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Sadržaj / Table of Contents

Wilms' tumor gene immunoreactivity in primary thyroid neoplasms73
Tulin Yalta, Ebru Tastekin, Arzu Calik Uygun, Nuray Can, Fulya Oz Puyan, Meltem Azatcam, Semra Ayturk, Atakan Sezer, Serhat Oguz, Tamer Sagiroglu, Ufuk Usta
Low, quantitatively equal and regular intake of carbohydrates in combined therapy (biphasic insulin aspart+metformin) improves glycaemic control in individuals suffering from type 2 diabetes: randomised controlled study
Variations of the intermeniscal ligaments of the knee joint
A 30-day clinical investigation of the safety and efficacy of KollaGen II-xs TM , a new avian sternal collagen type II hydrolysate
The Effect of Watching TV on Anxiety Levels and Tendency towards Violence in Children93 <i>Pinar Bekar, Duygu Arikan</i>
The incidence of operated children with Meningomyelomeningocele
Instructions for the authors

Wilms' tumor gene immunoreactivity in primary thyroid neoplasms

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Abstract

Background: Wilms tumor gene (WT1) has been known as a tumor-suppressor gene located at chromosome 11p13. On the other hand, antibodies against the product of this gene that might be applicable to formalin-fixed paraffin-embedded tissue have become available. Even though, these antibodies may stain the cytoplasm as well as the nucleus of cells, only nuclear immuno- reactivity should be evaluated for the potential expression of WT1 gene. Within this context, the present study focused on the expression levels of this gene in a variety of primary thyroid neoplasms.

Materials and Methods: A comparison was made among papillary carcinomas (n=30), follicular neoplasms (n=30) and adenomatous hyperplasia (n=30) of the thyroid in terms of WT1 gene expression through immunohistochemical staining.

Results: Evaluation of WT1 gene expression yielded a null result with no detectable nuclear staining in any of the groups along with an existing cytoplasmic staining exclusively in oncocytic cells.

Conclusion: These findings potentially suggest that WT-1gene has no role in the tumorigenesis of primary thyroid neoplasms.

Key words: WT1, immunohistochemistry, thyroid neoplasms

Introduction

Wilms' tumor gene (WT1) is a tumor-suppressor primarily encoding a zinc finger transcription factor that inhibits transcription of growth factor genes, growth factor receptor genes including bcl-2, RAR- α and c-myc.¹ It is expressed in kidney

glomeruli, sertoli cells of the testis and also epithelial and granulosa cells of the ovary.² WT 1 immunreactivity is seen in desmoplastic round cell tumor, ovarian, tubal and peritoneal serous carcinoma , malignant mesothelioma and Wilm's tumor .¹⁻⁶

Tumors exhibiting follicular cell differentiation (follicular adenoma, follicular carcinoma and papillary carcinoma) are the most common types of thyroid neoplasms.⁷ Some of the genes, mutations and rearrangements are well known to be implicated in the etiopathogenesis of primary thyroid neoplasms such as BRAF and RAS mutation, NTRK1, RET/PTC, PAX8/PPAR γ rearrangements in papillary carcinoma and RAS mutation in follicular adenoma/carcinoma.⁸⁻¹²

The study, herein primarily focuses on the analysis of the WT1 gene expression in primary thyroid neoplasms in an effort to uncover any potential implication of this gene in these neoplasms.

Material and method

Thyroidectomy specimens diagnosed as papillary carcinoma (n=30), follicular adenoma (n=15), follicular carcinoma (n=15) and adenomatous hyperplasia (n=30) were examined. All tissue samples that were paraffin- embedded and formalinfixed were completely available from the tissue bank of Pathology Deparment of Trakya University Medical School Hospital between years 2004-2010. Histological evaluation comprised the staining of a section from each specimen with haematoxylin-eosin (HE) along with a subsequent immunohistochemical study.

Immunohistochemical Staining

Specimens from paraffin-embedded blocks were sliced into 4µm sections, and were thereafter dewaxed using xylene and transferred to alcohol. Immunohistochemical staining was performed using a streptavidin-biotin immunoperoxidase methodology using Ventana systems. The incubation time for the primary antibodies (Neomarkers, Thermo Scientific, USA) WT1 Ab-5 (Clone 6F-H2) was 60 minutes. Ovarian serous carcinoma and a Wilm's tumor was selected as positive control for the immunohistochemical stain.

Each specimen was examined at a minimum of 10 fields and at x10 magnification. In this study, specimens were labeled as positive when > 5% of the sample demonstrated nuclear staining for WT1 antibody and as negative when <%5 of the sample demonstrated nuclear staining.

Statistical Analysis

Statistical analysis of the association between neoplastic /non-neoplastic thyroid tissue and nuclear staining with WT1 antibody was performed using c^2 (chi-square) test . A p-value of <0,05 was accepted as statistically significant.

Results

Table 1 demonstrates the number of WT1 positive and negative cases in each histological group. There was no difference among the three groups with no discernible nuclear staining in any of them. In other terms, all cases were immunohistochemically negative regarding nuclear reactivity for WT 1 along with an existing cytoplasmic staining, to some extent, exclusively in oncocytic cells. Microscopic appearance of specimens with null staining corresponding to each group are demonstrated in Figures 1, 2 and 3.



Figure 1. Papillary thyroid carcinoma with null staining,



Figure 2. Follicular neoplasm with null staining



Figure 3. Adenomatous hyperplasia with null staining (WT1 immunohistochemistry, x100)

Groups	Number of WT1 positive cases	Number of WT1 negative cases
1-Papillary Carcinoma(n=30)	0	30
2-Follicular Neoplasm(follicular adenoma n=15, follicular carcinoma n=15)	0	30
3-Adenomatous Hyperplasia(n=30)	0	30

Table 1. WT1 expression in neoplastic (papillary carcinomas and follicular neoplasms) and non-neoplastic

Discussion

WT1 gene primarily works as a zinc finger transcription factor that is well known to play a fundamental role in the development of the kidneys, gonads, spleen, mesothelial cell lining of the viscera and hematopoietic precursors.^{13,14} It has also been regarded as a tumor suppressor gene involving in a variety of neoplams including childhood malignancy of the kidney known as Wilms' tumor in which there is an inactivation of the both allels of this gene.¹⁵ Besides Wilms' tumor, WT1 gene also appears to be implicated in tumorigenesis of a variety of adult cancers including ovarian serous carcinoma^{4,14,16}, mesothelioma¹⁷, some types of (especially micropapillary) breast carcinoma^{3,18}, leukemia¹⁹, desmoplastic round cell tumor²⁰, colorectal carcinoma²¹, desmoid fibromatosis²² and some melanocytic tumors²³.

Incidence of thyroid neoplasms including papillary carcinomas has been on the rise over the past two decades²⁴. In an effort to initiate a novel therapeutic strategy (cancer cells expressing WT1 are deactivated by WT1 antisense oligomers), Oji et al analyzed WT1 gene expression immunohistochemically in primary thyroid cancers (n=34), follicular adenomas (n=17) as well as normal thyroid tissue (n=6). The authors considered cytoplasmic WT1 reactivity as a valuable finding based on their demonstration of cytoplasmic reactivity for WT1 antibody in most of their papillary carcinoma (n=24) and in a portion of follicular adenoma (n=4) series¹. In the present study, we were unable to demonstrate any nuclear reactivity for WT1, and were able to demonstate cytplasmic reactivity only in oncocytic cells. However, as opposed to Oji et al (1), we tend to ignore cytoplasmic staining since, based on a general consensus, only a positive nuclear staining denotes an existing WT1 immunoreactivity. Therefore, our findings strongly suggest that WT1 gene has no significant role in tumorigenesis of primary thyroid neoplasms. Our study probably appears as the second one in the literature (besides the one Oji et al (1)) investigating WT1 immunoreactivity in thyroid tissue. On the other hand, it probably emerges as the first demonstrating a null association between nuclear WT1 reactivity and thyroid tissue.

Based on a pathological perspective, WT1 immunohistochemistry has been generally used for diagnostic purposes: for instance; the presence of nuclear WT1 positivity in a variety of ovarian and peritoneal serous carcinomas might potentially be regarded as a marker of serous differentiation in these carcinomas. Moreover, it might also used to differentiate uterine serous carcinoma (WT1negative) from ovarian serous carcinoma (WT1 positive)^{16,4}, and mesothelioma(WT1 positive) from lung adenocarcinoma (WT1 negative)⁶. Based on our findings, WT1 might also work well as a valuable tool to differentiate papillary thyroid carcinoma (with no staining) from ovarian and peritoneal serous carcinomas (with staining) as these tumors closely resemble each other particularly with regard to their typical features including formation of papillary structures and psammoma bodies. In other terms, differantiation based on WT1 staining might be of utmost diagnostic value particularly in the setting of metastatic tumoral disease between organs with otherwise similar morphological characteristics.

