: 228-37.*

8. *Common Terminology criteria for adverse events ver. 4., 2009. Available from; http://ctep.cancer.gov/protocol Development/electronic_applications/ctc.htm*

9. *Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European Journal of Cancer. 2009; 4 5: 228-47.*

10. *Rossi D, Graziano F, Catalano V, Giordani P, Fedeli SL, et al. A new cisplatin/gemcitabine schedule in locally advanced (IIIB) and metastatic (IV) non-small cell lung cancer: relationship between dose-intensity and efficacy. A phase II study. Anticancer Res. 2002; 22(5): 3087-92.*

11. *Font A, Moyano AJ, Puerto JM, Tres A, Garcia-Giron C, et al. Increasing dose intensity of cisplatin-etoposide in advanced nonsmall cell lung carcinoma: a phase III randomized trial of the Spanish Lung Cancer Group. Cancer. 1999; 85(4): 855-63.*

12. *Pignon JP, Tribodet H, Scagliotti GV, Douillard JY, Shepherd FA, et al; LACE Collaborative Group. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J Clin Oncol. 2008; 26(21): 3552-9.*

13. *Mohan A, Singh P, Kumar S, Mohan C, Pathak AK, et al. Effect of change in symptoms, respiratory status, nutritional profile and quality of life on response to treatment for advanced non-small cell lung cancer.Asian Pac J Cancer Prev. 2008; 9(4): 55762.*

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KoACT, a calcium-collagen chelate dietary supplement, increases bone mineral density and strength in an ovariectomized rat model of osteoporosis

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Abstract

Introduction: The present *in vivo* study investigated the efficacy of KoACT, a novel calcium-collagen chelate dietary supplement, in an ovariectomized rat model of osteoporosis.

Material and methods: Wistar rats were ovariectomized and separated into four experimental groups. Two different dosages of KoACT were compared to a control group (Ca) and a HC group.

Results and discussion: KoACT increased bone mineral density by 3.5% as compared to control group. Furthermore, the calcium-collagen chelate dietary supplement increased bone strength by 9.9% as compared to control.

Conclusion: The obtained data support the view that KoACT, a novel calcium-collagen chelate, is efficacious and may be ingested as a nutritional supplement.

Key words: bone mineral density, bone strength, calcium-collagen chelate, KoACT, ovariectomized rat model.

Introduction

The most common cause of related bone loss is osteoporosis associated with ovarian hormone deficiency following menopause (postmenopausal osteoporosis). A sharp decrease in ovarian estrogen production is the predominant cause of rapid hormone-related bone loss during the first decade after menopause[1].

Traditional therapies for postmenopausal osteoporosis have emphasized agents that inhibit bone resorption as estrogen[2], calcitonin[3] and bisphosphonates[4].

Although the most effective method to reduce the rate of postmenopausal bone loss is estrogen replacement therapy, it may be accompanied by side effects and is thus recommended only for women who are at high risk of osteoporosis and who have no contraindications[5].

Recent advances in bone biology have led researchers to suggest using a combination of anti-resorptive agents, such as estrogen, and formation-stimulating agents, such as growth hormone, toward a cure for osteoporosis[6].

However, the potential bone forming agents available today either may have serious side effects (e.g., growth hormone, anabolic steroids), may not improve bone quality, or may not decrease susceptibility to fracture (e.g., sodium fluoride). Therefore, it would be most helpful to discover a substance that minimizes bone loss in postmenopausal women, thus decreasing the necessity for drug therapy[7].

Some reports have indicated that KoACT, a proprietary calcium-collagen product, provides calcium and collagen through a unique process that models natural bone structure. The result may be a synergistic effect of both calcium and collagen into the bones creating superior bone strength. It seems to a step further than only supplementing with calcium, as in most bone health supplements currently on the market[8].

These promising reports regarding the beneficial effects of KoACT have led to hypothesize that food ingredients with concentrations of bioavailable calcium-hydrolyzed collagen type I chelate might be effective in modulating bone mass due to ovarian hormone deficiency.

Material and methods

Twenty-six female Wistar rats, aged 80 days, were purchased from SLC Japan (Shizuoka, Izu) and used for this study when they were 84 days old. Upon arrival at our institution, the rats were housed in an environmentally controlled animal laboratory.

Rats were acclimated to a standard laboratory nonpurified diet for 5 days. After acclimation, rats were divided by initial body weight into four blocks of eight rats each, using a randomized complete block design.

The animals were ovariectomized and separated into four experimental groups. Two different dosages of KoACT were compared to a control group (Ca) and a HC group. The control group contained the same amount of elemental calcium as the KoACT group, and the HC group contained the same amount of calcium and collagen as the KoACT group, but in a simple mixture. Thus, KoACT dosage was equivalent to 3 g/day for a human dosage; and 10X KoACT dosage was equivalent to 30 g/day for a human dosage.

All rats were anesthetized with an intraperitoneal injection of ketamine hydrochloride and xylazine at doses of 100 mg/kg body weight and 5 mg/kg body weight, respectively. Bilateral ovariectomies were performed, and animals were subjected to sham operation[9].

The rats had free access to deionized water. The animals were euthanized 30 days after surgery; right femurs and fourth lumbar bones were dissected out for bone analyses. Blood was collected, and serum was separated, divided into small samples and stored at -20°C until required for analyses. Guidelines for the ethical care and treatment of animals from the Animal Care Committee were strictly followed.

The right femurs and the fourth lumbar vertebra were freed of soft tissue using small scissors, tweezers and cotton gauze. The length of each femur was measured with a vernier caliper. Before measurement of the bone density, the femur was cut at the mid-diaphysis and the marrow washed out.

Bone volume and density were measured by Archimedes' principle. Briefly, each bone was put in a vial filled with deionized water, and the vial was placed under a vacuum for 90 minutes to ensure that all the trapped air diffused out of the bone. Each bone was removed from its vial, blotted with gauze sponge, weighed, and returned to the vial containing deionized water. The bone was reweighed in water and the density was calculated[10].

The bones were hydrolyzed with 6 mol/L HC1 at 110°C for 20 h. To measure calcium, aliquots of hydrolysate were properly diluted using 3.1 mmol/L lanthanum solution. Calcium was determined by atomic absorption spectrophotometry (model 503, Perkin-Elmer, Norwalk, CT), and the values were expressed as milligrams of calcium per cubic centimeter of bone volume. Aliquots of bone hydrolysate were also used for the colorimetric analysis of phosphorus. Serum was appropriately diluted with 3.1 mmol/L lanthanum solution, and calcium was measured using atomic absorption spectrophotometry[11].

Data analysis (GraphPad Instat Software version 2.00, 1993, San Diego, CA) involved estimation of means and so for each of the groups[12]. Analysis of variance was performed to determine whether there were significant ($P < 0.05$) differences among the groups. When an ANOVA indicated any significant difference among the means, the Newman-Keuls multiple comparison test was used to determine which means were significantly different[13].

Results and discussion

Nutritional supplementation for people with osteoporosis has long been focused on calcium and vitamin D. Calcium increases bone mineral density and vitamin D facilitates the absorption of calcium. A relative new comer to bone health supplements includes vitamin K. It may help focus calcium to the right tissue. Studies have shown that vitamin K plus vitamin D and calcium work more effectively to improve bone mineral density, as compared to calcium alone[8].

However, all these approaches are addressing the calcium deficiency only. A closer look at the bone structure provides great insights for new approaches: Seventy-five percent of the dry bone mass is inorganic minerals, mostly calcium phosphate crystals. The other twenty-five percent is organic matrix, mostly made of bone collagen (Figure 1).

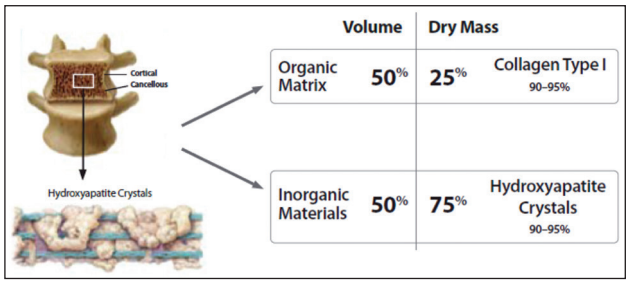

Figure 1. Bone structure

Calcium builds bone density, but collagen builds the frame work for calcium to attach to. It is more like the skyscraper. Collagen is the steel frame, while calcium is the cement. Collagen is essential to improving bone flexibility which helps bones absorb impact. Without it, even the strongest bones can crack, shatter or break, and running, jumping and other activities become painful. Although the body produces collagen naturally, its production diminishes as we age.

KoACT increased bone mineral density (BMD) by approximately 3.5% as compared to control (Ca) group. Both groups were fed same amount of calcium after 8 weeks of intake (Figure 2).

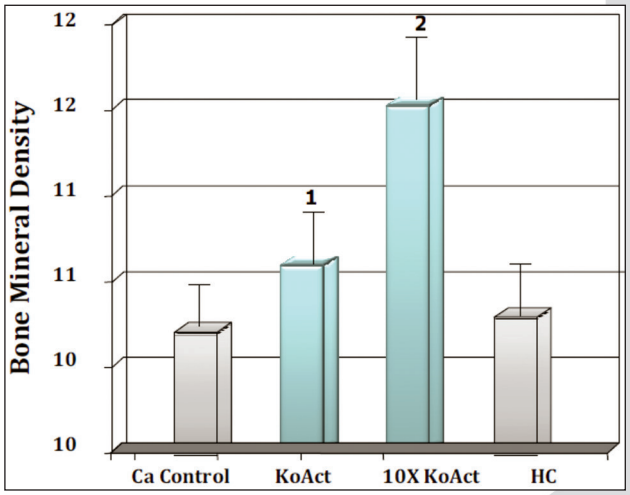

Figure 2. Effects of KoACT on BMD

Furthermore, when these groups were measured for the optimal force to break the bone as a direct indication of bone strength, KoACT increased femur bone strength by about 9.9% as compared to control (Ca) group. This result is consistent with the hypothesis that KoACT not only provides calcium support, but most importantly provides bone matrix support that is critical for bone strength (Figure 3).

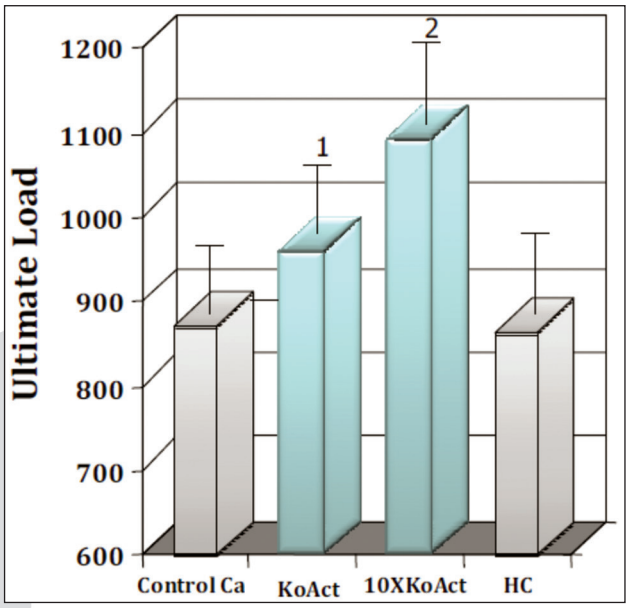

Figure 3. Effects of KoACT on bone strength

Conclusion

The study has shown that KoACT dose-dependently increased femur bone strength and bone mineral density in this animal model of osteoporosis. KoACT can provide an additive effect on femur bone strength and bone mineral density from its unique calcium and hydrolyzed collagen type I chelate composition. This unique property of KoACT is not observed with calcium alone.

References

1. *Gruber HE, Ivey JL, Baylink DL, Mathews M, Nelp WB, Sisom K, et al. Long term calcitonin therapy in postmenopausal osteoporosis. Metabolism, 1984; 33: 295-303.*

2. *Centrella M, Canalis E. Local regulators of skeletal growth: a perspective. Endocr. Rev. 1985; 6: 544-551.*

3. *Canalis H, McCarthy T, Centrella M. Growth factors and the regulation of bone remodeling. J. Clin. Invest. 1988; 81: 277-281.*

4. *Rudman D, Kutner MH, Rogers CM, Lubin MF, Fleming GA, Bain RP. Impaired growth hormone secretion in the adult population. J. Clin. Invest. 1981; 67: 1361-1369.*

5. *Bennet AE, Wahner HW, Riggs BL, Hintz RL. Insulin-like growth factors I and II: aging and bone density in women. J. Clin. Endocrinol. & Metab. 1984; 59: 701-704.*

6. *Genant HK, Baylink D, Gallagher JC. Estrogens in the prevention of osteoporosis in postmenopausal women. Am. J. Obstet. Gynecol. 1989; 161: 1842-1846.*

7. *Turner CH. Toward a cure for osteoporosis: reversal of excessive bone fragility. Osteoporosis Int. 1991; 2: 12-19.*

8. *Hooshmand S, Elam ML, Browne J, Campbell SC, Payton ME, Gu J, et al. Evidence for bone reversal properties of a calcium-collagen chelate, a novel dietary supplement. J. Food & Nutr. Disor. 2013; 2: 1.*

9. *Waynforth HB. Experimental and Surgical Technique in the Rat. Academic Press, New York, NY, 1980.*

10. *Kalu DN, Liu CC, Salerno E, Hollis BW, Echon R, Ray M. Skeletal response of ovariectomized rats to low and high doses of 17/3-estradiol. Bone Miner. 1991; 14: 175-187.*

11. *Taussky HH, Shorr E. A microcolorimetric method for the determination of inorganic phosphorus. J. Biol. Chem. 1953; 202: 675-685.*

12. *Snedecor GW, Cochran WG. Statistical Methods. Iowa State University Press, Ames, IA, 1967.*

13. *Chew V. Comparisons among Treatment Means in an Analysis of Variance. U.S. Department of Agriculture, Hyattsville, MD, 1977.*

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Influence of nutritional status, gender and intensity of physical activity to blood pressure and metabolic parameters in patients with diabetes mellitus type 2

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Abstract

Type 2 diabetes mellitus (DM2) is a worldwide public health problem that increases mortality and affects quality of life. Diabetes self-management education (DSME) is a necessary component of quality care for all people with diabetes. DSME helps patients to develop knowledge, skills and ability necessary for effective self-care. Diabetes mellitus is a lifetime disease. Therefore, its management requires a life-style modification. The epidemic of overweight and obesity is a major driver of the growing prevalence of type 2 diabetes mellitus globally. From 80% to 90% of people with DM2 are overweight or obese, and adiposity worsens the metabolic and physiologic abnormalities associated with type 2 diabetes, weight loss is recommended as the cornerstone management measure.