In conclusion, the present study appears as the first to demonstrate that WT1 gene has no role in tumorigenesis of primary thyroid neoplasms suggesting its failure to serve as a novel molecular target for the management of thyroid neoplasms, yet still indicating its diagnostic role as a marker of immunohistochemistry in the setting of general pathology.

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Low, quantitatively equal and regular intake of carbohydrates in combined therapy (biphasic insulin aspart+metformin) improves glycaemic control in individuals suffering from type 2 diabetes: randomised controlled study

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Abstract

Objective: The goal of this study was to determine efficiency and safety of diabetes diet according to 2013. ADA Guidelines compared to the standard diabetes diet according to 2003 ADA Guidelines in combined therapy (BIAsp 30 + metformin) for glycaemic control of type 2 diabetes (T2DM) patients.

Research design and methods: Individuals with T2DM (n=40) were randomised in an open study with parallel Groups under 24-week monitoring. Group A (n=20) was treated with the 2013 ADA Guidelines diet and Group B (n=20) with the 2003 ADA Guidelines diet. Both Groups were treated with combined therapy (BIA sp 30 + metformin) and until target glycaemia values were reached. Primary measures of outcomes were fasting plasmaglucose (pre-prandial), HbA1c, hypoglycaemiarates, body weight and daily dose of insulin per kilogram of body mass (DDI/BMI kg/m²).

Results: Out of 40 patients in total, 20 (50%) were women, and 20 (50 %) were men, age 52, with 8 years of diabetes, BMI 29 kg/m² with HbA1c of 8.6%. There were no significant differences between the Groups in their mean HbA1c values before meal (8.6% vs. 8.5%, p<0.9), but after 24 weeks of therapy, significantly lower values of HbA1c in Group A were recorded (6.7 % vs. 7.3, p<0.05), with a difference of 0.6 % between treatments compared to subGroup B. During the combined-therapy treatment, until the target glycaemic control was reached subGroup A

recorded significantly less, by 21%, of all symptomatic hypoglycaemia over a period of 24 hours (RR=0.79, 95%CI: 0.72-0.86, p<0.02), while total proven symptomatic hypoglycaemias showed a 29% decrease (RR=0.71, 95%CI: 0.61-0.79, p<0.004), and proven symptomatic nocturnal hypoglycaemias 43 % (RR=0.57, 95% CI: 0.22-0.72, p<0.001), compared to Group B. Group A showed significantly smaller difference in body weight (29.4 vs. 30.8, p< 0.05) with absolute difference of -1.4 kg/m², compared to Group B at the end of the treatment. Daily dose of insulin after treatment in Group A was significantly lower (46 vs. 65, p< 0.05) with absolute difference of -19 IU, compared to Group B.

Conclusions: Low, qualitatively equal and regular intake of carbohydrates in combined therapy (BIAsp 30 + metformin) efficiently and safely improves glycaemic control with patients suffering from type 2 diabetes compared to the standard diet according to the ADA Guidelines from 2003.

Key words: Type 2 diabetes, diabetes diets according to the ADA Diabetes Guidelines, combined therapy (BIAsp 30+ metformin), metabolic control.

Introduction

Type 2 diabetes (T2DM) is a dysregulation of glucose homeostasis, characterised by persistent hyperglycaemia, impaired function, progressive failure of beta cells and insulin resistance (1) liver, and \u03b2-cell (triumvirate. About 50% of patients

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with T2DM, after oral combined therapy (OAD) require insulin therapy 6 years after confirmed diagnosis (2,3)"ISBN" : "0149-5992 (Print. Metabolic control is the basis for con-trollingdiabetes. Study results have shown that reduced hyperglycaemia leads to reduction and progression of micro and macrovascular compli-cations, reduced risk of cardiovascular diseases (CVD), especially in newly diagnosed patients (4,5,6)but the effect on macrovascular complications is unknown. There is concern that sulphonylureas may increase cardiovascular mortality in patients with type 2 diabetes and that high insulin concentrations may enhance atheroma formation. We compared the effects of intensive blood-glucose control with either sulphonylurea or insulin and conventional treatment on the risk of microvascular and macrovascular complications in patients with type 2 diabetes in a randomised controlled trial. Methods 3867 newly diagnosed patients with type 2 diabetes, median age 54 years (IQR 48\ u201360 years. The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) published a paper on control of hyperglycaemia in patients with T2DM. Glycaemic control is a major focal point in monitoring T2DM patients. One of the possible therapy protocols in treating T2DM is medical nutrition therapy (MNT), metformin and premix insulin (7) the American Diabetes Association (ADA. Diabetes diet is usually made according to ADA charts, body mass index, and macronutrient distribution (15-20% protein, 60-70% carbohydrates and <7% fat (8). Intake of carbohydrates directly affects postprandial glucose in diabetic patients, therefore it is the first macronutrient for glycaemic control. Standard control of carbohydrate intake, either by adding or by estimating based on experience, is still the crucial strategy for achieving glycaemiccontrol (9). Results of randomised control tests (RCT) show efficiency of the diet therapy in improving glycaemic, lipid control, and reduction of hypertension and cardiovascular risk (10). Medical nutritional therapy (MNT) can improve the overall clinical outcome of treatments, and can reduce overallcosts of diabetes treatment (11). Glycaemic index (GI) is important for improving glycaemic control, based on the existing research, intake of fibre should be > 50 g/day (12). INITATE study, biphasic insulin aspart (BIAsp 30) 2 times a day efficiently reduced HbA1c \leq 7% in

66% of patients (13)"ISBN" : "0149-5992 (Print. BIAsp 30 controls postprandial and pre-prandialglycaemia (14). Metformin has anti-hyperglycaemia effects, reduces glycaemia before meal, after meal, and overall cardiovascular risk (2).

The goals of the research is to estimate efficiency and safety of diabetes diet according to 2013 ADA Guidelines compared to the diet according to 2003 ADA Guidelines in combined therapy (BIAsp+metformin) in T2DM patients.

Materials and Methods

Study population

This 24-week prospective randomised, clinical, controlled, parallel-Group, open study was implemented as an out-patient regimen over the period 03.01.2015 to 31.12. 2015, on the territory of the Tuzla Canton (Bosnia and Herzegovina). The study included T2DM patients chosen according to ADA-WHO criteria, age 40 to 65, with HbA1c > 7 < 11% of those who had been on OAD + baseline insulin combined therapy with 6 years of diagnosed diabetes. The study excluded patients with BMI > 40 kg/m² and damaged renal, liver, and heart function, and patients who refused to participate. All patients were submitted to blood tests for glucose parameters (FPG, 2hpp blood sugar, HbA1c), BMI, daily dose of insulin, and DDI/BMI kg/m². Parameters of metabolic control were measured at baseline, and after 24 weeks of treatment. Body mass index was calculated using data on height and weight of the patients and the following formula: BMI = weight in kg/ height in m². FPG was measured from vein blood using a device value of FPG being 4.4 mmol/l to 6.1 mmol/l). Self-monitoring of blood glucose (SMBG) was measured also using the device ACCU-CHECK, ROSCHE, using a test stripe for quantification of glucose levels in capillary vein blood in the range of 0.6 - 33.3 mmol/l. Reference values of blood glucose before meal were in the range from 4.4 mmol/l to 5.6 mmol/l. HbA1c was determined also using enzyme method based on turbidimetric inhibition (TINIA PRINCIPLE). The original Flex reagents cartridge from DADE BOEHRING will be used on the DIMENSION clinical chemistry system device. Reference values: 4.8% - 6.0 %.

Study design

Prospective randomised controlled study included 40 individuals with T2DM selected according to the ADA/WHO criteria for 2000. The patients were divided into two equal Groups. Group A was treated with low-carb diabetes diet (<45% kcal/day), with four meals in regular intervals and constant dose of carbohydrates per meal (2013 ADA Guidelines), and Group B was treated with 60-75 g of carbs per day diabetes diet, with 6 meals, without quantified intake of carbohydrates per meal (2003 ADA Guidelines). In addition to the diet, both Groups were treated using combined therapy (BIAsp 30 + metformin) until targetglycaemic values of 4-7 mmols before insulin were reached. Titration was done with gradual adding or elimination of 2 IU of insulin until target glycaemic values were reached.

Outcome measures

Primary outcome was to determine efficiency of treatment using diabetes diet according to the 2013 ADA Guidelines, (HBA1c <7%, without body weight increase), and safety (reduces number of total symptomatic hypoglycaemias, and total nocturnal hypoglycaemias). Secondary outcome was to determine DDI/day, and DDI/BMI kg/m²/day.

Statistical analysis

Collected data will be stored in a special database created on a personal computer. Statistical processing will be powered by an application named "IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp". Numerical data will be presented using mean value \pm SD, as a median, number in % and 95 % CI. Hypothesis testing between two independent Groups with multiplemeasuring will be done using ANOVA model, non-parametric tests with significance level of p < 0.05.

Ethical approval

Testing was implemented in line with the 1964 Helsinki Declaration (declaration review at the 50th WHO Assembly, 2000, Glasgow). All the tests done on the patients were routine procedure for accurate diagnosing and improving therapy approach.

Results

RESULTS- Out of 40 patients in total, 20 (50%) were women, and 20 (50%) were men, age 52 ± 10 , with 8 years of diabetes, BMI 29 kg/m². Baseline and demographic characteristics of patients provided in Table 1.

Before treatment, **Group A** of patients had HbA1c of 8.5 %, and after 24 weeks of treatment it was 6.7 %. (8.5% vs. 6.7%, p<0.05); there was a significant difference between treatments with absolute risk of 1.8 % (95%CI: 1.3-2.2). Before treatment, **Group B** of patients had HbA1c of 8.6 %, and after 24 weeks of treatment it was 7.3 %. (8.6% vs. 7.3%, p<0.05); there was a significant difference between treatments with absolute risk

Table 1. Baseline clinical characteristics	s of patient with type 2 diabetes in the study	

Variable	Group A n=20	Group B n=20	P-value
Age (years)	55.7 (36-65)	55.3 (35-64)	0.20
Male (n, %)	8 (50)	1 (45)	0.30
Female (n, %)	12 (60)	11 (55)	0.10
Duration of diabetes (years)	8±20	8±30	0.80
BMI kg/m ²	29.6±2.3	29.4±3.4	0.60
HbA1c (%)	8.6±1.2	8.4±1.3	0.90
Fasting plasma glucose (mmol/L)	9.8±2.8	9.5±2.6	0.80
OAD regimen			
Metformin (n, %)	19 (95)	18 (90)	0.90
Sulfonylurea (n, %)	18 (90)	18 (90)	0.90
Baseline insulin (n, %)	20 (100)	19 (95)	0.90

Note: Values are the mean \pm SD, number %, range, P<0.05 for Group A vs. Group B: Univariante analysis (t-test or x^2 test with p<0.05), Man Witney test for Group A vs. Group B, BMI- body mass index.

of 1.3 % (95%CI: There were no significant differences between the Groups in their mean HbA1c values before meal (8.6% vs. 8.5%, p<0.9), but after 24 weeks of therapy, significantly lower values of HbA1c in Group A were recorded (6.7 % vs. 7.3, p<0.05), with a differential difference of 0.6 % compared to Group B. (Tables 2 and 3).

In Group A, mean value of FPG was 9.5 mmol/l, and after 24 weeks of therapy it was 6.5 mmol/l (9.5 vs. 6.5, p<0.05), with absolute difference of 3.0 mmol/l between treatments. In Group B, mean FPG value was 9.4 mmol/l, and after 24 weeks of therapy it was 7.4 mmol/l (9.4 vs. 7.4, p<0.05), with absolute difference of 2.0 mmol/l between treatments. There were no significant differences between the Groups at the beginning of the treatment (9.5 vs. 9.4, p<0.9), however, FPG was significantly lower in Group A at the end of the 24-week treatment (6.5 % vs. 7.4, p<0.05), with a difference of 0.90 % (95%CI, -1.58 to-0.21, p<0.01) (Tables 2 and 3).

In Group A, BMI before treatment was 31.6 kg/m², and after treatment it was 29.4 kg/m² recording significant difference in body mass after treatment (31.6 vs. 29.4, p<0.05) of -1.7 kg/m². In Group B, BMI before treatment was 30.8 kg/m², and after treatment it was 30.6 kg/m² 30.6, p=ns), showing no significant differences in body mass after treatment. Group A showed significant difference in body weight (29.4 vs. 30.8, p< 0.05) of -1.4 kg/m² compared to Group B at the end of the treatment (Tables 2 and 3).

Glucose was measured over a period of 24 hours using blood glucose 7 points profile: before breakfast, lunch, dinner, 2h after breakfast, lunch, dinner, at 22h and 04h AM. Both treatments recorded significant difference (p<0.05) at all checkpoints of blood glucose profile after 24 weeks of therapy (Figure 1 and 2). After 24 weeks of combined therapy, Group A went through a significant decrease in mean values 2h blood glucose after lunch (7.3 vs. 10.1, p<0.001) with absolute differ-

Variable	Group A	Group B	Group B Mean		95% CI difference	
variable	N=20	N=20	Difference	Lower	Upper	r-value
♥HbA1c %	8.57 ±0.91	8.60±1.09	-0.03	-0.67	0.61	0.93
▼FPG (mmol/L)	9.50±1.04	9.40±1.09	0.10	-0.58	0.78	0.77
♥BMI kg/m ²	30.60±1.04	29.90±1.09	0.70	0.01	1.38	0.46
♥DDI/BMI						
♣HbA1c %	6.70±1.04	7.30±1.09	-0.50	-1.18	0.18	0.05
♣FPG (mmol/L)	6.50±1.05	7.40±1.07	-0.90	-1.58	-0.21	0.01
♣BMI kg/m ²	27.81±1.07	29.59±1.09	-1.79	-2.48	-1.11	0.001
♣DDI/BMIkg/m ²	0.46±0.02	0.65±0.04	-0.19	-0.21	-0.17	0.001

Table 2. Outcome measures between Groups before and after 24 weeks of treatment

Note: Values are the mean \pm SD, \forall Basalmesaures, P<0.05 for \forall Group A vs. \forall Group B; \bigstar After24weeksof treatment P<0.05 for \bigstar Group A vs. \bigstar Group B, Independent Samples T test. HbA1c- Glycated haemoglobin, FPG-Fasting Plasma Glucose, BMI-Body mass index, DDI/BMI-daily insulin dose

Table 3. Comparison of diabetic diets in Groups A and B, before and after therapy

Variable	The	erapy	95% CI difference		CI difference	
variable	Before	After	Lower	Upper	l	P-value
^a HbA1c %	8.57±0.91	6.70±1.04	1.52	2.22	11.19	0.001
^a FPG (mmol/L)	9.50±1.04	6.50±0.99	2.89	3.00	119.90	0.001
^a BMI kg/m ²	30.60±1.04	27.81±0.91	2.47	2.89	26.97	0.04
^b HbA1c %	8.60±1.09	7.30±1.09	1.39	1.45	103.07	0.001
^b FPG (mmol/L)	9.40±1.09	7.40±1.10	1.99	2.02	305.81	0.001
^b BMI kg/m ²	29.90±1.09	29.61±1.27	0.15	0.41	4.62	0.76

Note: Values are the mean \pm SD, "P<0.05 for Group A before vs. After 24weeksof treatment P<0.05 for Group A before vs. after 24weeksof treatment, Paired Samples t-test T test.HbA1c- Glycatedhaemoglobin, FPG-Fasting Plasma Glucose, BMI-Body mass index, DDI/BMI-daily insulin dose

ence of -2.8 mmol/L, blood glucose before dinner (7.11 vs. 8.20, p<0.01) with absolute difference of -1.09 mmol/L, 2h blood glucose after dinner (8.12 vs. 10.22, p<0.0011) with absolute difference of -2.10 mmol/l, while the mean value of blood glucose at 04h was significantly higher (5.6 vs. 4.1, p<0.01) with absolute difference of -1.5 mmol/L, compared to Group B (Figure 1 and Figure2).



Figure 1. Glycemic efficacy in seven point profiles of SMBG at baseline.