This study included 100 patients with DM2 who were treated in the Education Center of Family Medicine in the Public Health Center Tuzla. The aim was to analyze the influence of nutritional status, gender and intensity of physical activity on the blood pressure and metabolic parameters in patients with DM2. In order to determine the nutritional status, the National Health and Nutrition Examination Survey (NHANES) was used.

Statistically significant differences were found in intensity of physical activity between patients with healthy eating habits, and those with an unhealthy diet. Of patients who are engaged in physical activity of light intensity, 71.0% had a unhealthy diet. Also, there is statistically significant difference between male and female subjects in nutritional status. Most male patients (88.0%) had a unhealthy diet. Gender and type of diet (healthy or unhealthy) have no influence to metabolic parameters and blood pressure level in patients with DM2. Intensity of physical activity has made a slighty positive correlation with diastolic blood pressure and duration of disease. Gender and diet did not significantly correlate with any observed variables. Intensity of physical activity achieved a slight positive correlation with gender, and also a slight negative correlation with types of therapy. Gender has negative correlation with type of diet. Body weight did not have significant correlation with any observed variables.

Key words: diabetes mellitus type 2, body mass index, nutritional status, intensity of physical activity

Introduction

Diabetes is a complex, chronic illness requiring continuous medical care with multifactorial risk reduction strategies beyond glycemic control (ADA, 2018). Diabetes mellitus, a chronic metabolic disease, is characterized by an increase in the blood-glucose level resulting from a relative insulin deficiency or insulin resistance or both (Thent et al., 2013). Worldwide, an estimated 370 million people have type 2 diabetes mellitus (Bell et al., 2014), with 23.6 million in the United States (Wardian and Sun, 2014) – a number which is estimated to double over the next two decades (Lopez et al., 2014). Type 2 diabetes is commonly comorbid with (Teixeira and Budd, 2010), and often emergent from overweight/obesity (Wilding, 2014; Potter et al., 2015). The incidence of

type 2 diabetes which accounts for more than 90 to 95% of all cases of diabetes mellitus with its attendant economic stress on the health care system has been rising (Eleazu, 2016). Diabetes has become a widespread epidemic, primarily because of the increasing prevalence and incidence of type 2 diabetes (Colberg et al., 2010). Diabetes affects over 29 million Americans and is the sixth leading cause of death. Diabetes is the leading cause of kidney failure, lower-limb amputations, and adult-onset blindness. Diet and exercise therapy have been reported to be effective in improving blood glucose control and are an important part of treatment of type 2 diabetes mellitus (Coughlin et al., 2017). Regarding the management of DM2, researches have highlighted the use of modern medicines, alternative or herbal medicines and exercise management therapy (Thent et al., 2013). The prevalence of DM2 has increased markedly in high-income countries, resulting in high burdens of disease and related disability. The risks of DM2 are particularly high in older people, and as populations are aging, prevention of DM2 in older adults is a key priority (Jefferis et al., 2012). Physical activity is defined as any bodily movement produced by skeletal muscles that results in energy expenditure beyond resting expenditure. Exercise is a subset of physical activity that is planned, structured, repetitive, and purposeful in the sense that improvement or maintenance of physical fitness is the objective. As with pharmacological therapy, for aerobic or resistance exercise therapy it is necessary to prescribe the right dose (intensity, volume, and frequency) and to carefully consider the potential side effects and contraindications (De Feo et Schwaz, 2013). Regular participation in moderate to vigorous intensity physical activity (MVPA) is considered a key strategy in the prevention and management of type 2 diabetes mellitus (Healy et al., 2015). Regular physical activity has been shown to contribute to the prevention and management of over 20 chronic health conditions, including heart disease, stroke, diabetes, cancer, obesity and musculoskeletal conditions as well as mental health problems (Tully and Hunter 2014).

The aim of this study was to analyze influence of nutritional status, gender and intensity of physical activity to blood pressure and metabolic parameters in patients with DM2.

Patients and methods

This study included 100 patients with DM2 aged between 40 and 84 years. There were 25 males and 75 females. Patients with DM2 were divided into several groups. According to the nutritional status, subjects were divided into 2 groups, who have eaten healthy and unhealthy food. A National Health and Nutrition Examination Survey (NHANES) was used to determine nutritional status. According to body weight, three groups of subjects were formed. The first group consisted of 8 subjects with normal body weight, the second group had 31 subjects who were overweight, and third one had 61 subjects with obesity. Based on the intensity of physical activity, 3 basic groups were formed. The first group consisted of 69 patients who were engaged in physical activity of light intensity, the second group of 23 patients who were engaged in physical activity of moderate intensity, and the third group of 8 patients who dealed with vigorous intensity physical activity. In this study we have examined: gender (GE), age (AGE), serum glucose level (GL) in mmol/L, serum cholesterol (CHL) in mmol/L, triglyceride level (TGL) in mmol/L, systolic blood pressure (SBP) in mm Hg, diastolic blood pressure (DBP) in mm Hg, body mass index (BMI), and intensity of physical activity (IPHA). Intensity of physical activity was classified by the International Physical Activity Questionnaire for a person aged between 15 and 69 years, which we use to examine the level of physical activity in their every-day activities. The statistical analyses were performed using Statistical Package for Social Sciences (SPSS version 16.0). For the differences between groups regarding continuous data, paired t-test was used, Chi-squared test and Pearson's test for correlation, if $p \leq 0.05$ difference was considered statistically significant.

Results

Out of the total number of patients with DM2, there were 25 men (25.0%) and 75 women (75.0%). The average BMI for women was 31.51 ± 5.65 kg/m^{2}and for men 29.56 ± 3.83 kg/m^2 (figure 1).

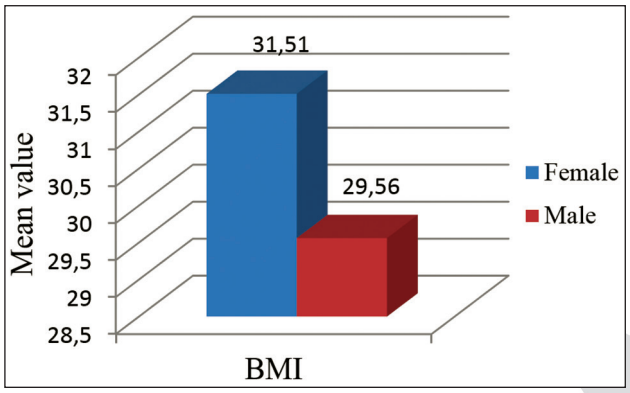

Figure 1. Mean values of body mass index in male and female patients with DM2

Using the t-test, we examined significance of differences in the arithmetic mean of the observed variables between female and male patients with DM2. It was established that there are no statistically significant differences (Table 1).

Results have shown that there was no statistically significant difference among all analyzed parameters in patients with DM2 who have had a healthy or an unhealthy diet (Table 2).

Using Spearman's correlation test, it was found that type of therapy achieved a slight positive correlation with cholesterol, and a slight negative correlation with duration of disease. Intensity of physical activity has made a slight positive correlation with diastolic blood pressure and duration of disease. Gender and diet did not significantly correlate with any of observed variables (Table 3).

It was found that the intensity of physical activity achieved a slight positive correlation with gender, and a slight negative correlation with types of therapy. Gender has a negative correlation with the diet. Body weight did not have a significant correlation with any of observed variables (Table 4).

Table 1. Age, blood pressure, metabolic parameters and duration of DM2 according to gender

Variables	Male		Female		t-test	df	p
	$\bar{x}$	SD	$\bar{x}$	SD			
AGE	66.04	9.46	68.83	8.14	-1.423	98	0.158
BMI	29.56	3.83	31.51	5.65	-1.603	98	0.112
GL	8.56	1.92	8.58	3.29	-0.038	98	0.969
CHL	5.27	1.02	5.29	1.05	-0.105	98	0.917
TGL	2.24	0.98	1.99	0.90	1.120	98	0.266
SBP	129.80	15.71	135.73	17.16	-1.528	98	0.130
DBP	80.00	7.36	82.20	9.52	-1.054	98	0.295
DD	9.92	9.03	10.72	9.02	-0.384	98	0.702

AGE-years; BMI-body mass index; GL-glucose (mmol/L); CHL-cholesterol (mmol/L); TGL-triglycerides (mmol/L); SBP-systolicblood pressure; DBP-diastolic blood pressure; DD-duration of diabetes (years)

Table 2. Age, blood pressure, metabolic parameters and duration of DM2 according to the type of diet

Variables	Healthy diet (N=33)		Unhealthy diet (N=67)		t-test	df	p
	$\bar{x}$	SD	$\bar{x}$	SD			
AGE	68.52	7.52	67.94	9.02	0.316	98	0.753
BMI	31.76	6.11	30.66	4.86	0.976	98	0.331
GL	8.06	2.10	8.83	3.33	-1.203	98	0.232
CHL	5.39	1.14	5.24	0.99	0.700	98	0.486
TGL	2.27	1.22	1.95	0.73	1.605	98	0.112
SBP	133.33	16.85	134.70	17.08	-0.378	98	0.706
DBP	83.03	9.60	80.97	8.76	1.072	98	0.287
DD	10.21	8.58	10.67	9.23	-0.239	98	0.811

AGE-years; BMI-body mass index; GL-glucose (mmol/L); CHL-cholesterol (mmol/L); TGL-triglycerides (mmol/L); SBP-systolicblood pressure; DBP-diastolic blood pressure; DD-duration of diabetes (years)

Table 3. Results of Spearman's correlation analysis among observed variables

Variables		AGE	BMI	GL	SBP	DBP	CHL	TGL	DD
GE	Spearman (rs)	0.111	0.139	-0.064	0.128	0.054	0.037	-0.112	0.040
	psig	0.270	0.168	0.529	0.203	0.592	0.718	0.267	0.692
	N	100	100	100	100	100	100	100	100
TT	Spearman (rs)	-0.011	0.033	0.047	-0.015	0.026	0.215*	0.177	-0.524**
	psig	0.912	0.748	0.641	0.879	0.795	0.031	0.079	0.000
	N	100	100	100	100	100	100	100	100
BW	Spearman (rs)	-0.010	0.864**	0.023	0.159	0.000	0.085	0.164	0.007
	psig	0.918	0.000	0.824	0.113	0.999	0.398	0.102	0.944
	N	100	100	100	100	100	100	100	100
IPHA	Spearman (rs)	0.137	0.035	0.028	0.136	0.224*	-0.075	-0.181	0.268**
	psig	0.173	0.733	0.780	0.176	0.025	0.456	0.072	0.007
	N	100	100	100	100	100	100	100	100
DI	Spearman (rs)	-0.009	-0.078	0.091	0.030	-0.074	-0.084	-0.048	0.032
	psig	0.930	0.441	0.370	0.767	0.466	0.405	0.638	0.754
	N	100	100	100	100	100	100	100	100

** Significance level of 5%*
*** Significance level of 1%*
GE-gender; TT- type of therapy; BW- body weight; IPHA- intensity of physical activity; DI-diet

Table 4. Results of Spearman's correlation analysis among IPHA, GE, BW, TT and DI

Variables		IPHA	GE	BW	TT	DI
IPHA	Spearman (r_s)	1.000	0.208*	0.051	-0.201*	0.079
	p_{sig}		0.037	0.618	0.045	0.437
	N	100	100	100	100	100
GE	Spearman (r_s)	0.208*	1.000	0.114	-0.013	-0.258**
	p_{sig}	0.037		0.258	0.895	0.010
	N	100	100	100	100	100
BW	Spearman (r_s)	0.051	0.114	1.000	-0.032	0.011
	p_{sig}	0.618	0.258		0.752	0.913
	N	100	100	100	100	100
TT	Spearman (r_s)	-0.201*	-0.013	-0.032	1.000	0.037
	p_{sig}	0.045	0.895	0.752		0.716
	N	100	100	100	100	100
DI	Spearman (r_s)	0.079	-0.258**	0.011	0.037	1.000
	p_{sig}	0.437	0.010	0.913	0.716	
	N	100	100	100	100	100

** Significance level of 5%*
*** Significance level of 1%*
GE-gender; TT- type of therapy; BW- body weight; IPHA- intensity of physical activity; DI-diet

Our results have shown there were statistically significant differences in intensity of physical activity between groups with healthy and unhealthy diet (chi-squared=10.20; df = 2; p = 0.006). Namely, among patients who were engaged in physical activity of light intensity, 71.0% of them belong to patients with unhealthy diet.

There were statistically significant differences between male and female patients according to type of diet (chi-squared = 6.65; df = 1; p = 0.010). Majority of male subjects (88.0%) belong to patients with unhealthy diet. There are no statistically significant differences in body weight between male and female patients with DM2 (chi-squared = 1.38; df = 2; p = 0.502).

There are statistically significant differences in the intensity of physical activity between male and female subjects (chi-squared = 11.61; df = 2; p = 0.003). Consequently, most female patients engaged in low-intensity physical activity (73.3%), while 24.0% were engaged in moderate activities and only 2.7% of them engaged in high-intensity physical activity.

Comparing body weight between healthy and unhealthy diet patients, it has been found there are no statistically significant differences (chi-squared = 0.08; df = 2; p = 0.960).

There are no statistically significant differences in the type of therapy they used, among the groups of subjects according to the diet (chi-squared = 0.13; df = 1; p = 0.713).

Discussion

Type 2 diabetes mellitus (T2DM) is a worldwide public health problem that increases mortality and affects quality of life. Diabetes self-management education (DSME) is a necessary component of quality care for all people with diabetes. DSME helps patients to develop knowledge, skills, and ability necessary for effective self-care (Funnell et al., 2007), (Miller, 2014). Diabetes mellitus is a lifetime disease to the patients. Therefore, its management requires a life-style modification. It is estimated that the number of people with T2DM worldwide will increase from 246 million in 2012 to 592 million by 2035 (Wang et al., 2016). Management of diabetes mellitus is generally divided into primary and secondary therapy. The primary therapy includes education, diet, and exercises; while secondary therapy may include oral hypoglycemic drug or insulin, and pancreas implantation (Sinorita et al., 2008). Exercise has been considered one of the three cornerstones in the management of diabetes, the other two being dietary measures and drug therapies. The American Diabetes Association (ADA) now recommends that patients with type 2 diabetes engage in moderate to rigorous aerobic exercise of moderate intensity (50 to 70% of maximal heart rate) for at least 150 minutes spread out over at least three days a week, with no more than two consecutive days between exercise sessions (Park and Lee, 2015). Exercise is an effective therapy for glycemic control and reduction of cardiovascular disease risk in individuals with type 2 diabetes mellitus. Unfortunately, only 29% of patients with diabetes engage in physical activity once a week or less, which is a major clinical and public health concern given the widespread diabetes epidemic and the well-known benefits of exercise (Nam et al., 2012). Although physical activity (PA) is a key element in the prevention and management of type 2 diabetes, many with this chronic disease do not become or remain regularly active. High-quality studies establishing the importance of exercise and fitness in diabetes were lacking until recently, but it is now well established that participation in regular PA improves blood glucose control and can prevent or delay type 2 diabetes, along with positively affecting lipids, blood pressure, cardiovascular events, mortality, and quality of life. Structured interventions combining PA and modest weight loss have been shown to lower type 2 diabetes risk by up to 58% in high-risk populations. Most benefits of PA on diabetes management are realized through acute and chronic improvements in insulin action, accomplished with both aerobic and resistance training. The benefits of physical training are discussed, along with recommendations for varying activities, PA-associated blood glucose management, diabetes prevention, gestational diabetes mellitus, and safe and effective practices for PA with diabetes-related complications (Colberg et al., 2010). He et all (2016) found in their study that almost all the patients spent the majority of their daily time sitting and sleeping. Just 30,64% of the patients spent more than 150 min/week on moderate to vigorous physical activity, and 60,46% of the patients did not take any activity of this intensity during the whole week. The mean BMI level of the male patients was 24.32 – 3.53 kg/ m², and 22.94 – 3.73 kg/m² for female patients. In our study, the mean BMI level of the female patients was 31.51 ± 5.65 kg/m^2 and 29.56 ± 3.83 kg/m^2 for male patients. In 2013, the American Diabetes Association released new nutritional guidelines. The guidelines calls for all adults diagnosed with diabetes to eat a variety of nutrient-dense foods in appropriate portion sizes as part of an eating plan that takes into account individual preferences, culture, religious beliefs, traditions and metabolic goals. A new section was included on eating patterns, e.g.,

Mediterranean, vegetarian, or lower-carbohydrate eating plan. In choosing an appropriate eating plan, people with diabetes should consider individual metabolic goals such as their glucose, lipid levels, and blood pressure (Coughlin et al., 2017).

Logue et all (2011) found in their study that men are diagnosed with type 2 diabetes at lower BMI than women across the age range. The mean BMI level of the male patients was 31,83 kg/ m², and 33,69 kg/m² for female patients. This observation may help explain why type 2 diabetes is more common among middle-aged men in populations of European extraction. Medication in conjunction with exercise improves glycemic control beyond that achieved by medication alone (Boulé et al., 2001; Castaneda et al., 2002; Dunstan et al., 2002). Moreover, an intensive lifestyle intervention consisting of exercise and diet has been shown to induce a partial remission of type 2 diabetes among overweight adults (Gregg EW et al., 2012). Even without weight loss, exercise has been shown to effectively lower blood glucose, cholesterol, and blood pressure (Marwick et al., 2009; Sigal et al., 2006). Future research should examine factors that can promote greater uptake of exercise and other lifestyle modifications among individuals with diabetes (Leung et al., 2014). Diabetes is considered '*the epidemic of the 21st century'*, affecting nearly 12% of US adults. Obesity is another important public health problem in the US, as two in three adults are classified as overweight or obese (body mass index [BMI] ≥ 25 kg/m2) and one-third are frankly obese (BMI ≥ 30 kg/m2).2 Among patients with diabetes in the US, approximately 45–65% of them are obese (Li et al., 2015). Many researches have shown that exercise plays a crucial role in improving T2DM. Exercise not only improves the glycemic control, but it can also improve the insulin sensitivity and restore the diabetic associated complication such as cardiovascular damage, which considered as one of the major complications (Thent et al., 2013). It has long been established that exercise is powerful medicine for those with type 2 diabetes mellitus, such that it should represent a priority in the treatment and management of that condition. Published guidelines for aerobic exercise in those with type 2 diabetes mellitus recommend only moderate intensity, due to the elevated risk of untoward outcomes with more vigorous exercise ina persons with chronic disease (Buresh and Berg, 2017). Sedentary behavior has been considered an independent risk factor for type-2 diabetes (T2D), with a negative impact on several physiological outcomes, whereas breaks in sedentary time (BST) have been proposed as a viable solution to mitigate some of these effects. However, little is known about the independent associations of sedentary pursuits, physical activity, and cardiorespiratory fitness (CRF) variables with glycemic control. The results from the study Sardinha et al. (2017) suggest that sedentary time and patterns are relevant for the glycemic control in patients with T2DM. Aerobic exercise has been known to improve glycosylated haemoglobin (HbA1c) levels and insulin sensitivity in patients with type 2 diabetes mellitus (T2DM). The present study was undertaken to evaluate the effect of eight week moderate-intensity aerobic (heart rate reserve 40-60%) exercise on glycaemic control in elderly patients with T2DM and diabetic peripheral neuropathy (DPN). The participants (n=87) were randomly assigned to an eight-week programme by a computer-generated random number table to the study or control group, respectively. There were 47 participants in the control group and 40 participants in the study group after randomization. There was a significant difference in the mean values of glycated hemoglobin (HbA1c) at baseline and 8th week between the two groups. Moderate-intensity aerobic exercise of eight weeks duration helped in achieving enhanced glycaemic control in the T2DM patients with DPN (Dixit et al., 2017). Although regular physical activity (PA) is a cornerstone of treatment for type 2 diabetes (T2D), most adults with T2D are sedentary. Randomized controlled trials (RCTs) have proven the effectiveness of PA behavioral interventions for adults with T2D but have rarely been conducted in healthcare settings (Luoma et al., 2017). Inadequate physical activity accompanied by poor dietary habits is associated with the development of obesity and type 2 diabetes mellitus. Adoption of a friendly diet and adoption of moderate physical activity are essential not only for the prevention and treatment of diabetes mellitus but also in maintaining physical and mental health.

Physical activity of 30 minutes five times a week, and the interruption of prolonged sitting with short bouts of physical activity every 30 minutes

is strongly advised (Al-Mountashiri et al., 2017). Physical activity includes all movement that increases energy use, whereas exercise is planned, structured physical activity. Exercise improves blood glucose control in type 2 diabetes, reduces cardiovascular risk factors, contributes to weight loss, and improves well-being. Regular exercise may prevent or delay type 2 diabetes development. Aerobic exercise involves repeated and continuous movement of large muscle groups. Activities such as walking, cycling, jogging, and swimming rely primarily on aerobic energy-producing systems. Resistance (strength) training includes exercises with free weights, weight machines, body weight, or elastic resistance bands. Flexibility exercises improve range of motion around joints. Balance exercises benefit gait and prevent falls. Activities like tai chi and yoga combine flexibility, balance, and resistance activities (Colberg et al., 2016). In middle age, physical activity (PA) provides important protection against the onset of type 2 diabetes; a recent meta-analysis reported that even moderate-intensity leisure-time activity or brisk walking reduced diabetes incidence by 30% . However, the levels of PA required to protect against the onset of diabetes in older people (many of whom have low fitness levels or functional limitations) are much less established. The protection provided by PA may be stronger in older (60 years) than younger adults; large intervention trials conducted in high-risk population groups, which compare medication with lifestyle changes, reported greater relative and absolute benefits from lifestyle changes in the older than in the younger age-groups. Yet, to date, few epidemiologic studies have examined associations between PA in later life and diabetes onset, but evidence suggests that even occasional activity in older adults compared with sedentariness is associated with 50% lower diabetes risks and also 28% lower total mortality risks (Jefferis et al., 2012). A low level of physical activity (PA) is associated with increased prevalence of T2DM and the metabolic syndrome. Conversely, in patients with T2DM, a moderate-high level of PA was associated with reduced total and cardiovascular mortality, and a lifestyle intervention to achieve and maintain weight loss through decreased caloric intake and increased PA improved glycemic control and cardiovascular risk factors. However, evidence of efficacy of supervised exercise intervention on modifiable cardiovascular risk factors in patients with T2DM is mainly derived from small-sized studies, and it is unclear which volume of exercise or PA is required to reduce cardiovascular burden and which is the best strategy for promoting PA in these high-risk individuals (Balducci et al., 2010). Structured exercise training that consists of aerobic exercise, resistance training, or both combined is associated with HbA1c reduction in patients with type 2 diabetes. Structured exercise training of more than 150 minutes per week is associated with greater HbA1c declines than that of 150 minutes or less per week. Physical activity advice is associated with lower HbA1c, but only when combined with dietary advice (Umpierre et al., 2011). Results from the population based diabetes cohort of over 95 000 people confirms an inverse association between BMI and age at diagnosis of type 2 diabetes, substantially extending a previous report based on data for 2437 adults. Logue et al 2011. show that this relationship varies by sex, so that at most ages men have lower BMI around the time of diagnosis of diabetes than women, though the sex differential decreases with age. In summary, they confirm an inverse relationship between age and BMI at diagnosis of diabetes, but importantly extend existing knowledge to show that men across the age spectrum are diagnosed with diabetes at a lower BMI than women. This novel observation could explain the higher male prevalence of type 2 diabetes in populations of European extraction. Any increase in physical activity is to be encouraged and positively reinforced in T2DM. Sustained increase in physical activity through walking with pedometer has also been shown to improve glucose control, metabolic control and cardiovascular fitness independently.

Physical activity must also be targeted according to the need of individuals with appropriate guidance and support (Guglani et al., 2014). Summarizing the evidence from reports relating to exercise recommendations, it appears that the most important factor is to design a program for individuals that will provide the proper amount of exercise to attain maximal benefit at the lowest risk (Zanuso et al., 2010). Several studies have shown preventive effects of physical activity in individuals with impaired glucose tolerance and physical activity in persons with type 2 diabetes clearly lowers the risk of cardiovascular disease and premature death (Rossen et al.,

2015). Physical activity (PA) is the cornerstone of lifestyle modification aimed at preventing and managing Type 2 diabetes and its related morbidities. PA has been shown to improve glycemic control through increased insulin sensitivity and glucose tolerance. Despite evidence of the benefits of exercise, the majority of people with Type 2 diabetes are physically inactive (Hui et al., 2014). Despite the established benefits, many type 2 diabetes patients do not participate in regular physical activity (Dyck et al., 2011). Health Benefits of Aerobic and Resistance Training in individuals with type 2 Diabetes (HART-D; n = 262) was a 9-month exercise study comparing the effects of aerobic training, resistance training, or a combination of resistance and aerobic training versus a nonexercise control group on hemoglobin A1c (HbA1c) in sedentary individuals with type 2 diabetes. In conclusion, the current study provides evidence that adults with type 2 diabetes mellitus are likely to benefit from adopting an exercise training regimen regardless of exercise training modality (aerobic, resistance, or a combination of both) (Myers et al., 2013). Aerobic exercise alone or combined with RT improves glycemic control, SBP, triglycerides, and waist circumference (Chudyk and Petrella, 2011). Individuals with type 2 diabetes are at increased risk of developing cardiovascular disease (CVD) and have poorer survival rates after diagnosis of CVD in comparison with those without diabetes. Although physical inactivity is an important and well-established cardiometabolic risk factor, individuals with diabetes are less likely to meet current physical activity guidelines compared with the general adult population. Encouraging people to increase their physical activity and decrease their sedentary time may have beneficial effects on their waist circumference, blood pressure and CCMR (clustered cardiometabolic risk) (Lamb et al., 2016). Aerobic exercise is more common in clinical practice compared to resistance exercise in managing T2DM. Treatment of T2DM with exercise training showed promising role in USA. A large number of researches are mandatory in the developing countries for incorporating exercise in the effective management of T2DM (Thent et al., 2013). Regular exercise (with or without caloric restriction) has been increasingly viewed as an effective therapeutic strategy for the management of T2DM (De Lemos et al., 2012).

References

1. *American Diabetes Association. Standards of medical care in diabetes Diabetes Care, 2018; Volume 41, Supplement 1.*
2. *Al-Mountashiri NA, AL-Zhrani AM, Ibrahim SFH, Mirghani HO. Dietary habits, physical activity and diabetes perception among patients with type 2 diabetes mellitus in Tabuk City, Saudi Arabia. 2017; 9(9): Pages 5179-5184.*
3. *Balducci S, Zanuso S, Nicolucci A, De Feo P, Cavallo S, Cardelli P, et al. Effect of an Intensive Exercise Intervention Strategy on Modifiable Cardiovascular Risk Factors in Subjects With Type 2 Diabetes Mellitus. A Randomized Controlled Trial: The Italian Diabetes and Exercise Study (IDES). Arch Intern Med. 2010; 170(20): 1794-1803.*
4. *Buresh R, Berg K. Exercise for the management of Type 2 Diabetes Mellitus. Factors to consider with current guidelines. J Sport Med Phys Fitness, 2017; doi: 10.23736/S0022-4707.17.06969-9. [Epub ahead of print] PubMed PMID: 28462566.*
5. *Chudyk A, Petrella RJ. Effects of Exercise on Cardiovascular Risk Factors in Type 2 Diabetes. Diabetes Care, 2011; 34: 1228–1237.*
6. *Colberg SR, Sigal RJ, Fernhall B, Regensteiner JG, Blissmer BJ, Rubin RR, et al. Exercise and Type 2 Diabetes. Diabetes Care, 2010; 33(12): e147-e167.*
7. *Colberg SR, Ronald J. Sigal RJ, Yardley JE, Michael C. Riddell MC, et al. Physical Activity/Exercise and Diabetes: A Position Statement of the American Diabetes Association. Diabetes Care, 2016; 39: 2065–2079 | DOI: 10.2337/dc16-1728.*
8. *Coughlin SS, Hatzigeorgiou C, Anglin J, Xie D, Besenyi1 GM, De Leo G, et al. Healthy lifestyle intervention for adult clinic patients with type 2 diabetes mellitus. Diabetes Manag (Lond). 2017; 7(2): 197–204.*
9. *De Feo P, Schwarz P. Is Physical Exercise a Core Therapeutical Element for Most Patients With Type 2 Diabetes? Diabetes Care, 2013; Volume 36, Supplement 2: S149-S154.*
10. *De Lemos ET, Oliveira J, Pinheiro JP, Reis F. Regular Physical Exercise as a Strategy to Improve Antioxidant and Anti Inflammatory Status: Benefits in Type 2 Diabetes Mellitus. Hindawi Publishing Corporation, Oxidative Medicine and Cellular Longevity, Volume 2012, Article ID 741545, 15 pages doi:10.1155/2012/741545.*