During the combined therapy treatment (BIA30+metformin+ADA diet), until target glycaemic control was reached in Group A there was significantly less, by 21%, of all symptomatic hypoglycaemias over the 24 hour-period 21% (RR=0.79, 95%CI: 0.72-0.86, p<0.04), 33% less proven symptomatic hypoglycaemias (RR=0.67, 95%CI: 0.61-0.79, p<0.01), 41% less all symptomatic nocturnal hypoglycaemias (RR=0.59, 95%CI: 0.22-0.72, p<0.001), and 41% less proven nocturnal hypoglycaemias (RR=0.59, 95%CI: 0.22-0.72, p<0.001) than in Group B. (Table 4).



Figure 2. Glycaemic efficacy in seven point profiles of SMBG after 24 weeks treatments between Groups. p<0.05

Figure 3 shows percentages of patients achieving target values of HbA1c. During the treatment aimed at reaching glycaemic control using combined therapy in Group A 76% of patients reached HbA1c<7%, while in Group B 61% of patients reached HbA1c <7%, (76% vs. 61%, p< 0.04) with absolute significant difference between treatments of -15%.

Discussion

Type 2 diabetes, due to complex etiopathogenesis, requires a multidisciplinary therapy approach. In 2012, ADA/EASD published guidelines for treating and monitoring hyperglycaemia in T2DM patients (15). Diabetes diet is the basic principle of therapy for T2DM patients. Medical diabetes diet (MDD) recommended for persons with diabetes is often based on the theory of arbitrary food intake (watch the food), and the focus is usually put on

Type of hypoglycaemia	Group A	Group B	Relative risk (95% CI)	P-value	Reduction risk %*
Overall symptomatic (%)	13.9	17.4	0.79 (0.54-0.96)	P = 0.04	21
Overall confirmed (%)	9.1	13.6	0.67 (0.48-0.83)	P = 0.01	33%
Overall nocturnal symptomatic (%)	3.6	6.1	0.59 (0.40-0.93)	P = 0.001	41%
Confirmed nocturnal (%)	2.6	5.1	0.51(0.39-0.71)	P = 0.001	49%

Table 4. Number of hypoglycaemic episodes per patient over the year

Note: %= 1-relative risk x 100, * = relative risk in percent, PG = plasma glucose.

medical treatment using drugs. Diabetes patients are often frustrated and confused, for they have heard that low-carb diet is idealfor their condition, however,other sources inform them that they require high-carb, high-protein diet, with low intake of fat. Medical recommendation, including diet therapy for T2DM uses the approach of medical diet based on evidence (16). Traditional diabetes diet made according to the ADA Guidelines is consisted of 60-70% of carbohydrates in total kcal. / day, 15-30% of fat and 10-15% of protein (17). Modified ADA diabetes diet with optimal combination of macronutrients per meal contains low doses of carbohydrates per day (Low dose CH, Moderate low dose) <45% carbohydrates, 36-40% of fat and 16-18% of protein. Combination of macronutrients per meal used in diabetes patients is not an ideal mix, so intake of macronutrients in percentages should be designed to meet the needs of the individual. Total intake of daily energy value should be determined according to body weight. The definition of "low dose" of carbohydrates we find appropriate is determined in the range from very low-carb diet (21-70 g/day) to moderately low (30 to 40% of carbohydrate calories) with increased intake of protein and fat (18), RCT show no significant difference in glycaemic control between the diet with lower carb intake and the diet with higher intake of carbohydrates (19,20).

In 2013, ADA issued new guidelines with previously reduced intake of sodium of <2.3 g. and quantitative insulin and carbohydrates ratio per meal (17) In 1999, Institute of Medicine IOM reported useful evidence showing that individualises medical nutritional therapy (MNT) is a part of multidisciplinary therapy, that it can improve clinical outcome, and potentially reduce costs of controlling diabetes (11). Nutritional diabetes therapy also uses vegan and vegetarian diet (21)including total vegetarian or vegan diets, are healthful, nutritionally adequate, and may provide health benefits in the prevention and treatment of certain diseases. Well-planned vegetarian diets are appropriate for individuals during all stages of the life cycle, including pregnancy, lactation, infancy, childhood, and adolescence, and for athletes. A vegetarian diet is defined as one that does not include meat (including fowl as well as DASH diet (22). Indian diabetes diet includes 60-70% of carbohydrates, 15-30% of fat and 5-12% of protein. Results of Barnard et al (2006) show that low-fat vegan diet and ADA basic nutritional diet improve glycaemic control and reduce the overall CV risk (23).

In this study, Group A patients used modified ADA diet with low doses of carbohydrates (45%) with quantified ratio and standard insulin/glucose ratio. Patients had 4 instead of 6 meals a day. While Group B used the basic ADA diet with 60% of carbohydrates per day, with 3 meals and 3 snacks. Results of this study have shown that both combined therapy treatments (BIAsp 30 + Metformin+ ADA diet) show significant reduction of HbA1c. Group A of patients treated with ADA diet with <45 % of carbohydrates per day showed significantly lower values of HbA1c, less increase in body weight (BW), smaller number of total and nocturnal hypoglycaemic episodes, and lower daily dose of insulin compared to the traditional ADA diet. Results can be explained by known facts: Firstly, pharmacokinetics of insulin (PK) BIAsp 30 injected in two doses. Results of the study Luzio et all. (2006) showed that after taking insulin BIAsp 30 in the dosage of 0.5 IU per kg/m^2 , the quantity of infused glucose increased with a peak 4.5 hours after first administration, and 3.5 hours after the second (24)70% protaminated insulin aspart [IAsp]. After every injection of insulin BIAsp 30, concentration of insulin would suddenly increase, reaching its peak after 2-3 hours. Secondly, 4 meals according to PK with the standard insulin/glucose ration (one unit of insulin per 4 g of carbohydrates). Thirdly, patients were educated to stick to the daily regimen, to prepare their proscribed diet with constant intake of carbohydrates and regular distribution of carbohydrates per meal. Fourthly, insulin BIAsp 30 efficiently controls post-prandial and pre-prandialglycaemia (14).

Results of the PRESENT study show that BI-Asp 30, after a 6-month therapy efficiently reduced HbA1c by 1.58%, FPG by 2.9 mmol/l., 2h ppPG by 4.8 mmol/l with significantly lower number of hypoglycaemic episodes compared to the patients previously treated with biphasic human insulin (BHI 30) (25). BIAsp 30 significantly reduced the risk of severe, total symptomatic and nocturnal hypoglycaemias compared to BHI 30 (26)so it is conceivable that twice-daily biphasic insulin analogs might reduce hypoglycemia in patients with insu-

lin-treated type 2 diabetes. We used a continuous glucose monitoring system (CGMS. Results of the INITATE study showed that BIAsp 30 significantly reduces HbA1c compared to insulin glargine. After treatment with BIAsp30 twice a day, 66% of patients reached HbA1c<7%, while 40% of the patients treated with Glargine reached the target value of HbA1c<7% (13)"ISBN" : "0149-5992 (Print. In addition, results of the EuroMix study showed that after 26 weeks of therapy with BI-Asp 30, it was successful in reducing HbA1c with absolute difference of 0.5 % compared to insulin glargine (14). Results of the GALAPAGOS study showed that BIAsp 30 provides more significant reduction of HbA1c than basal plus (1.6 vs. 1.5, p < 0.008), that it is as efficient as basal bolus (BBT), bit with fewer injections (27).

Conclusions

To conclude, both diets in combined therapy (BIAsp 30+metformin) were efficient in glycaemic control in T2DM patients. Diabetes diet with low-carb intake <45 % and quantified standard insulin/carbohydrates ratio (2013 ADA Guidelines) was significantly more efficient in glycaemic control with less body weight increase, and significantly smaller number of total and nocturnal hypoglycaemia episodes compared to the traditional ADA diabetes diet.

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Variations of the intermeniscal ligaments of the knee joint

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Abstract

Aim: To determine variations of meniscal connections of knee joint, namely: anterior and posterior intermeniscal ligament (*ligamentum transversum genus anerior et posterior*), and oblique ligament of meniscus (*ligamentum intermeniscale obliquum, mediale et laterale*). It is important to be aware of anatomic variations of the knee joint structure since they might have clinical importance and contribute to the pain, may cause damage to other structures, or be misinterpreted as meniscus disease or cruciform ligaments, as well as osteochondral or meniscus fragments or pseudosplitting lateral meniscus.