11. *Dixit S, Maiya A, Shastry BA. Effect of moderate-intensity aerobic exercise on glycosylated haemoglobin among elderly patients with type 2 diabetes & peripheral neuropathy. Indian J Med Res. 2017; 145(1): 129-132. doi: 10.4103/ijmr.IJMR_699_14. PubMed PMID: 28574026; PubMed Central PMCID: PMC5460559.*

12. *Dyck DV, De Greef K, Deforche B, Ruige J, Tudor-Locke CE, Kaufman J-M, et al. Mediators of physical activity change in a behavioral modification program for type 2 diabetes patients. International Journal of Behavioral Nutrition and Physical Activity, 2011; 8: 105 http://www.ijbnpa.org/content/8/1/105.*

13. *Eleazu OC. The concept of low glycemic index and glycemic load foods as panacea for type 2 diabetes mellitus; prospects, challenges and solutions. African Health Sciences, 2016; 16(2).*

14. *Guglani R, Shenoy S, Sandhu JS. Role of Pedometer Based Walking in the Management of Type 2 Diabetes: A Review. International Journal of Science and Research (IJSR) ISSN (Online): 2319-7064. 2014; 3(3).*

15. *He X, Pan J, Pan M, Wang J, Dong J, Yuan H, et al. Dietary and physical activity of adult patients with type 2 diabetes in Zhejiang province of eastern China: Data from a cross-sectional study. Journal of Diabetes Investigation Open access, 2016; 7(4): 529-538.*

16. *Healy GN, Winkler EAH, Brakenridge CL, Reeves MM, Eakin EG. Accelerometer-Derived Sedentary and Physical Activity Time in Overweight/Obese Adults with Type 2 Diabetes: Cross-Sectional Associations with Cardiometabolic Biomarkers. PLOS ONE, 2015; | DOI:10.1371/journal.pone.0119140.*

17. *Hui SS-C, Hui GP-S, Xie YJ. Association between Physical Activity Knowledge and Levels of Physical Activity in Chinese Adults with Type 2 Diabetes. PloS ONE, 2014; 9(12): e115098. doi:10.1371/journal.pone.0115098.*

18. *Jefferis BJ, Whincup PH, Lennon L, Wannamethee SG. Longitudinal Associations Between Changes in Physical Activity and Onset of Type 2 Diabetes in Older British Men. Diabetes Care, 2012; 35: 1876–1883.*

19. *Lamb MJE, Westgate K, Brage S, Ekelund U, Long GH, Griffin SJ, et al. Prospective associations between sedentary time, physical activity, fitness and cardiometabolic risk factors in people with type 2 diabetes. Diabetologia, 2016; 59: 110–120, DOI 10.1007/s00125-015-3756-8.*

20. *Lau DC, Teoh H. Benefits of modest weight loss on the management of type 2 diabetes mellitus. Can J Diabetes. Apr; 2013; 37(2): 128-34. doi: 10.1016/j.jcjd.2013.03.023. Epub 2013 Apr 23. Review. PubMed PMID: 24070804.*

21. *Leung LA, Swaminathan S, Trivedi AN. Diabetes diagnosis and exercise initiation among older Americans. Prev Med. 2014; 65: 128–132. doi:10.1016/j.ypmed.2014.05.001.*

22. *Li W, Katzmarzyk PT, Horswell R, Zhang Y, Zhao W, Wang Y, et al. Body mass index and stroke risk among patients with type 2 diabetes. Stroke. 2015; 46 (1): 164–169. doi:10.1161/STROKEAHA.114.006718.*

23. *Logue J, Walker JJ, Colhoun H, Leese GP, Lindsay RS, McKnight JA, et al. Do men develop type 2 diabetes at lower body mass indices than women? Diabetologia. 2011; 54(12): 3003–3006. doi:10.1007/s00125-011-2313-3.*

24. *Luoma KA, Leavitt IM, Marrs JC, Nederveld AL, Regensteiner JG, Dunn AL, et al. How can clinical practices pragmatically increase physical activity for patients with type 2 diabetes? A systematic review. Transl Behav Med. 2017; doi: 10.1007/s13142-017-0502-4. [Epub ahead of print] Review. PubMed PMID: 28589531.*

25. *Miller K, C, Kristeller L, J, Headings A, Nagaraja H. Comparison of a Mindful Eating Intervention to a Diabetes Self-Management Intervention Among Adults With Type 2 Diabetes: A Randomized Controlled Trial. Health Educ Behav. 2014; 41(2): 145–154. doi:10.1177/1090198113493092.*

26. *Myers VH, Mcvay MA, Brashear MM, Johannsen NM, Swift DI, Kramer K, et al. Exercise Training and Quality of Life in Individuals With Type 2 Diabetes. Diabetes Care, 2013; 36: 1884–1890.*

27. *Nam S, Dobrosielski DA, Stewart KJ. Predictors of exercise intervention dropout in sedentary individuals with type 2 diabetes. J Cardiopulm Rehabil Prev. 2012; 32(6): 370-378.*

28. *Park H-J, Eun Lee Y. Effects of exercise on glycemic control in type 2 diabetes mellitus in Koreans: the fifth Korea National Health and Nutrition Examination Survey (KNHANES V). J. Phys. Ther. Sci. 2015; 27: 3559–3564.*

29. *Potter L, Wallston K, Trief P, Ulbrecht J, Juth V, Smyth J. Attributing discrimination to weight: Associations with well-being, self-care, and disease status in patients with type 2 diabetes mellitus. J Behav Med. 2015; 38(6): 863–875. doi:10.1007/s10865-015-9655-0.*

30. *Rossen J, Yngve A, Hagströmer M, Brismar K, Ainsworth BE, Iskull C, et al. Physical activity pro-*

motion in the primary care setting in pre- and type 2 diabetes – the Sophia step study, an RCT. BMC Public Health, 2015; 15: 647, DOI 10.1186/s12889-015-1941-9.

31. *Sardinha LB, Magalhaes JP, Santos DA, Judice PB. Sedentary Patterns, Physical Activity, and Cardiorespiratory Fitness in Association to Glycemic Control in Type 2 Diabetes Patients. Front Physiol. 2017; 28(8): 262. doi: 10.3389/fphys.2017.00262. eCollection 2017. PubMed PMID: 28503154; PubMed Central PMCID: PMC5409266.*

32. *Sinorita H, Saádah, Jazakillah S. Effects of Dietary Pattern and Education on Glycemic Control in Patients with Type 2 Diabetes Mellitus at Dr. Sardjito Central General Hospital, Yogyakarta. Acta Med Indones-Indones J Intern Med, 2008; Vol. 40: Num. 2.*

33. *Thent ZC, Das S, Henry LJ. Role of Exercise in the Management of Diabetes Mellitus: the Global Scenario. PloS ONE, 2013; 8(11): e80436. doi:10.1371/ journal.pone.0080436.*

34. *Tully M, Hunter R. The importance of doing regular physical activity to health, society and the economy: Time for a major re-think. POLICY BRIEFING. UKCRC Centre of Excellence for Public Health (NI), Centre for Public Health, Queen's University Belfast, 2014.*

35. *Umpierre D, Ribeiro PAB, Kramer CK, Leita˜o CB, Zucatti ATN, Azevedo MJ, et al. Physical Activity Advice Only or Structured Exercise Training and Association With HbA1c Levels in Type 2 Diabetes. A Systematic Review and Meta-analysis. JAMA. 2011; 305(17): 1790-1799.*

36. *Wang S, Ma W, Yuan Z, Wang S, Yi X, Jia H, et al. Association between obesity indices and type 2 diabetes mellitus among middle-aged and elderly people in Jinan, China: a cross-sectional studyB-MJ Open 2016; 6: e012742. doi:10.1136/ bmjopen-2016-012742.*

37. *Zanuso S, Jimenez A, Pugliese G, Corigliano G, Balducci S. Exercise for the management of type 2 diabetes: a review of the evidence. Acta Diabetol, 2010; 47: 15–22, DOI 10.1007/s00592-009-0126-3.*

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Role of Sensory Integration Therapy in Sensory Processing Disorder in Children with Autism Spectrum Disorder (ASD)
Sensory Integration and Autism Spectrum Disorder in South Africa (Concise and Informative Article Title)

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Abstract

Treatment of autism is still poorly understood. The condition is typically characterized by developmental disruptions in social-emotional behavior and communication. Sensory integration can be used to improve difficulties in coping with everyday activities in children with autism spectrum disorder. The study explored the role of a sensory integration intervention program, using the Sensory Disorder checklist, in children with autism spectrum disorder and to determine the timeframe within which the effects of such an intervention could be observed.

The study was conducted at a special needs center in Northern KwaZulu-Natal, South Africa. Twelve children, aged 2 to 7 years were purposively sampled. A pre-test, post-test design was used to assess signs of sensory integration dysfunction in children over a 4-week period. Movement sensitivity was found to significantly improve from pre- to post-test ($p = 0.010$), while no significant changes were observed for tactile sensitivity, taste/smell sensitivity ($p = 0.9$), unresponsive sensations ($p = 0.9$), auditory filtering ($p = 0.9$) and visual/auditory sensitivity ($p = 0.9$). A strong, positive correlation was observed between behavior, mood and cognition, and movement ($R = .761$). A 4-week sensory integration intervention program can positively influence movement sensitivity, which assists with mood control, cognition and overall behavior in children with autism spectrum disorder to improve the quality of caregiving and children's' performance of daily activities.

Key words: Autism Spectrum Disorder, Movement, Interventions, Sensory Integration

- At the start of the study it was unclear how Sensory Integration would change and influence children diagnosed with Autism Spectrum Disorder and the factors that might contribute to or influence these changes.
- It is now understood that with the help of an Occupational Therapist, sensory integration can positively influence movement in children diagnosed with Autism Spectrum Disorder.
- Even though the intervention program only covered a period of 4 weeks, movement was one of the areas that showed improvement.

Introduction

Autism is associated with developmental interruption in social-emotional behavior and communication (Szatmari, 2000; American Psychiatric Association, 2000; Tyfron, Foster, Ouimet, Doyle-Thomas, Anagnostu, Sharda & Hyde, 2017) and African children with ASD are vulnerable to, and at risk of health issues (Zhang, Mason, Boys, Sikich & Banarek, 2016; Iannuzzi, Cheng, Broder-Fingert & Bauman, 2015). Autism was first listed as a disability with the passing of the Disabilities Education Act which was introduced in October, 1990 in the United States of America (Auxter, Pyfer & Heuttig, 2005; Roth, Zittel, Pyfer & Auxter, 2016). Numerous studies have documented that, across the spectrum of disability, individuals with

autism spectrum disorder (ASD) display poor social and affective relatedness, and difficulty in developing and maintaining social relationships (Fox & Riddoch, 2000; Banarek, 2002; Bundy, Lane, Murray & Fisher, 2002; American Psychiatric Association, 2000). Characteristics such as the absence of speech or an idiosyncratic way of speaking that is not part of an ideal conversation, fascination with objects, and a nervous obsessive desire for preserving the same familiar routine every day (Ben-Sasson, Hen, Fluss, Cermak, Engel-Yeger & Gal, 2009; Zimmer, Desch, Rosen & Bailey, 2012; Baio, Wiggins, Christensen, Maenner, Daniels, Warran, et al, 2018), evidence of high intelligence or skills in performing specific tasks are also some of the signs and symptoms of autism (American Psychiatric Association, 2013; Bodfish, Symons, Parker & Lewis, 2000; Leekam, Nieto, Libby, Wing & Gould, 2007).

Sensory integration (SI) is the way in which the mind stores and processes the information that is sent through to the brain during physical activity (Johnson-Ecker & Parham, 2000; Zimmer, Desch, Rosen & Bailey, 2012). Sensory, in this context, is related to sensation or to the physical senses like smell, hearing, touch, taste and vision (Johnson-Ecker & Parham, 2000; De Jager & Condy, 2011; Baio, Wiggins, Christensen, Maenner, Daniels, Warran, et al, 2018; American Psychiatric Association, 2013). Implementing SI therapy is not something new in the world of practical therapeutic methods (Lang, O'Reily, Healy, Rispoli, Lydon, Streusand, et al, 2012). Some of the earliest, as well as some of the later theories (Kashefimehr, Kayihan & Huri, 2018; Huebner & Dunn W, 2001; Iarocci & McDonald, 2006; 36; Lane & Schaaf, 2010) on autism are based on the premise that children diagnosed with the condition process sensory information differently from non-autistic children (Brock, Brown & Boucher, 2002; Just, Cherkassky, Kellar & Minshaw, 2004). Sensory integration dysfunction is relatively common among children with ASD (Banarek, Parham & Bodfish, 2005; Yunus, Lui, Bisset & Penkala, 2015; Kashefimehr, Kayihan & Huri, 2018).

Sensory integration (SI) can also be the organizing of sensory information for usage, which could come from the perception of the body and or of the surrounding world (Zimmer, Desch, Rosen & Bailey, 2012; Pfeiffer, Koenig, Kinnealey, Sheppard & Henderson, 2011; Smith, Press, Koenig & Kinnealey, 2005). Children with ASD often show different reactions in adaptable responses to sensations and specific stimuli. They may use self-stimulation to compensate for limited sensory input or to avoid overstimulation (Roger, Hepburn & Wehner, 2003; Schaaf & Nightlinger, 2007 Smith, Press, Koenig & Kinnealey, 2005, Lang, O'Reily, Healy, Rispoli, Lydon & Streusand, et al, 2012). Studies have shown that for effective perceptual-motor and cognitive functioning, sensory input stimuli must be organized so that functioning can be developed by the central nervous system (Miller & Lanne, 2000, Miller & Ozonoff, 2000). From previous research it is known that autism is caused by either abnormal brain structure, abnormal organization within the central nervous system or both (Schriber, 2012). One can use sensory integration such as physical activities and games to improve behavior, cognition and mood in children with ASD (Zimmer, Desch, Rosen & Bailey, 2012). Many educators and occupational therapists are using SI therapies daily as part of their therapeutic plan to improve behavior, cognition, and mood and have witnessed changes in the children who took part in class activities such as dance, music, and drama, as well as obstacle courses. Some children struggle to adapt to the specific tests on SI, leading the child to feel overwhelmed (Koomar, Kranowitz, Szklut, Balzer-Martin, Haber & Sava, 2001). Younger children benefit more from SI interventions because their nervous systems are developing quickly and they respond better to therapeutic interventions (Koomar, Kranowitz, Szklut, Balzer-Martin, Haber & Sava, 2001).

Although therapists and educators have tried to apply SI therapy in treating children with autism (Pfeiffer, Koenig, Kinnealey, Sheppard & Henderson, 2011; Fazilioglu & Baran, 2008), the gains have not been scientifically researched or are not yet conclusive (Sniezyk, Zane & Carolyn, 2015; Case-Smith & Abresman, 2008; Watling & Rietz, 2007), necessitating the need for further research. This is especially prudent given SI's wide use (Dawson & Watling, 2000; Banarek, David, Poe, Stone & Watson, 2006; Auxter & Pyfer & Heuttig, 2005).

Despite the vast amount of research conducted in recent years on the spectrum of autistic disorders, the condition remains poorly understood in

some respects (Bateman, 2013). The considerable behavioral and developmental heterogeneity, even among those individuals who fully meet the diagnostic criteria for autism, makes the search for causes and treatments extremely complex. It is therefore imperative to develop a test protocol, as well as to determine how SI may affect behavior, cognition and mood in children with ASD, and to investigate how and whether interventions lead to effective changes, in what respects there can be improvements, and whether the conditions they modify are chronic or acute. The purpose of the present study reported here, was to determine whether there would be a change in the behavior, specifically cognition, and mood in children with ASD following the application of a SI intervention, and to determine to what extent SI therapy can make a difference in the short term.

Methodology

Study design and Populations

This study was quantitative in nature, following a quasi-experimental design using a questionnaire to collect and record data. The main focus was to evaluate the effects of a 4-week sensory integration intervention program on mood, behavior and cognition in children with autism.

Twelve children of various ethnic groups between the ages of 2 and 7 years (Roth, Zittel, Pyfer & Auxter, 2016; Kashefimehr, Kayihan & Huri, 2018) were recruited for this study. The children attend a special center for autism in a town in the KwaZulu-Natal province, South Africa. Only 12 participants were sampled since autism diagnosis rates are low in South Africa (Bateman, 2013), and also specifically in the KwaZulu-Natal (Bateman, 2013) and also due to the general fear of participation in research by parents and guardians. Accurate national statistics on ASD in South Africa are hard to come by and there are only 9 specialized schools in South Africa, yet there are an estimated 135 000 children with ASD not getting specialized interventions/education (Bateman, 2013). These low levels of diagnosed Autism are possibly due to the continued cultural stigma associated with having a child with Autism and the lack of health professionals to diagnose and/or care for children with ASD (De Vries, 2016, Bateman, 2013).

Informed consent was obtained from parents or guardians of children before the study commenced. To enhance familiarity, the researchers spent one-week prior to the intervention in the participants' surroundings. Thereafter, the participants were evaluated on tactile and vestibular, proprioceptive and auditory, oral and olfactory, visual, auditory-language processing dysfunction, social and emotional play and self-regulation dysfunction by their tutor. Their parent/guardian was required to complete the SPD checklist and Short Sensory Profile (SSP) questionnaire by the tutors (Dunn, 1999) at the pre- and 4-week post-test. The SPD Checklist covers the characteristics associated with autism, since birth to the present (DUNN, 1999). The participants were assigned a code at pre-test in lieu of identification information to limit bias throughout the study.

Data collection, measurement validity and reliability

The SPP is a 38-item questionnaire. Initial studies done by McIntosh et al (1999); Tomcheck & Dunn (2007) and Miller et al (2001) on the validity of the SSP have demonstrated a discriminate validity of more than 95% in identifying children with and without sensory modulation difficulties. Together, these findings provide initial support for the use of the SSP as a valid measure of sensory processing in children with autism. Tutors were required to use the questionnaire to assess their participants' typical responses to tactile, vestibular, auditory and visual stimuli on a five-point Likert scale ranging from "never" to "always" in response to each individual stimulus (Baker, Lane, Angley & Young, 2008; Dunn, Myles & Orr, 2002; Dunn1999). It took approximately 10 minutes to complete.

The 4-week intervention program consisted of four lesson plans outlined in Table 1. Week one tested tactile and vestibular sense. Tactile senses that included input from the skin receptors about touch, pressure, temperature, pain, and movement of the hairs on the skin. Vestibular sense that includes input form the inner ear about the equilibrium, gravitational changes, movement experiences, and position in space. The second week proprioceptive and auditory senses was tested. Proprioceptive sense includes input form the muscles and joints about the bodies position, weight, pressure, stretch, movement, and changes in position in space. The

third week included oral (hypersensitivity to oral input) and olfactory dysfunction (hypersensitivity to smells). Week four included visual input dysfunction (hypersensitivity to visual input) and auditory-language processing dysfunction and social, and emotional paly and self-regulation dysfunction.

Table 1. 4-Week Sensory Intervention Program followed by the Tutors and the Occupational Therapist

Week Area of Sensory Integration Intervention
Week 1 Lesson 1: Tactile and vestibular senses
Week 2 Lesson 2: Proprioceptive and auditory senses
Week 3 Lesson 3: Oral and olfactory dysfunction
Week 4 Lesson 4: Visual dysfunction, auditory-language processing dysfunction and social, emotional play and self-regulation dysfunction

Data management and statistical analysis

Data was analyzed using commercial software (Statistical Package for Social Sciences (SPSS) Version 20, Chicago, IL). Pre- and post-test comparisons were performed using paired t-tests. Alpha levels were set at $p \leq 0.05$ for establishing statistical significance.

The data collected in this study were interpreted using a Pearson's chi-squared test at $\alpha = 0.05$ and log linear analysis.

Results

In Table 2 the results are summarized and it indicates that movement sensitivity was found to be significantly different from pre- to post-test ($p = 0.010$), (see Pair 3).

Discussion

This study found that a 4-week sensory integration intervention program can positively influence movement sensitivity in children with ASD aged 2 to 7 years, which is the most crucial age group for whom the practice of sensory integration is essential for development (Zwaigenbaum, Bauman, Stone, Yirmiya, Estes & Hansen, et al, 2015). This is, as it is important to practice sensory integration as early as possible in a child with ASD to ensure optimum outcomes Samouildou & Valakova, 2006).

Previous studies reported that the behavior of children with ASD suggests that they experience difficulty with sensory integration (Bettison, 1994, Myles & Simpson, 1998; Myles & Southwick, 1999; Stagnitti, Raison & Ryan, 1999; Fling, 2000; Igwanaga, Kawasaki & Tsuchida, 2000; Attwood, 2006). Other researchers noted a link between sensory processing and the ability to cope successfully with daily life (Fisher, Murray & Bundy, 1991; Dunn, 1997; Cook & Dunn, 1998; Dunn, 1999).

Throughout the 4-week period, little or no changes were found in most of the areas that were evaluated using the SSP (Dunn, 2002; Dunn, 1999). Only movement was found to be significantly different as a result of the intervention. This could be since other actions (touch, taste/smell, sensation seeking, auditory filtering, energy usages, and visual processing) are mainly practiced in a controlled timeframe (O'Neil & Jones, 1997; Gabriels, Cuccaro, Hill, Ivers & Goldson, 2005). Movement, however, is an inherent, continuous process, where the child is physically active whether in the classroom or at home. Movement

Table 2. Pre-test and post-test results

Variable	Pre-test	Post-test	Significance
Tactile sensitivity	4.26±0.56	4.38±0.57	0.438
Taste and smell	3.56±1.33	3.70±1.19	0.461
Movement	4.33±0.89	3.58±1.46	0.010
Under responsive	3.24±0.89	3.46±0.81	0.443
Auditory	3.46±0.96	3.58±0.91	0.673
Low energy	4.33±0.65	3.90±0.83	0.293
Visual	4.12±0.56	3.82±1.09	0.250
Combination of Pre-and Post-test	3.82±0.55	3.78±0.77	0.786

Values are means ± standard deviation

**: Indicates $p \leq 0.05$ compared to pretest*

Pair 1: Tactile sensitivity; Pair 2: Taste and smell; Pair 3: Movement; Pair 4: Under responsive; Pair 5: Auditory; Pair 6: Low energy; Pair 7: Visual; Pair 8: Combination of Pre and Post-test.

is a part of everyday living and although sensory integration of movement is practiced once a day or sometimes more frequently (as in movement exercise) (Khodabakhshi, Abedi & Malekpour, 2014; Tomcheck & Dunn, 2007), it is still an action that is performed naturally all day long without deliberation, whether jumping, running, walking, or climbing steps. Movement of some kind occupies most of everyday living while awake and is therefore applied more than the other areas of a child's sensory processes such as stacking building blocks or sorting colors and shapes (Khodabakhshi, Abedi & Malekpour, 2014).

Further, movement could also have been significantly improved since movement gets driven by a child's intellectual abilities (Green, Charman, Pickles, Chandler, Loucas, Simonof & Baird, 2009). Also, factors such as coordination and motor planning and control, may also influence movement (Green & Brennan, 2002; Lloyd, MacDonald & Lord, 2013).

That lack of significant improvements in the other variables could be related to the teaching environment and the duration of the intervention. Fisher, Murray and Bundy (Fisher, Murray & Bundy, 1991) points out that an intervention program should be no less than 6 months and can even exceed a year (Pfeiffer, Koening, Kinnealey, Sheppard & Henderson, 2011), but in a mere 4 weeks of intervention it resulted in movement showing an improvement. This can also be attributed to the time it takes for a child with ASD to process information, to adapt to external changes, and to be able to perform what they have been taught.

Conclusion

A 4-week sensory integration intervention program can positively influence movement sensitivity, which assists with mood control, cognition and overall behavior in children with autism spectrum disorder thereby enabling them to cope with life more successfully. This study indicates that movement shows a better response to change over a short period of time compared to cognition and mood. But it is essential to take cognizance that cognition and mood also influence movement, although the influence may be small (Ashburner, Ziviani & Rodger, 2008).

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References

1. *American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th Ed. Arlington, VA: American Psychiatric Association. 2013.*
2. *American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th Ed. Washington, DC: American Psychiatric Association. 2000.*
3. *Ashburner T, Ziviani J, Rodger A. Sensory Processing and Classroom emotional behavioral and educational outcomes in children with Autism Spectrum Disorder. Am J Occup Therap. 2008; 62: 564-573.*
4. *Attwood T. The complete guide to Asperger's syndrome. London: Jessica Kingsley; 2006.*
5. *Auxter D, Pyfer J, Huettig C. 10th Ed. Principles and Methods of Adapted Physical Education and Recreation. New York: McGraw Hill. 2005.*
6. *Baio JL, Wiggins L, Christensen DL, et al. Prevalence of Autism Spectrum Disorder Among Children Aged 8 Years — Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2014. MMWR Surveill Summ, 2018; 76(6): 1-23.*
7. *Baker AE, Lane A, Angley MT, Young RL. The relationship between sensory processing patterns and behavioral responsiveness in Autistic Disorder: a pilot study. J Autism Dev Disord. 2008; 38: 867–875.*
8. *Banarek GT, David FJD, Poe MD, Stone WL, Watson LR. Sensory Experiences Questionnaire: discriminating sensory features in young children with autism, developmental delays, and typical development. J Child Psychol Psychiatry. 2006; 47(6): 591-601.*
9. *Banarek GT, Parham LD, Bodfish JW. Sensory and motor feature in autism: Assessment and intervention. In: F.R. Volkmar, R. Paul, A. Klin, D. Cohen (Eds.). Handbook of autism and pervasive developmental disorders (3rd ed.). 2005; 831-881.*
10. *Banarek GT. Efficacy of sensory and motor interventions for children with autism. Journal of Autism Development Disordered. 2002; 32(5): 397–422.*

11. *Bateman C. Autism – mitigating a global epidemic. SAMJ. 2013; 103(5): 276-277.*

12. *Ben-Sasson A, Hen L, Fluss R, Cermak SA, Engel-Yeger B, Gal E. A meta-analysis of sensory modulation symptoms in individuals with autism spectrum disorders. J Autism Dev Disord. 2009; 39: 1–11.*

13. *Bettison S. Abnormal responses to sound and the long-term effects of a new treatment program. Sydney Australia: Autism Research Institute. 1994.*

14. *Bodfish JW, Symons FJ, Parker DE, Lewis MH. Varieties of Repetitive Behavior in Autism: Comparisons to Mental Retardation. J Autism Develop Disord. 2000; 3(3): 237-243.*

15. *Brock J, Brown CC, Boucher J. The temporal binding deficit hypothesis of autism. Dev Psychopathol. 2002; 14: 209–224.*

16. *Bundy AC, Lane SJ, Murray EA, Fisher AG. Sensory integration theory and practice. Philadelphia: F.A. Davis Company; 2002.*

17. *Case-Smith J, Abresman M. Evidence-based Review of Interventions for Autism used in or of Relevance to Occupational Therapy. Am J Occup Therap. 2008; 65: 416-429.*

18. *Cook DG, Dunn W. Sensory integration for students with autism. Austin Texas: R.L Simpson, Myles, B.S; 1998; 191-229.*

19. *Dawson G, Watling R. Interventions to facilitate auditory, visual, and motor integration in autism: a review of the evidence. J Autism Dev Disord. 2000; 30(5): 415-521.*

20. *De Jager P, Condy J. The identification of sensory processing difficulties of learners experiencing Asperger's Syndrome (AS) in two mainstream Grade R classes'. SAJCE. 2011; 1(2): 1-16.*

21. *De Vries PJ. Thinking globally to meet local needs: autism spectrum disorders in Africa and other low-resource environments. Curr Opin Neurol. 2016; 29(2): 130-136.*

22. *Dunn W, Myles BS, Orr S. Sensory processing issues associated with Asperger's syndrome: A preliminary investigation. Am J Occup Therap. 2002; 56: 97-102.*

23. *Dunn W. The sensory profile. San Antonio, TX: Psychological Corporation; 1999.*