Methods: Prospective observational study of 50 patients of both sexes (38 males and 12 females) suffering from suspected injury of the meniscus or cruciform ligaments, who underwent magnetic resonance imaging (MRI) of the knee joint.

Results: Anterior intermeniscal ligament was detected in 38 (76.0 %) individuals. In our study we have not detected posterior intermeniscal ligament. In 2 (4.0 %) of respondents we noted *lig. intermeniscale obliquum med.* and *lig. intermeniscale obliquum lat.*

Conclusion: There is a considerable level of anatomic variations of all intermeniscal ligaments of the knee joint (40.0 % of all cases), and practicing clinicians should be aware of this, since it might have important clinical implications.

Key words: Knee joint, intermeniscal ligaments, anatomic variations

Introduction

Musculoskeletal system is responsible for initiating the human body and it's static and consists of bones, cartilage, tendons, muscles, ligaments, joint linings and various soft - tissue structures in the joints, such as discs, menisci, and the like. The knee is the largest joint in the human body, the most complex structure and the joint that is most frequently injured. A structure can be injured, but most injuries happen to meniscus, ligaments and cartilage. Knee injuries are the most acute, and if they are not treated immediately after the injury, they become chronic. This is the reason for frequent visits to an orthopaedic surgeon and for the need of either conservative or operative treatment. Tests that follow clinical examination include: arthroscopy, knee radiography, and MRI, which is temporarily considered gold standard to observe the meniscus. It helps in confirming the diagnosis and provides additional information about the status of the ligaments and cartilage of the joint, but it should not necessary be performed in all cases before arthroscopy. In order to properly interpret the results of various diagnostic methods, particularly MRI, it is necessary to have the knowledge of the local anatomy of the knee joint. Knowing the variations of the structure of the knee joint is essential because they can have clinical importance and may contribute to the pain, can cause damage to other structures, or they can lead the less knowledgeable ones to suspect the meniscus disease and cruciform ligaments. They can also be misinterpreted as osteochondral or meniscus fragments and pseudo-splitting lateral meniscus (1, 2). The aim of this research was to determine variations of meniscal connections of knee joint, namely: anterior and posterior intermeniscal ligament (lig. transversum genus ant. and post.), oblique ligament of meniscus (lig. intermeniscale obliquum, med. and lat.).

Patients and methods

This was a prospective observational study conducted in 50 patients of both sexes (38, e.g. 76.0 % male, 12, e.g. 24.0 % female) who under-

went MRI of the knee joint on suspicion of injury to the meniscus or cruciform ligaments. Study was performed at Zenica Cantonal Hospital, Zenica, Bosnia and Herzegovina, from 1st Jan 2014 to 31st Dec 2014. The acting director of the Hospital approved the study. Magnetom Avanto 1,5 T, Siemens Medical Solutions, was used.

The average age of our study group of patients was 37.45 ± 2.3 years (men 46.78 ± 3.2 , and women 28.12 ± 4.7). The patients were predominantly, 35 of them e.g. 70.0 % of cases, referred for MR of the right knee joint. Most of the respondents - 32 of them e.g. 64.0 % - had a lesion of the medial meniscus, and 18 e.g. 36.0 % of lateral meniscus.

Results

We found a considerable level of anatomic variations of all intermeniscal ligaments of the knee joint (20 patients – 40.0 % of all cases). The MR images of knee joint showed existence of "standard" intermeniscal connections as well as variable ones.

Lig. transversum genus (lig. intermeniscale ant.), was noted in 38 patients e.g. 76.0 % of pateints.

There were two types of this ligament discovered, based on the insertion position: a) type I – insertions on the rear horns of both menisci (found in 32 patients e.g. 64.0 %), b) type II – insertions on the rear edges of both menisci (found in 18 patients e.g. 36.0 %).

Variations in incidence and morphology of *lig. meniscofemorale post posterius-Wrisberg*, were also noted. It was observed in 32 respondents (64.0 %). Two types of *lig. meniscofemorale*, were observed: a) type I - upper-proximal insertion of the rear part of the inner side of the medial condyle-femur, and b) type II - proximal half of the *lig. cruciatum post*. Type I was observed in 20 respondents (62.5%), and type II in 12 or 37.5% of the respondents (*lig. meniscofemorale ant.*), out of the entire number of respondents with present ligaments-condition. The both rear meniscofemoralligaments, were observed in 7 patients (14.0 %).

Lig. intermeniscale obliquum med. and *lig. intermeniscale obliquum lat.* were obsereved in 2 patients (4.0 %) (Figure 1 i 2). *Lig. intermeniscale anteromediale*, was not observed in our group of the respondents.



Figure 1. Lig. intermeniscale obliquum med.



Figure 2. Lig. intermeniscale obliquum lat.

Posterior intermeniscal ligament wasn't detected in any patient in our study.

Discussion

Meniscomeniscal ligaments have functional and clinical significance. However, in the classical anatomy textbooks they are rarely described, and even if they are described there is a variety of accounts of their origin, relationship, size and incidence. In the available medical literature there are four distinct types of intermeniscal ligaments. Ligaments that interconnect the meniscus are: transverse ligament of meniscus (*lig. transversum genus*, *lig. intermeniscale transversum seu anterius*) and *lig. intermeniscale post.* (*lig. transver-* *sum post.*) (2, 3). Transverse meniscal ligament connects the anterior and posterior horns of the meniscus. Leaning meniscomeniscal ligaments of meniscus are connecting the front to the back ends of the meniscus. There are two of such ligaments, and they are called after their starting point. Medial oblique ligament (*lig. intermeniscale obliquum, med.*) starts from the front of the medial meniscus passing between the tibial condyle and ends at the rear end of the lateral meniscus. Lateral meniscus oblique ligament (*lig. intermeniscale obliquum lat*) connects the front end of the lateral meniscus and the rear end of the medial meniscus (4, 5).

They hook the rear end of the lateral meniscus with the inside of the medial condyle of the femur or with the rear crossed ligament, and they are located in front, that is, behind the rear cruciate ligament. The most extensive study of the knee joint anatomy, using MR with 1.900 patients, which was completed by Snoeckx et al., confirmed the great variability of bone and connective tissue structures of the knee joint, which was observed in 28.4% of patients (2). The most variable structures were ligaments, and their variations were observed in 13.4% of individuals (6). Transverse ligament of meniscus is missing in 6 - 40% of people (7). Very rarely there is a rear transverse ligament of meniscus (lig. transversum post., lig. intermeniscale post.) in 1% of individuals (8). In our study group, we found transverse ligament of meniscus missing in 34% of patients.

Timothy *et al.* (9) explored the variable anatomy of intermeniscal ligaments using MRI and found the existence of oblique meniscus ties (*lig. intermeniscale obliquum med. et lat.*) in 5.7% of individuals. Several different authors have indicated the existence of oblique ligaments of meniscus in 1 - 4% individuals (4, 5, 9-11).

Knowing the normal anatomy and variations of meniscal ligaments is essential for proper interpretation of MRI findings and in order to avoid false positive or negative diagnosing of meniscus damage (12). Leaning/oblique meniscofemoral ligaments can be easily mistaken for flap and bucket - handle tears (13). They can also be misinterpreted as ostechondral or meniscal fragments and pseudo-splitting of lataral meniscus (1, 2). Injuries to the anterior horn of the medial meniscus and posterior horn of the lateral meniscus are often misdiagnosed and mistaken for existence of the front cross-meniscal and rear meniscofemoral ligaments of knee joint (6, 14).

Knowing the variations of the structure of the knee joint is essential because they can have clinical importance and may contribute to the pain, can cause damage to other structures, or they can lead the less knowledgeable ones to suspect the meniscus disease and cruciform ligaments.

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A 30-day clinical investigation of the safety and efficacy of KollaGen II-xs[™], a new avian sternal collagen type II hydrolysate

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Abstract

The present prospective and single-center investigated the safety and efficacy of KollaGen IIxsTM, an avian sternal collagen type II hydrolysate. The range of motion, general pain, and muscle strength were evaluated. The results indicated that administration of 1500 mg/day of collagen type II hydrolysate for 30 days improved essential symptoms in individuals suffering from joint diseases, including range of motion, general pain, and muscle strength. These data support the view that collagen type II hydrolysate may be administered to patients suffering from joint diseases. No adverse effects were observed during the trial. These data support its use for patients suffering from degenerative joint diseases, including cartilage injuries, connective tissue disorders, polychondritis, joint defects, osteoarthritis, and rheumatoid arthritis.