24. *Dunn W. The impact of sensory processing abilities on the daily lives of young children and their families: A conceptual model. Infants and Young children. 1997; 9(4): 23-35.*

25. *Fazilioglu Y, Baran G. A Sensory integration program on sensory problems for children with autism. Percept Mot Skills. 2008; 106(2): 415-422.*

26. *Fling E. Eating an artichoke: A mother's perspective on Asperger's Syndrome. London: Jessica Kingsley; 2000.*

27. *Fisher A, Murray E, Bundy A. Sensory integration: Therapy and practice. Philadelphia: F. A. Davis; 1991.*

28. *Fox KR, Riddoch C. Symposium on Growing up with good nutrition: A focus on the first two decades. Charting the physical activity patterns of contemporary children and adolescents. Proc Nutr Soc. 2000; 59: 497–50.*

29. *Garbriels RL, Cuccaro ML, Hill DE, Ivers BJ, Goldson E. Repetitive behaviors in autism: relationship with associated clinical features. Res Dev Disabil. 2005; 26(2): 169-181.*

30. *Green D, Charman T, Pickles A, Chandler S, Loucas T, et al. Impairment in movement skills of children with autistic spectrum disorder. Dev Med Child Neurol. 2009; 51(4): 311-316.*

31. *Green G, Brennan LC, Fein D. Intensive behavioral treatment for a toddler at high risk for autism. Behav Modif. 2002; 26: 69-102.*

32. *Huebner RA, Dunn W. Introduction and basic concepts. In R. A. Huebner (Ed.), Autism: A sensorimotor approach to management. Gaithersburg, MD: Aspen; 2001.*

33. *Iannuzzi DA, Cheng ER, Broder-Fingert S, Bauman ML. Brief Report: Emergency Department Utilization by Individuals with Autism. J Autism Dev Disord. 2015; 45: 1096-1102.*

34. *Roth K, Zittel L, Pyfer J, Auxter (12th ed). Principles and Methods of Adapted Physical Education and Recreation. Burlington, MA. Jones & Bartlett Learning; 2016.*

35. *Iarocci G, McDonald J. Sensory integration and the perceptual experience of persons with autism. J Autism Develop Disord. 2006; 36: 77-90.*

36. *Igwanaga R, Kawasaki C, Tsuchida R. Brief report: Comparison of sensory-motor and cognitive function between autism and Asperger syndrome in preschool children. Journal of Autism and Developmental Disorders. 2000; 30: 169-174.*

37. *Johnson-Ecker CL, Parham LD. The evaluation of sensory processing: A validity study using contrasting groups. Am J Occup Ther. 2000; 54(5): 494-503.*

38. *Just MA, Cherkassky VL, Keller TA, Minshew NJ. Cortical activation and synchronization during sentence comprehension in high-functioning autism: Evidence of under-connectivity. Brain: A Journal of Neurology. 2004; 127: 1811-1821.*

39. *Kashefimehr B, Kayihan H, Huri M. The Effect of Sensory Integration Therapy on Occupational Performance in Children with Autism. OTJR. 2018; 38(2): 75-83.*

40. *Khodabakhshi M, Abedi, A, Malekpour M. The effect of Sensory Integration Therapy on Social Interactions and Sensory and Motor Performance in Children with Autism. Iran J Cogn Educ. 2014; 1(1): 35-45.*

41. *Koomar J, Kranowitz C, Szklut S, Balzer-Martin L, Haber E, Sava DI. Answers to questions teachers ask about sensory integration. (3rd edition.). Watertown, MA: Future Horizons; 2001.*

42. *Lane SJ, Schaaf RC. Examining neuroscience evidence for sensory-driven neuroplasticity: Implications for sensory-based occupational therapy for children and adolescents. A J Occup Ther. 2010; 64: 375-390.*

43. *Lang R, O'Reiley M, Healy O, Rispoli M, Lydon H, et al. Sensory integration therapy for autism spectrum disorders: A systematic review. Res Autism Spectr Disord. 2012; 6: 1004-1018.*

44. *Leekam SR, Nieto C, Libby SJ, Wing L, Gould J. Describing the sensory abnormalities of children and adults with autism. J Autism Develop Disord. 2007; 37: 894-910.*

45. *Lloyd M, MacDonald M, Lord C. Motor skills of toddles with autism spectrum disorder. Autism. 2013; 17(2): 133-146.*

46. *McIntosh DN, Miller LJ, Shyu V, Hagerman RJ. Sensory-modulation disruption, electrodermal responses and functional behaviors. Dev Med Child Neurology. 1999; 41(9): 608-615.*

47. *Miller JS, Gabrielsen T, Villalobos M, Alleman R, Wahmhoff N, et al. The each child study: systematic screening for autism spectrum disorders in a pediatric setting. Pediatrics. 2011; 127(5): 866-871.*

48. *Miller LJ, Lane SJ. Toward a consensus interminology in sensory integration theory and practice: Part1: Taxonomy of neurophysiological processes. SIS. 2000; 23: 1–4.*

49. *Miller JN, Ozonoff S. The external validity of Asperger disorder: Lack of evidence form the domain of neuropsychology. J Abnorm Psychol. 2000; 109: 227-238.*

50. *Myles BS, Simpson RL. Asperger syndrome: A guide for educators and parents. Austin TX: PRO-ED. 1998.*

51. *Myles BS, Southwick J. Asperger syndrome and difficult moments: Practical solutions for tantrums, rage and meltdowns. Shawnee Mission, KS: Autism Asperger Publishing. 1999.*

52. *O'Neil M, Jones RS. Sensory-perceptual abnormalities in autism: a case for more research. J Autism Dev Disord. 1997; 27(3): 283-293.*

53. *Pfeiffer BA, Koenig K, Kinnealey M, Sheppard M, Henderson L. Effectiveness of Sensory Integration Interventions in Children with Autism Spectrum Disorders: A Pilot Study. Am J Occup Ther. 2011; 65: 76-85.*

54. *Roger SJ, Hepburn S, Wehner E. Parents report of sensory symptoms in toddlers with autism and those with other development disorders. J Autism Dev Disord. 2003; 33(6): 631-642.*

55. *Samouildou A, Valakova H. Motor skill assessment and early intervention for pre-schoolers with mental and developmental disorders (case study). ACTA Universitatis Palackianeae Olomucensis Gymnica. 2006; 37(1): 19-30.*

56. *Schaaf RC, Nightlinger KM. Occupational therapy using a sensory integrative approach: A case study of effectiveness. Am J Occup Therap. 2007; 61: 239-246.*

57. *Schriber L. Autism: A Neurological and Sensory Based Perspective. In: JH Stone, M Blouin, editors. International Encyclopedia of Rehabilitation; 2010.*

58. *Smith SA, Press B, Koenig KP, Kinnealey M. Effects of sensory integration intervention on self-stimulating and self-injurious behaviors. Am J Occup Therap. 2005; 59: 418–425.*

59. *Sniezyk CJ, Zane TL, Carolyn L. Investigating the Effects of Sensory Integration Therapy in Decreasing Stereotyping. Focus Autism Other Dev Disabl. 2015; 30(1): 13-22.*

60. *Stagnitti K, Raison P, Ryan P. Sensory defensiveness syndrome: A pediatric perspective and case study. Australian Occupational Therapy Journal. 1999; 46(6): 175-187.*

61. *Szatmari P. The classification of autism, Asperger's syndrome, and pervasive development disorder. Can J Psychiatry. 2000; 45(8): 731-739.*

62. *Tomcheck SD, Dunn W. Sensory Processing in Children with and Without Autism: A Comparative Study Using the Short Sensory Profile. Am J Occup Therap. 2007; 61: 190-200.*

63. *Tryfon A, Foster NE, Ouimet T, Doyle-Thomas K, Anagnostu E, et al. Auditory-motor rhythm synchronization in children with autism spectrum disorder. Res Autism Spectr Disord. 2017; 36: 51-61.*

64. *Watling RI, Dietz J. Immediate effect of Ayres's sensory integration-based occupational therapy intervention on children with autism spectrum disorders. Am J Occup Therap. 2007; 61: 574-583.*

65. *Yunus FW, Lui KPY, Bisset M, Penkala S. Sensory-Based Intervention for Children with Behavioral Problems: A Systematic Review. J Develop Disord. 2015; 45: 3565-3579.*

66. *Zimmer M, Desch L, Rosen LD, Bailey, M.L. Sensory Integration Therapies for children with developmental and behavioral disorders. Pediatrics. 2012; 1186-1189.*

67. *Zhang W, Mason AE, Boys B, Sikich L, Baranek G. A Rural-Urban Comparison in Emergency Department Visist for U.S Children with Autism Spectrum Disorder. J Autism Dev Disord. 2016; 47(3): 590-598.*

68. *Zwaigenbaum L, Bauman LM, Stone L, Yirmiya N, Estes A, et al. Early Identification of Autism Spectrum Disorder: Recommendations for Practice and research. Pediatrics. 2015; 136: 10-40.*

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Risk assesment of death according to bode index in chronic opstructive lung disease Prospective control study

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Abstract

Introduction: Chronic obstructive pulmonary disease (COPD) is one of the leading causes of disease and death in developed countries in the world. It is the fourth most common cause of lethality in adults in world and, predictied, by the 2020 it will become the third most common cause of lethality in adults. Very significant outcome of chronic obstructive pulmonary disease is acute worsening that leads to loosing of respiratory function and lethal outcome.

The aim: The aim of this research is to evaluate increasement of lethality risk according to BODE index and according to parameters (forced respiratory volume in first second (FEV1), dyspnea scale (MRC), body mass index (BMI), six minutes walk test (6MTH) on day of admission, in period of acute egzacerebation of chronic obstructive lung disease (AECOPD) and 6 weeks later, when clinical stabilization of illness is accomplished in all respondents.

Respondents and methods: The prospective control study included 50 respondents treated in Tuzla county clinic for pulmonary diseases. Evaluation unit for COPD lethality included evaluation of valorization according to BODE index. All pulmonary functional tests were conducted by spirometry (Jaeger Masterlab ML 3500). BMI was calculated on basis of weight kg/height m². 6MTH is used in diagnostics of dyspnea level according to scale MRC from 0-4. Statistical evaluation of data was conducted with statistical package for social researches (SPSS) version 10.0.

Results: In our sample, the most common cases with COPD in Tuzla county were men older than >70 years. Decreasement in values in FEV1 in AECOPD was evident and this change was statistically significant (Wilcoxon Z=-2.33; p=0.02).

Values in phase of stability were statisticaly signifficantly different compared to period of egzacarebation (t0:t1 v.s. FEV1: FEV2; ANOVA for repeated measurements; P=0.002). In stabile phase after AE, respiratory function ireversibly and significantly decreased (negative trend >-4; FEV3). Values of 6MTH in stable phase were statistically significantly different compared to period of acute egzacerebation (ANOVA for repeated measurfements; P=0.014). One respondent had increased mortality risk from AECOPD according to BMI. In period of egzacerebation, median of BODE index was 8 (interquartile range 7 – 9), while in period of stabilization was also 8 but with interquartile range 6,75 – 9 /BODE =1; mortality risk in our case is 1,6.

Conclusion: In Tuzla county, the most frequent COPD cases were men (78 %), with age group 40-86 years. The rate of decline of FEV1 is good indicator of illness progression and mortality rate increasement. BODE index turned out to be a good predictor of COPD outcome.

Key words: mortality, bode index, chronic obstructive lung disease

Introduction

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of disease and death in developed countries in the world (1). It is the fourth most common cause of lethality in adults in the world and predictions are that by the 2020 it will become the third most common cause of lethality in adults. Very significant outcome of chronic obstructive pulmonary disease are acute egzacereba-

tions that leads to disability and and lethal outcome (2, 3). The aim of this research was to evaluate increasement of lethality risk according to BODE index in period of acute egzacerebation and 6 weeks after clinical stabilization.

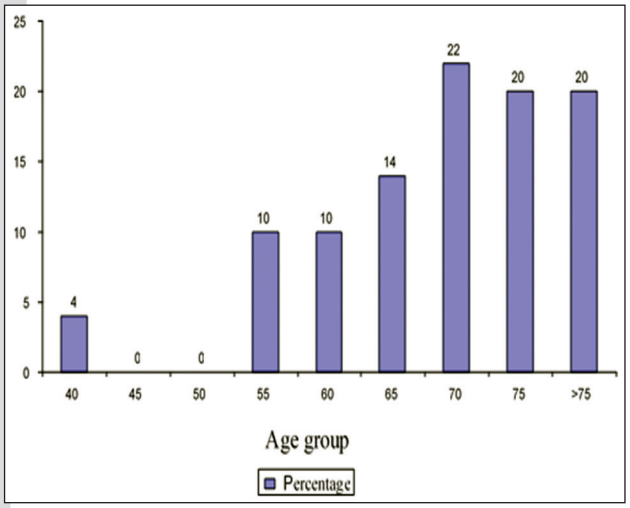
Respondents and methods

In prospective and control study our research included 50 respondents, age 40 to 86, 39 men and 11 women, who were both experimental and control group. All respondents were diagnosed with III or IV stage of COPD in Clinic for pulmonary disesases Tuzla. Research was conducted in 3 time intervals: t0 – interval in which, a year earlier were AECOPD and t1 – interval during AE, parameters were recorded (forced expiratory volume in first second (FEV1) scale of dyspnea (MRC), body mass index (BMI), six minutes walk test (6MTH) which were experimental group during egzacerebation and t2 interval- 6 weeks of stabilisation of COPD, when all measurements were repeated with same respondents who were control group. Assessment for COPD lehality risk was conducted according to BODE index which is displayed in table 1. Each point increases risk from lethal outcome for 1,62 times (4).

All pulmonary functional tests were conducted with spyrometer (Jaeger Masterlab ML 3500; curve flow – volume, FEV1 i FVC) according to method of American thoracic society (5).

BMI index was calculated according to body mass (kg) and body surface (sq. meter) (weight kg/ height m²). Normal values were 21-25 kg/m2 of body mass. BMI <21 was negative predictive factor of mortality (4). Dyspnea point was evaluated on basis of dyspnea scale of medical research council (MRC) (6). Also, testing of ergometrical load and six minute walk test was conducted like in diagnosing of level of dyspnea by dyspnea scale (MRC) 0-4. The six minute walk is a simple exercise test. Patients with COPD should walk more than 350m in 6 minutes of time. The shorter walking length without dyspnea means higher level of disease (7). Statistical evaluation of data was conducted with statistical package for social researches (SPSS) version 10.0. In statistical processing of results standard methods of descriptive statistics were conducted. χ2-test and t-test were used for testing of statistical significance in difference of chosen variables. Values of spyrometric classification according to GOLD were coordinated in ordinal variable and Wilcoxon non- paremetric test was used. Univariant and multivariant analyses of variance with linear and logistic analysis – ANOVA were used for multivariant correlation analysis.

Results



Picture 1. Distribution of all respondents (n=50) in total sample according to

There are significant differences in values: six minute walking test, functional breathing parameters for GOLD and BODE score in repeat measurements (t0, t1, t2).

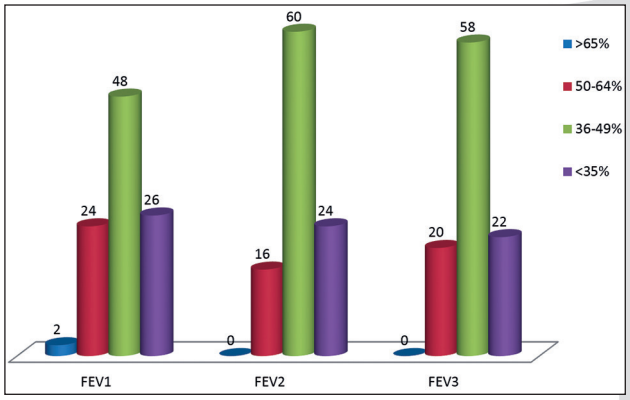
Table 1. BODE index as prognosis sign of lethal outcome risk

Points	0	1	2	3
FEV1 (%)	≥65	50-64	36-49	≤35
Six Minute Walk Test (6MWT)	≥350	250-349	150-249	≤149
Dyspnea scale (MRC*)	0-1	2	3	4
BMI	≥21	≤21	≤21	≤21

Table 2. Evaluation of condition level according to COPD markers in previous stable period t0, period of acute egzacerebation t1, on day of admission and period of stabilization t2 .

Points	Measuring period	Maximum	Minimum	AS±SD*	p-value **
Bodi mass index	t0	16.98	43.75	27.08±5.17	0.087
	t1	16.65	42.97	26.39±5.25	
	t2	16.00	40.63	26.13±5.29	
Six Minute Walk Test (6MWT)	t0	30.00	375.00	180.18±86.42	0.014
	t1	25.00	300.00	125.38±60.32	
	t2	25.00	350.00	158.38±90.62	
	Measuring period	**Maximum**	**Minimum**	**Median (interquartile range)**	**p-value**
GOLD[1]	t0	1	4	3 (3-4)	0.002
	t1	2	4	3 (3-4)	
	t2	2	4	3 (3-3)	
BODE score	t0	5	12	9 (8-10)	0.050[2]
	t1	4	12	8 (7-9)	
	t2	4	12	8 (7-9)	
Dyspneascale (MRC*)	t1	2	5	4 (3-5)	0.330
	t2	2	5	4 (3-4)	

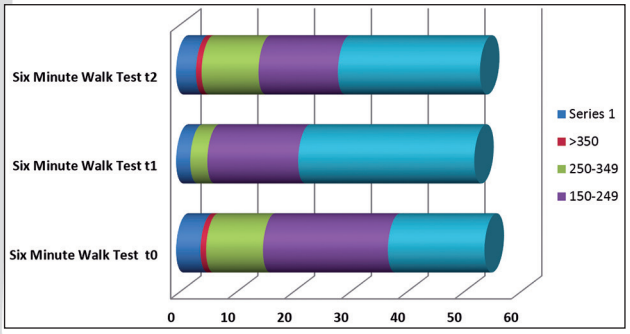
**SD- standard deviation*
***ANOVA for repeated measurements*
t0- stable phase; t1- exacerbations; t2- after exacerbation
[1] Spatial metric classification by GOLD: Categories 1 through 4 corresponds to Stage I to IV
[2] z= 1.95



Picture 2. Contrast between different values of FEV1 in repeated measurements (t0, t1, t2)

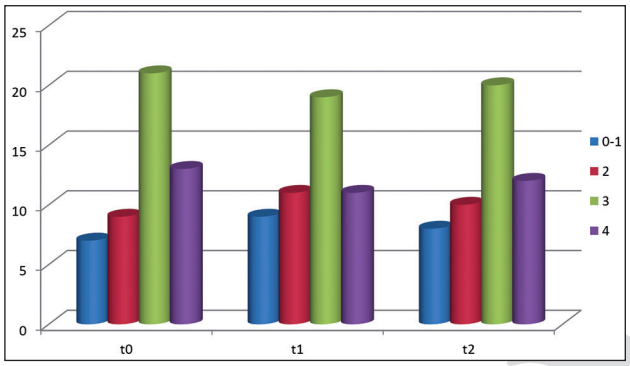
Values in stabile phase were significantly different in statistics regarding time of AECOPD (t0:t1 v.s. FEV1: FEV2; ANOVA for repeated measurements; P=0.002). In period of stabilization after AE, respiratory function declined irreversibly and significantly (negative trend >-4; FEV3).

According to GOLD, values of spyrometric classification were in range of ordinal variable and nonparametric Wilcoxon test was used. Decline of GOLD stage was evident in 8 cases. There was increasement in single case while in 41 cases changes were not evident according to GOLD. Therefore, the cases with declining values were dominated and this change was statistically significant (Wilcoxon Z=-2.33; p=0.02).



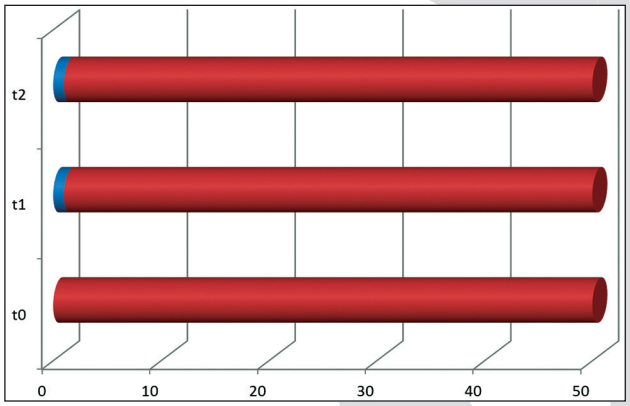
Picture 3. Contrastive display of differences of 6MTH test in repeated measurements

Values of 6 minutes test walking in stabile phase were statistically different in comparing to time of egzacerebation (ANOVA for repeated measurements; P=0.014)



Picture 4. Contrastive display of differences in value of MRC scale od dyspnea measured in t1 and t2

Declining of values was evident within 10 respondents according to MRC scale, 9 were with increase of values and 31 without change in values. This difference, tested with Wilcoxon test was not statistically significant (Z=-0.198; p=0.843).



Picture 5. Contrastive display of differences in categories of BMI in repeated measurements

Significant difference was not evident for categories of BMI for repeated measurements. One respondent had increased risk for mortality from AECOPD according to BMI.

Values of Bode index measured in period of egzacerebation and in period of clinical stabilization were compared sith those in period of egzacerebation, medial values of BODE index were 8 (interaquartile range 7 -9), while in period of stabilization the values were also 8 but with interquartile range 6,75 – 9/ BODE =1; risk of lethal outcome in our sample was 1,6. Decline in BODE index was evident in 20 respondents, from egzacerebation to stabilization. 10 respondents shown increase of values and 20 were without changes in values of BODE index. Therefore, dominant decrease of values in BODE index were evident and this difference was statistically significant (Z=-1.95; p=0.05; Table 3). However, BODE score was statistically different compared to period of stabilisation and after stabilization, and assumption can be made that each new episode of AECOPD stage III and IV increases the risk of lethal outcome.

Discussion

According to results of numerous studies in world, incidence, prevalence and COPD mortality rate are increasing (8). Nowdays, COPD represents global public and health problem with high morbidity and mortality rate. During 2010, 1770 patients were treated in Clinic for pulmonary dis-

Table 3. Contrastive display of parameters in BODE score and BODE score in stabile phase and in period after stabilization

Points	Measuring time	Minimum	Maximum	AS±SD	p-value
BMI	t0	16.98	43.75	27.07± 5.17	0.001[1]
	t2	16.00	40.63	26.13±5.29	
Six Minute Walk Test	t0	30.00	375.00	180.18±86.42	0.023[2]
	t2	25.00	350.00	158.38±90.62	
	Measuring time	**Minimum**	**Maximum**	**Median (interquartile range)**	**p-value**
FEV1	t0	1	4	3 (3-4)	
	t2	2	4	3 (3-3)	0.782
BODE scor	t 1	5	12	9 (8.00-10.0)	
	t2	4	12	8 (6.75-9.0)	0.001[3]

[1]*t- test= 4.51, average difference 0.94 (%95 CI=0.52-1.36)*
[2]*t- test= 2.35; average difference21.3 (%95 CI=3.05-39.55)*
[3]*z= -4.12; 33 subjects with a fall in value and 5 with a rise in value; 12 no change in value (BODE)*

eases in Tuzla. Chronic obstructive lung disease was leading cause of illness and admission. Increase in incidence and prevalence of illness including COPD in Tuzla county is supported by environmental risk factors i.e. exposure to harmful particles and gasses regarding fast mining development and all other industrial branches during 20th century. Acute exacerbations of chronic lung disease represents significant area due to markers that estimate the level and progression of illness as well as outcomes. Results of our research proved that COPD is dominant in men (age 40 – 86) in Tuzla county with accent on men above 70 years of age (n =31), with high and very hard stage of COPD according to GOLD (III stage n=37, IV stage n=13), and with developed emphysema.

Regarding the age, according to our results, it was forwarded to older age groups in men unlike in women where it was moved to younger age groups, what can be explained by increased prevalence of smoking and many professional risk factors. In our research, significant difference in BMI values was not evident and average values were (from 27,08 ± 5,17 to 26,13 ± 5,9. P=0,087) in repeated measures and does not represent mortality predictor. Low index of BMI is related with lethal outcome risk (9,10). Other physiological marker for 6MTH is measure of intolerance on physical load of patients with COPD, which leads to statistically significant increase of morbidity and invalidity. Results of six minutes walk test in our research in stabile phase were statistically and significantly different regarding the period of acute exacerbation (ANOVA for repeated measurements P=0.014). Risk of lethal outcome in patients with COPD is often estimated with usage of one physiological variable – forced expiratory volume in first second (FEV1) (11.12). Our values in stabile phase are statistically and significantly different regarding time of exacerbation (t0:t1 vs FEV1: FEV2; ANOVA for repeated measurements; P=0.002). In period of stabilization after AE, respiratory function irreversibly and significantly declines (negative trend >-4; FEV1-t2). Therefore, cases with decrease in value of FEV1 were dominant and this change was statistically significant (Wilcoxon Z=-2.33; p=0.02). Decrease rate of FEV1 is good indicator of illness and mortality progression. For example, FEV1 weakly correlates with degree of dyspnea. We compared values of MRC scale for dyspnea measured in t1 and t2. In both measurements, significant medial value 4 with interquartile range 3 – 5 is evident. The fall of values according to MRC scale is also evident in 10 respondents as well as increase in 9 cases and in 31 case without change in values in MRC scale. This difference, tested with Wilcoxon test was not statistically significant (Z=-0.198; p=0.843). Also, the significant difference for repeated measurements in dyspnea categories are not evident. One of main COPD characteristics, especially in prolonged illness with larger degree according to GOLD is intolerance on physical load which is caused by numerous factors. It is proved that muscular skeleton disfunction is the most important reason for mentioned intolerance on physical load, and consequence is deconditioning of organism. In patients who can not tolerate other ergometric tests of load regarding the body weight, 6 MTH (6MWD) is conducted for diagnosing of level of dyspnea according to scale of dyspnea MRC. Less walking length without dyspnea is with worse prognosis (7). Frequency and level of exacerbation leads to: worsening of dyspnea, malnutrition and low life quality (1). BMI index and dyspnea are better predictors of COPD progression and lethal outcomes than FEV1 (13). We have found major differences in dyspnea levels in respondents grouped in same or similar GOLD levels of COPD.

According to results of sequent researches, nutritive status points out on connection of malnutrition with increased risk of lethal outcome. The loss of body weight in COPD respondents, especially in loss of muscular mass, leads to increased morbidity and invalidity. The values of BMI in malnutritive respondents <21kg/m2, for respondents >50 years of life are related to increased mortality rate. Significant difference between BMI category and dyspnea expressed in FEV1 for repeated measurements is not evident in our research. Single respondent was with increased risk of mortality in AECOPD according to BMI. There is not statistically related connection between BMI and FEV1 in any point of time in measurement in our research, and factor of mortality in our sample is not indicative. Compared values of BODE index in time of exacerbation and in time of COPD sta-

bilization, medial values were (8 v.s. 8). BODE =1 or risk of lethal outcome in our sample is 1,6. Decrease in BODE index from exacerbation to stabilization is noted in 20 respondents, where 10 were with increase and 20 were without change in BODE index value. Therefore, there was a dominant decrease in BODE index values and this difference was statistically significant (Z=-1.95; p=0.05). However, BODE score is significantly different in comparing to time of stability and time after stabilization and it can be assumed that with each attack of AE in COPD in III and IV stage, risk of lethal outcome increases what matces with results of similar studies. Hard, repeated AECOPD are one of main causes of lethal outcome in COPD. In study of Hoogendoorn M. mortality in case of exacerbation is estimated on 15,6 %, what indicates on influence of AECOPD on mortality, what is in ordinance with our results (14).

Conclusions

In Tuzla county COPD is present mostly in men (78%), in age 40 – 86 years of life. In stabile phase of COPD there are higher values of 6MTH statistically significant (158.88 m±(90,62 m), average difference of 33,5 m in comparing to time AE. BMI is not significant negative predictive mortality factor. In time of stabilization after AECOPD, statistically irreversible and significant decrease of respiratory function (negative trend >-4; FEV1-t2), is evident what confirms small reversibility of respiratory function. With each new AE in COPD GOLD stage III and IV the risk of lethal outcome increases. Hard and repeated AE are one of the main causes of lethal outcomes in COPD. Statistically significant decrease od BODE index happens in point from exacerbation to stabilization and the risk from lethal outcome was 1,6 showing as a good predictor of COPD outcome.