Key words: avian sternal collagen type II hydrolysate, joint diseases, range of motion, general pain, muscle strength.

Introduction

KollaGen II-xsTM, an avian sternal collagen type II hydrolysate, is a dietary supplement that may be beneficial for patients suffering from degenerative joint diseases, including cartilage injuries, connective tissue disorders, polychondritis, joint defects, osteoarthritis, and rheumatoid arthritis. Its use in the treatment of degenerative joint diseases has increasingly gained support in medical community and among consumers¹.

Kollagen II-xs[™] has an average molecular weight of between about 45 and 65 kilodaltons (kDA). It is obtained from desiccated young avian sternal carti-

lage. Preferably, the avian sternal cartilage is collected from 4 to 8 week-old chicks. It is partially watersoluble and the composition comprises 20% to 30% of mucopolysaccaride, 65% to 70% of collagen type II and 1% to 3% of lipids. It may provide a method of helping cartilage formation in humans². Non clinical studies have demonstrated that

Non chinical studies have demonstrated that orally administered preclinical studies, it has been demonstrated that orally administered collagen type II hydrolysate is can be thoroughly absorbed by the intestine and circulated in the blood stream. These studies also revealed that that a significant amount of collagen type II hydrolysate-derived peptides reach cartilage tissue³. In addition, it was demonstrated that treatment of cultured chondrocytes with hydrolyzed collagen induced a statistically significant dose-dependent increase in type II collagen synthesis of the chondrocytes in cell culture experiments⁴.

Based on the findings that collagen hydrolysate is absorbed in its high molecular form, accumulating in cartilage, and is able to stimulate chondrocyte metabolism, it might be reasonable to use collagen type II hydrolysate as a nutritional supplement to activate collagen biosynthesis in chondrocytes in humans, especially patients suffering from degenerative joint diseases. Thus, the aim of this prospective and single-center investigation is to extend these earlier findings with KollaGen II-xsTM, an avian sternal collagen type II hydrolysate.

Materials and methods

Study design

This prospective and single-center clinical trial was approved by the Ethics Committee of Mortec Scientific, Inc. (Cambridge, ON, Canada) and managed in its Department of Clinical Medicine. According to study schedule, the consent form was discussed, signed and a complete physical examination was executed at screening. Activity level, diet history, medication/supplement use and medical history were recorded.

Subjects' complaints of joint discomfort were recorded using pre- and post-treatment questionnaires to evidence personal data and issues related to an individual's functional quality. A goniometer was used to measure the range of motion⁵, a pain scale (Borg) was applied to subjectively percept the pain⁶, and a properly calibrated sphygmomanometer was utilized to evaluate muscle strength⁷.

Urine was collected for a pregnancy test for women of childbearing potential. A blood sample was taken for determination of alanine transaminase (ALT), aspartate transaminase (AST), bilirubin, blood urea nitrogen (BUN) and creatinine. Upon review of blood test results, eligible subjects were instructed to get an X-ray of the affected joints to confirm diagnosis.

A total of 15 subjects were recruited using the inclusion and exclusion criteria outlined in Table 1. At the first visit, selected subjects, properly informed by the Consent Term approved by the Scientific Committee of the Institute, were assigned to receive 1500 mg kollaGen II-xsTM (Certified Nutraceuticals, Inc., San Diego, CA) daily. At the final visit, subjects were required to come to the clinical division for clinical assessment. A subject treatment diary was completed by each patient throughout the study period to determine product compliance, side effects, and supplementation use.

Statistical method

For comparing non-parametric values, the Wilcoxon's test was used, and for comparing parametric values, the variance analysis (ANOVA) test were used. A significance level of 5% was adopted in all comparisons and statistically significant results were marked with an asterisk (*).

Table 1. Inclusion and exclusion criteria

Inclusion criteria						
Males and females 45-75 years old						
Females of childbearing potential must agree to use a medically approved form of birth control and have a negative urine pregnant test result						
Disorder of the knee for more than three months						
Able to walk						
Availability for duration of study						
Subject agrees not to start any new therapies during the course of the study						
Able to give informed consent						
Exclusion criteria						
History of asthma, history of diabetes						
Hyperuricemia						
Hypersensitivity to NSAIDs						
Abnormal liver or kidney function tests						
Abnormal findings on complete blood count						
Uncontrolled hypertension						
History of allergic reaction to any ingredients in the test product						
Hyperkalemia (potassium > 6.2 mmol/L)						
History of cancer as well as gastrointestinal, renal, hepatic, cardiovascular, hematological, or neurological disorders						
Anticipated problems with product consumption						
High alcohol intake (>2 standard drinks per day)						
History of psychiatric disorder that may impair the ability of subjects to provide written informed consent						
Use of concomitant prohibited medication (narcotics, NSAIDs)						
Any other condition that, in the opinion of the investigator, would adversely affect the subject's ability to complete the study or its measures						

Results

Baseline characteristics of patients are summarized in Table 2. Where applicable, values are expressed as mean \pm standard deviation.

Table 2. Baseline characteristics of patients.

Characteristics of patients	Values
Age (years)	53.7 ± 8.72
Sex (male/female)	8/7
Height (cm)	168.3 ± 9.74
Weight (kg)	82.9 ± 16.3
Systolic blood pressure (mm)	121.8 ± 8.92
Diastolic blood pressure (mm)	80.6 ± 7.71
Heart rate (bpm)	69.4 ± 7.56

The results are presented in Table 3 and Table 4 listing values for average, and standard deviation for each analyzed variable. Statistically significant results are marked with an asterisk (*)

Table 3. Range of motion, pain and muscle strength.

Treatment	Range of motion ⁵		General pain ⁶		Muscle strength ⁷	
	Pre	Post	Pre	Post	Pre	Post
Average	105,22	169,87	8,73	2,36	58,43	102,89
Standard deviation	13,46	10,54	10,54	13,15	10,54	11,46
Standard error	4,22	4,76	4,76	5,37	4,76	5,21

Table 4.	Pre-	and	post-	treatment	groups
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Comparison	Р
Range of motion	0,021*
General pain	0,007*
Muscle strength	0,005*

These results indicate that administration of 1500 mg/day of collagen type II hydrolysate for 30 days improved essential symptoms in individuals suffering from joint diseases, including range of motion, general pain, and muscle strength. No adverse effects occurred during the 30-day trial period. The treatment was reported to be well tolerated by subjects.

Discussion

In the last few years, various nutritional supplements, including chondroitin, glucosamine, soybean unsaponifiables and diacerein have emerged as new treatment options for joint disorders⁸. The aim of this prospective and single-center investigation is to evaluate the safety and the efficacy of KollaGen II-xsTM, an avian sternal collagen type II hydrolysate, which is a complex structural protein that may provide strength and flexibility to connective tissues.

An observational study investigated the use of collagen type II hydrolysate as a nutritional supplement to reduce symptoms of joint damage, with the hope that this change would reflect improvements in joint health. In that study, individuals were recruited who had not been diagnosed with degenerative joint disease but who complained about joint pain that both the treating physician and the subjects interpreted as being a result of stressful exercising. It was reported that 78% of individuals at the end of the study noticed substantial improvement of their joint symptoms, including range of motion, pain, and muscle strength⁹.

The evaluation of muscle strength is an important technique to diagnose the etiology of the disease, and to define rehabilitation strategies. The muscle weakness, which was observed in our study during the pre-treatment assessments, is directly associated with knee joint pain and joint disability¹⁰.

Osteoarthritis results in changes that affect not only intracapsular tissue, as well as periarticular tissues, such as ligaments, capsules, tendons and muscles. Osteoarthritis patients compared to healthy individuals of the same age had muscle weakness, reduced knee proprioception, reduced balance and position sense¹¹.

The presence of joint effusion, even in small amounts, is a potent inhibitory mechanism reflex muscular activity of the joints. A reduced reflex muscular activity causes hypotrophy and weakness early, with the resultant associated mechanical damages, such as decreased range of motion¹².

Muscle strength declines rapidly during the detention of a member by decreasing the size of the muscle and stress per unit of the muscle cross-sectional area. The largest absolute loss of muscle mass occurs at the beginning of hypotrophy pro-

cess¹³. The pain inhibits reflex muscular activity, causing atrophy, and muscle weakness. The pain-ful process is prior to the muscular weakness¹⁴.

This prospective and single-center investigation suggests that KollaGen II- xs^{TM} , an avian sternal collagen type II hydrolysate, may be beneficial for patients suffering from degenerative joint diseases, including cartilage injuries, connective tissue disorders, polychondritis, joint defects, osteoarthritis, and rheumatoid arthritis.

Conclusion

The purpose of this study was to determine whether administration of 1500 mg of avian sternal collagen type II hydrolysate daily would reduce joint pain in patients suffering from joint diseases. The design of the clinical trial was appropriate to reveal that collagen type II hydrolysate as a nutritional supplement ingested over 30 days was safe and efficacious in reducing symptoms of joint discomfort. The results of the trial provide data supporting the view that collagen type II hydrolysate may be administered to patients suffering from joint diseases. Further research will elucidate additional benefits from collagen type II hydrolysate.

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The Effect of Watching TV on Anxiety Levels and Tendency towards Violence in Children

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Abstract

Introduction: This descriptive study was conducted in order to examine the effects of watching Television (TV) on the anxiety levels and tendency towards violence in children.

Methods: This study was conducted among 360 students receiving education in three different secondary schools (5th, 6th, 7th and 8th grades) in a Turkish city centre between September 2013 and June 2014. The data were collected using a questionnaire, the State-Trait Anxiety Inventory for Children (STAIC) and the Violence Tendency Scale.

Results: In the study, the state of anxiety mean score of children was 35.22 ± 5.72 , their trait anxiety mean score was 32.89 ± 6.75 and their violence tendency mean score was 32.20 ± 10.51 . It was determined that the daily duration of TV watching among the children, as well as their desire to be like the characters on TV and the level of violence of the TV programs affected their anxiety levels and their tendencies towards violence. Their willingness to watch TV and the frequency with which they watched it were observed to affect only their tendency towards violence (p<0.05).

Conclusions: It was determined that all children who were included in the study watched TV, and they all showed mild levels of anxiety and tendency towards violence.

As a consequence, families, legislators, and publishers are responsible for protecting children from the negative effects of TV.

Keywords: Child, nurse, anxiety, violence, TV

Introduction

TV has an important place in many children's lives. Reasons for watching TV generally differ between children and adults. While a majority of adults watch TV for entertainment, children watch

in order to gain knowledge and understanding about the world (1, 2).

TV performs a number of positive services, as it is an efficient form of media aimed at both visual and audial senses; however, the behaviour that results from watching TV can cause negative results, unless it is kept under control (3, 4).

According to the literature, there was a relationship between the habit of watching TV that features sexual content and substance abuse and an insensitivity to violence, fear and increase in aggressive behaviours among children (3, 5).

Due to the features of their mental processes, children perceive and get influenced by what they watch in a different and more complete way than adults do. They perceive the fictional elements on TV programs as reality (6-8). In numerous regards, children are more vulnerable to TV compared to adults (6, 8). While playing games in their daily lives, children mimic the heroes of TV series, which may cause them to display aggressive behaviours (9).

Anxiety is a tension being felt as a reaction against an expected threat to the integrity of selfrespect. Tension is defined as a disturbing emotion caused by danger, irritability or panic (10). TV programs cause negative changes in the cognitive, affective, and behavioural processes of children who watch it, especially those who watch violent programs (2, 11-13).

Repeated broadcasting of violent programs causes anxiety, fear and tension in everyone and makes them desensitized towards violence (2). Additionally, these programs create wrong behavioural models for both children and adolescents (14).

The nightmares, fears, anxieties, and tensions of children and adolescents increase with the duration of watching TV in a directly proportional way (15, 16). Children who had TV sets in their rooms and/ or watched TV before going to bed were observed to have many more nightmares and night terrors. In fact, 92% of children and adolescents who apply to clinics due to fear, anxiety, or nightmares are basically scared of what they watch on TV (14). Violence on TV may cause anxiety (17, 18).

A study conducted by Uysal (19) which yielded results similar to one conducted by the Turkish Institution of Family Research, determined that 57.8% of students aged 7-14 had a tendency towards violence at a "mild" level, 37.9% at a "high" level and 2.9% at a "very high" level.

Parents have the greatest responsibility for protecting their children from the harmful effects of TV (20). The guideline published by the American Academy of Pediatrics in 2002 suggested preventing children from watching TV for more than two hours a day, especially for children younger than two years old. Furthermore, the guideline suggested they should watch TV under the supervision of parents, who should direct them towards social activities rather than TV (21, 22).

In Turkey, the Radio and TV High Council (RTUK) started a program of warning signs titled "Smart Signs" on 23 April 2006 in order to protect children from the negative effects of TV. The system of Smart Signs offers information regarding two matters: the possible harmful content of programs and their target age group. These signs are displayed during the broadcast of programs on TV and in the printed/visual-audial media, together with the announcement of programs in question. Warnings to parents concerning the harmful effects of TV on children, in combination with Smart Signs, will be useful in protecting children from the effects of the TV (20).

According to a study conducted by Neely et al. (23) children's exposure to media violence is associated with aggressive behavior, desensitization to violence, anxiety, depression, and sleep disturbances. According to a study conducted by Strasburger et al. (24) children and teenagers learn from the media, and their behavior can be influenced by it. Additionally, the media can have significant effects on health: e.g., obesity, substance use, early sexual activity, and eating disorders. Parents, clinicians, and schools need to adapt to the world of new technology and understand the influence that the media can have on young people. According to a study conducted by Yilmaz and Ersoyol (25) parents who had graduated from a university showed higher levels of participation than those who only finished primary, secondary or high school in the negative effect of media on children. Subjects who were teachers also showed higher levels of participation than housewives and retired parents in the negative effect of media on children.

There has been no study conducted in Turkey or abroad on the effect of watching TV on the anxiety levels and tendency towards violence in children. The purpose of this study was to do just that. TV viewing among children is an issue of concern to medical professionals, paediatric psychologists and families, given the potential impact it can have on school performance in children. According to a study conducted by Neely et al. (23) interventions integrated into the primary care visit can affect children's media viewing habits and children's exposure to violence. Recent research has focused on the potential impact of viewing TV on attention, so this study is important.

Methods

Research design

This descriptive study was conducted in order to examine the effects of watching TV on the anxiety levels and tendency towards violence in children.

Setting and samples

The study was conducted between September 2013 and June 2014. The study population consisted of 5th, 6th, 7th, and 8th grade students receiving education in 17 elementary schools in a city centre of Turkey. According to the data from a Provincial Directorate for National Education in the school year of 2012-2013, the size of the population was determined as 6,758 individuals (number of 5th, 6th, 7th, and 8th grade students).

By using the formula $(n=N.t^2.pq/d^2(N-1)+t^2.pq)$ for cases in which the population is known, the size of our sample group was determined to be 360 individuals with a margin of error of 0.05 (26). The sample group for this study consisted of 5th, 6th, 7th, and 8th grade students receiving education in Cumhuriyet, Sümer and 13 Şubat secondary schools that were determined by lot-

tery among schools representing three different socioeconomic conditions. Students were selected randomly from the class lists until the sample size reached the number that was determined by the stratified sampling method. The study was conducted on students who were present at school on the days when the data collection forms necessary to participate were distributed and turned in. In total, 375 students were accepted to participate in the study. Since 15 students failed to sufficiently fill out the questionnaire, the study was completed with 360 students in total.

The main hypothesis of this study was about The Effect of the State of Watching TV on Anxiety Levels and Tendency towards Violence in Children. The results of the study supported this hypothesis.

Violence programs have included violence factors (fighting, shouting etc.). Students with physical and mental disabilities were excluded from the study.

Ethical permissions

In order to conduct the study, legal permissions were obtained from the relevant institutions. This study was approved by the ethical review boards at the authors' institution (and each hospital, 08. 07. 2013).

The investigation conforms to the principles outlined in the Declaration of Helsinki. Participants were informed of the purpose and nature of the study and assured of the confidentiality of the data.

They were also assured that their participation was voluntary and that they could

withdraw from the study at any time. Once the participants agreed verbally to take part in the study, written consent was obtained. The participants's parents also agreed verbally to take part in the study, written consent was obtained.

Measurements

Questionnaire

The questionnaire used to collect data in this study was developed by the researcher, in line with the current literature, and included questions about children and families (27-29). Specifically, the questionnaire included questions about the gender, age, and class of the child, as well as his/her number of siblings, educational level and employment status of her/his parents, and the subject's family structure. There were also questions about the state of the child to watch TV. The questionnaire consisted of 26 questions total.