References

1. *Celli BR. Update on the managment of COPD. Chest 2008; 133: 1451-62.*
2. *Rabe FK, Beghe B, Luppi F, Fabbri LM. Update in chronic obstructive pulmonary disease 2006. Am J Resp CritCare Med 2007; 175: 1222-32.*
3. *Sin DD, Anthonisen NR, Soriano JB, Agusti AG. Mortality in COPD: role of comorbidities. Eur Resp J 2006; 28: 1245-57.*
4. *Celli BR, Cote CG, Lareau SC, et al. Predictors of survival in COPD: more than just the FEV_1. Respir Med. 2008; 102(1): S27–S35.*
5. *Anonymous. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. American Thoracic Society. American journal of respiratory and critical care medicine. 1995; 152: S77–121.*
6. *Fletcher CM, Elmes PC, Wood CH. The significance of respiratory symptoms and the diagnosis of chronic bronchitis in a working populations. BMJ. 1959; 1: 257-66.*
7. *Lucas C, Stevenson LW, Johnson W, Hartley H, Hamilton MA, et al. The 6-min walk and peak oxygen consumption in advanced heart failure: Aerobic capacity and survival. Am Heart J. 1999; 138(4): 618-24.*
8. *Pauwels RA, Buist AS, Calverley PM, Jenkins CR, Hurd SS. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. American journal of respiratory and critical care medicine. 2001; 163: 1256–1276.*
9. *Casanova C, Cote C, de Torres JP, Aguirre-Jaime A, Marin JM, et al. Inspiratory-to-total lung capacity ratio predicts mortality in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2005; 171: 591-597. .*
10. *Dawkins PA, Dowson LJ, Guest PJ, Stockley RA. Predictors of mortality in alpha1-antitrypsin deficiency. Thorax. 2003; 58: 1020-1026.*
11. *Nishimura K, Izumi T, Tsukino M, Oga T. Dyspnea is a better predictor of 5 year survival than airway obstruction in patients with COPD. Chest. 2002; 121: 1434-1440.*
12. *Landbo C, Prescott E, Lange P, Vestbo J, Almdal TP. Prognostic value of nutritional status in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1999; 160: 1856-1861.*

13. *Burgel PR, Paillasseur JL, Caillaud D, Tillie-Leblond I, Chanez P, et al. Clinical COPD phenotypes: a novel approach using principal component and cluster analyses.Eur Respir J. 2010; 36: 531-539.*

14. *Hoogendoorn M, Hoogenveen RT, Rutten-van Mölken MP, Vestbo J, Feenstra TL. Case fatality of COPD exacerbations: a meta-analysis and statistical modelling approach. Eur Respir J. 2011; 37: 508-515.*

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Biochemical and hematological study of the supplementation with ATAMg, a new source of N-acetyl-based organic magnesium, on bioavailability

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Abstract

Introduction: The present *in vivo* study investigated the bioavailability of ATAMg, a novel N-acetyl-based organic magnesium, through biochemical and hematological assays.

Material and methods: Sprague-Dawley rats were used in this study. The effects of magnesium on the body were investigated 6 h after magnesium administration in four different experimental groups: control, magnesium sulfate, magnesium oxide, and magnesium acetyl taurate.

Results and discussion: Magnesium is one of the microelements that must be taken as supplement if it is deficient in the body. Orally administered magnesium acetyl taurate detected in the brain was quickly absorbed, besides its levels remained high for a long time in the serum.

Conclusion: The obtained data support the view that ATAMg, a new source of N-acetyl-based organic magnesium, has great bioavailability and may be ingested as a nutritional supplement.

Key words: ATAMg, acetyl taurate; bioavailability, biochemistry, hematology, magnesium.

Introduction

Magnesium acts as a cofactor in more than 300 metabolic reactions, playing a key role in glucose metabolism, in insulin and glycemic homeostasis, and in the synthesis of adenosine triphosphate, proteins and nucleic acids. It also acts on the stability of the neuromuscular and cardiovascular membrane, the maintenance of vasomotor tone and as a physiological regulator of hormonal and immunological function (1).

The body of a healthy adult has approximately 21 g to 28 g of magnesium, distributed in three main compartments: bone (65%), muscle (34%) and plasma and interstitial fluid (1%). In plasma, the normal concentration of this ion is maintained between 1.7 mg/dL and 2.4 mg/dL, of which about 60% is in the biologically active free form, while the rest circulates bound to proteins, such as albumin (33%), or complexed with anions (7%), such as phosphate, bicarbonate and citrate (1 to 2%) (2)

In erythrocytes, the normal concentration of magnesium is approximately 2.5 mmol/L. Within the cells, this mineral is found in the nucleus, in the mitochondria, in the endoplasmic and sarcoplasmic reticulum, linked to nucleic acids, intermembrane proteins, ribonuclear proteins and phospholipids (3).

The main food sources of magnesium are whole grains, green leafy vegetables, spinach, nuts, fruits, vegetables and tubers such as potatoes. The recommended daily intake of magnesium is 310 to 320 mg and 400 to 420 mg for women and adult men, respectively (4).

In recent years, there has been a reduction in the dietary intake of magnesium, mainly in Western countries, where the consumption of processed foods is increasing. These foods contain less of the mineral when compared to whole grains, which compromises their adequate intake and exposes individuals to increased risk for the development of chronic diseases (5).

In this perspective, data from several studies show that the reduced consumption of this mineral leads to an increased risk of developing insulin resistance, type 2 diabetes mellitus and cardiovascular diseases, as well as being related to neuromus-

cular disorders and in bone metabolism, cardiac arrhythmias, hypertension arterial, atherogenesis and eclampsia (6, 7, 8).

Therefore, considering the importance of magnesium in the metabolism and maintenance of the body's homeostasis, the scarcity of data on the consumption of this mineral, as well as the consequences of an inadequate intake, this study aims to bring new information about the bioavailability of this micronutrient.

Material and methods

Twenty adult male Sprague-Dawley rats were used in this study. All rats were housed in individual cages with free access to water and laboratory chow. They were kept in a 12-h light/12-h dark cycle at constant room temperature (22 ± 1 °C) and humidity (60%). Animal Care Committee approved all experimental procedures. Rats were divided into four groups: control group (n = 5), magnesium sulfate (n = 5), magnesium oxide (n = 5), magnesium acetyl taurate (n = 5).

The effects of magnesium on the body were investigated 6 h after magnesium administration (350 mg). Elementary magnesium levels of all compounds were calculated and then dissolved using phosphate-buffered saline (PBS). All magnesium compounds were given orally in 1-ml volume/each rat. Control animals were given the same volume of PBS.

The bioavailability assessment of magnesium was studied through different tissues. Eight hours after administration of magnesium, blood samples were drawn under carbon dioxide anesthesia. Then, brain was separated from the cerebellum, and magnesium level was measured in the whole brain. While measuring magnesium in muscle tissue, gastrocnemius was removed since it contains muscle fibers.

Blood, brain, and muscle samples were stored at -85 °C until they were analyzed. Magnesium levels in the brain, plasma, and muscle tissues were determined 8 h post administration by atomic absorption spectrophotometry. Magnesium level was measured at different time points using a Beckman Coulter AU 5800 analyzer. Tissue magnesium concentration was calculated per wet weight.

The bioavailability is a term which refers to the fraction of drug systemically absorbed. It can be measured by quantifying area under the curve (AUC) of a serum concentration against a time plot. The AUC of the plot of serum magnesium levels determined at different time points were calculated (AUC = (C1 + C2)/(t2-t1) + (C2 + C3)/(t3-t4) + (C3 + C4)/(t5-t4)).

The statistical procedures were performed by SPSS software for Windows, Version 11.0. Differences between groups were analyzed using ANOVA. Correlations among groups were calculated using the Pearson correlation analysis. Results are presented as mean ± S.E.M, where $p < 0.05$ was considered statistically significant.

Results and discussion

This study compared the bioavailability of one organic and two inorganic magnesium compounds. Bioavailability was assessed by investigating tissue magnesium levels.

At the sixth hour, blood magnesium levels were significantly higher in the magnesium acetyl taurate group when compared to all other groups ($p < 0.001$). No difference was observed in erythrocyte magnesium levels between the experimental and control groups.

The area under the curve is difference between all magnesium compounds. Magnesium acetyl taurate's AUC is much higher than all other groups ($p < 0.0001$). Magnesium sulfate's AUC is higher than magnesium oxide ($p < 0.0001$).

Brain magnesium levels were highest in the magnesium acetyl taurate group when compared

Table 1. Blood and brain magnesium levels

	Blood	Brain
Control	3.0 ± 0.3 mg/dL	145.4 ± 3.7 mg/g
Magnesium sulfate	3.5 ± 0.5 mg/dL	168.4 ± 2.9 mg/g
Magnesium oxide	3.2 ± 0.5 mg/dL	143.9 ± 1.6 mg/g
Magnesium acetyl taurate	3.7 ± 0.3* mg/dL	221.8 ± 1.8* mg/g

**p < 0.05 compared with control.*

with others ($p < 0.0001$). After oral administration, magnesium is absorbed from the intestine, and increased levels in the blood would not suffice, it would need to pass through the cell membrane and get inside the cell in order to participate in normal physiological functions. It was not observed any differences between the control group and the inorganic magnesium groups, which can be interpreted as the low bioavailability of these compounds.

Magnesium acetyl taurate (an organic compound) group had the highest brain magnesium levels. Magnesium is an essential mineral for the homeostasis of all living cells. It is a cofactor in over 300 biochemical reactions, regulating nucleic acid and protein synthesis, ATP synthesis, nerve and muscle cell functions, and body temperature (9, 10).

Also, magnesium is important in psychoneuroendocrine systems that attenuate stress hormone release and modulate the activity of the hypothalamus–pituitary–adrenocortical axis (11).

Conclusion

Nowadays, the reduced nutrient content of foods makes micronutrient supplementation necessary. Magnesium is one of the microelements that must be taken as supplement if it is deficient in the body. In this study, it has been demonstrated that orally administered magnesium acetyl taurate detected in the brain was quickly absorbed, able to pass through to the brain easily, besides its levels remained high for a long time in the serum. Further work is needed to explain the effects of these magnesium compounds on the body of long-term applications.

References

1. *Elin RJ. Assessment of magnesium status for diagnosis and therapy. Magnes. Res. 2010; 23: 194-198.*
2. *Volpe SL. Magnesium in disease prevention and overall health. Adv. Nutr. 2013; 4: 378S-383S.*
3. *Kolte D, Vijayaraghavan K, Khera S, Sica D, Frishman WH. Role of magnesium in cardiovascular diseases. Cardiol. Rev. 2014; 22: 182-92.*
4. *Institute of Medicine. Dietary reference intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride. Washington (DC). 1997; 190.*
5. *Jahnen-Dechent W, Ketteler M. Magnesium basics. Clin. Kidney J. 2012; 5: i3–i14.*
6. *Orchard TS, Larson JC, Alghothani N, Bout-Tabaku S, Cauley JA, Chen Z. Magnesium intake, bone mineral density, and fractures: results from the Women's Health Initiative Observational Study. Am. J. Clin. Nutr. 2014; 99: 926-33.*
7. *Hata A, Doi Y, Ninomiya T, Mukai N, Hirakawa Y, Hata J. Magnesium intake decreases Type 2 diabetes risk through the improvement of insulin resistance and inflammation: the Hisayama study. Diabet. Med. 2013; 30: 1487-1494.*
8. *Nielsen FH. Effects of magnesium depletion on inflammation in chronic disease. Curr. Opin. Clin. Nutr. Metab. Care, 2014; 17: 525-530.*
9. *Swaminathan R. Magnesium metabolism and its disorders. Clin. Biochem. Rev. 2003; 24: 47-66.*
10. *Morais JB, Severo JS, Santos LR, Melo SRS, Santos RO, et al. Role of magnesium in oxidative stress in individuals with obesity. Biol. Trace Elem. Res. 2017; 176: 20-26.*
11. *Murck H, Steiger A. Mg2+ reduces ACTH secretion and enhances spindle power without changing delta power during sleep in men—possible therapeutic implications. Psychopharm. 1998; 137: 247-252.*

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Instructions for the authors

All papers need to be sent to e-mail: healthmedjournal@gmail.com

Preparing Article for HealthMED Journal

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Abstract

In this paper the instructions for preparing camera ready paper for the Journal are given. The recommended, but not limited text processor is Microsoft Word. Insert an abstract of 50-100 words, giving a brief account of the most relevant aspects of the paper. It is recommended to use up to 5 key words.

Key words: Camera ready paper, Journal.

Introduction

In order to effect high quality of Papers, the authors are requested to follow instructions given in this sample paper. Regular length of the papers is 5 to 12 pages. Articles must be proofread by an expert native speaker of English language. Can't be accepted articles with grammatical and spelling errors.

Instructions for the authors

Times New Roman 12 points font should be used for normal text. Manuscript have to be prepared in a two column separated by 5 mm. The margins for A4 (210×297 mm2) paper are given in Table 1.

Table 1. Page layout description

Paper size	A4
Top margin	20 mm
Bottom margin	20 mm
Left margin	20 mm
Right margin	18 mm
Column Spacing	5 mm

Regular paper may be divided in a number of sections. Section titles (including references and acknowledgement) should be typed using 12 pt fonts with **bold** option. For numbering use Times New Roman number. Sections can be split in subsection, which should be typed 12 pt *Italic* option. Figures should be one column wide. If it is impossible to place figure in one column, two column wide figures is allowed. Each figure must have a caption under the figure. Figures must be a resolution of 300 DPI, saved in TIFF format, width 10 cm min. For the figure captions 12 pt *Italic* font should be used. (1)

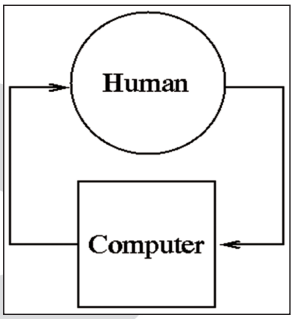

Figure 1. Text here

Conclusion

Be brief and give most important conclusion from your paper. Do not use equations and figures here.

Acknowledgements (If any)

These and the Reference headings are in bold but have no numbers.

References

1. *Sakane T, Takeno M, Suzuki N, Inaba G. Behcet's disease. N Engl J Med 1999; 341: 1284–1291.*
2. *Stewart SM, Lam TH, Beston CL, et al. A Prospective Analysis of Stress and Academic Performance in the first two years of Medical School. Med Educ 1999; 33(4): 243- 50.*

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