State-Trait Anxiety Inventory for Children (STAIC)

Theoretical debates continue regarding the nature of anxiety and whether it is learned or innate. The interpretation that "this theoretical ambiguity is caused by using the anxiety for two different conditions" was made for the first time by Cattel and Scheier (1958). Two different anxiety factors that were thereafter called "state and trait anxiety" by Spielberger (1966) were identified in this study (30).

The STAIC was translated into Turkish by Özusta. The scale can be used for children up to the age of 17 (31). Also called the "Questionnaire of How I Feel", STAIC intends to measure the permanent personal differences in anxiety susceptibility. It involves twenty items and children are required to evaluate how they "generally" feel and specify the most convenient option according to the frequency of the condition. Options for each condition include "hardly ever", "sometimes" and "frequently"; selecting the option "frequently" yields a score of 3, which is the highest score, and "hardly ever" yields a score of 1, which is the lowest score. While the total lowest score to be obtained from the Trait Anxiety Inventory is 20, the total highest score is 60 (30).

In the STAIC, children are required to evaluate how they feel in "that moment" and mark one of the three relevant options. Consisting of 20 items, the inventory aims to evaluate the emotions associated with the child's state of anxiety, such as tension, irritability, impatience and restlessness. While half of items reflect the absence of restlessness, rush, and tension, the rest of them reflect the presence of these conditions. When children state the presence of these emotions as "very much", the highest score (3) is given, and when children state the lack of these emotions, the lowest score (1) is given. The STAIC assessment is conducted by self-reporting and could be applied either individually or in groups. Its validity and reliability was demonstrated by Özusta in 1995 (30).

In the STAIC results, the Cronbach's alpha coefficient was found to be .82 for the state anxiety inventory and .81 for the trait anxiety inventory. In the entire group, the test-retest reliability coefficients of the STAIC results were .60 for the state anxiety inventory and .65 for the trait anxiety inventory (30). In this study, the Cronbach's alpha coefficient was found to be .81 for the state anxiety inventory and .86 for the trait anxiety inventory in STAIC results.

Violence Tendency Scale

This scale was developed by Göka, Bayat and Türkçapar in 1995 to be used in the study titled "The Aggression and Violence Tendencies of Students Receiving Education at Secondary Education Institutions". That study was conducted in the name of the Ministry of National Education. It was rearranged without changing its basic structure to measure the tendency of children aged between 7-14 towards violence in the study of the T.R. Turkish Institution of Family Research, titled "Domestic and Social Violence", and its content validity was confirmed. Students were required to read all 20 items and select the best option for them, among options of "not convenient at all", "a little convenient", "convenient", and "very convenient" (32).

Since the Violence Tendency Scale was previously analysed in terms of its validity by Göka et al., its reliability tests were conducted. In order to examine the reliability of the scale, the reliability coefficient of the scale was determined as .78 and .87 at two different times within the scope of the internal consistency. In the Split Half test that was performed, the alpha value was found to be .74 for the first half and .81 for the second half, and the result of the Spearman-Brown test was .86 overall (32). As a result of this study, the Cronbach's alpha coefficient of the Violence Tendency Scale was determined to be .89.

Data Collection

The data for this study were collected using three tools. We firstly applied the questionnaire that was prepared by the researcher using the literature and similar studies; secondly, we used Spielberger et al.'s STAIC; and thirdly, we used the Violence Tendency Scale that was developed by Göka, Bayat, and Türkçapar.

The principals of elementary schools within the scope of the study were consulted and the working hours were determined for the study. After informing the children, teachers and parents about the study and obtaining the written permissions of children and parents, the data collection tools were applied to students on the specified dates and hours in the company of the schools' counsellors. Each application lasted approximately 30-40 minutes.

Data analysis

In the study, the statistics package software of SPSS 18.00 for Windows was used to conduct the statistical analysis of the data. Additionally, the frequency, percentage, t test, One-Way Analysis of Variance, LSD Post Hoc test, Mann Whitney U test, Kruskal Wallis H test, Dunnet T3 Post Hoc test and the Cronbach Alpha test were used to assess the data.

Results

Socio-demographic characteristics of children and parents

It was determined that 29.2% of children included in this study were 13 years old, 56.1% of children were female, and 29.2% of children were 7th grade students. Further, 87.2% of participants' mothers were uunemployed, 56.9% of participants' mothers had received only primary education, 85.6% of participants' fathers were employed, and 39.4% of participants' fathers had received a primary education, A total of 87.8% of participants were from nuclear families, and the mean age for mothers was 37.00 ± 5.03 , while the mean age for fathers was 40.35 ± 5.94 (Table 1).

As a result of the study, it was determined that 62.8% of children liked watching TV. Examining the weekly frequency of TV watching in children, it was determined that 53.3% watched every day, 20.3% watched 3-4 days a week, and more than half of the children (54.4%) watched TV for 2-3 hours a day. When children were asked whether or not they desired to be like the characters on TV, 28.6% answered "yes" and 38.3% answered "sometimes".

Arithmetic mean and standard deviation values of the state- trait anxiety inventory and violence tendency scale

The state anxiety scores of children varied between 25 and 60, and their mean was 35.22 ± 5.72 . The trait anxiety scores of children varied between 20 and 53, and their mean was 32.89 ± 6.75 . Finally, the scores measuring the tendency towards violence in children ranged from 22 to 75, and their mean score was 32.20±10.51 (Table 2).

Table 1.	Socio-dem	ographic	characteristics	of
children d	and parents	(N=360)		

		<u>n (%)</u>
	11	78 21.7
1	12	79 21.9
Age	13	105 29.2
	14	98 27.2
Condor	Female	202 56.1
Gender	Male	
	5.	78 21.7
Crada	6.	79 21.9
Grade	7.	105 29.2
	8.	98 27.2
Working status	Employed	46 12.8
of mother	Unemployed	314 87.2
	Literate	77 21.4
Mother's	Primary Education	205 56.9
Education	Secondary Education	53 14.7
	Higher Education	25 6.9
Working status	Employed	308 85.6
of father	Unemployed	52 14.4
	Literate	65 18.1
Father's	Primary Education	142 39.4
Education	Secondary Education	101 28.1
	Higher Education	52 14.4
Family tyme	Nuclear family	316 87.8
Family type	Extended Family	44 12.2
The much on of	Absent	21 5.8
siblings	1	118 32.8
sionings	2 and above	221 61.4
Mother's age	X± SD	37.00±5.03
Father's age	X± SD	40.35±5.94

Considering the score interval of the state and trait anxiety inventories and the violence tendency scale, it could be asserted that children who watched a particular amount of TV showed mild levels of anxiety and tendency toward violence (Table 2).

Comparison of the state and trait anxiety and tendency to violence based on states of children to willingly watch TV

While the difference between the mean scores of children regarding the tendency towards violence was significant according to the how much they liked watching TV (p<0.05), the difference between the mean scores of state and trait anxiety was insignificant (p>0.05) (Table 3).

In order to understand the reason behind the differences in terms of the tendencies towards violence, the Dunnet T3 post hoc test was performed, and the difference was associated with those who liked watching TV. Children who liked watching TV had higher scores of violence tendency compared to those who did no (Table 3).

Comparison of the state and trait anxiety and tendency to violence based on the frequency of children to watch TV

While the difference between the mean scores of children regarding the tendency towards violence was significant according to the frequency with which children watched TV (p<0.05), the difference between their score averages of state and trait anxiety was insignificant (p>0.05).

The mean score of the children's tendency towards violence was 37.01 ± 11.01 for those watching TV every day and 30.50 ± 11.08 for those

Table 2. Arithmetic mean and standard deviation values of the state- trait anxiety inventory and violence tendency scale

	Score Interval	Min	Max	X± SD
State Anxiety	20-60	25	60	35.22±5.72
Trait Anxiety	20-60	20	53	32.89±6.75
Tendency to Violence	20-80	20	75	32.20±10.51

Table 3. Comparison of the state and trait anxiety and tendency to violence based on states of children to willingly watch TV

	State				
	Liking X±SD	Not liking X±SD	Sometimes liking X±SD	KW	р
State Anxiety	35.26±6.11	36.44±7.92	35.06±4.77	.20	.906
Trait Anxiety	33.15±6.63	32.89±8.48	32.40±6.86	1.10	.578
Tendency to Violence	36.02±10.58	28.33±7.62	34.22±10.37	7.13	.028

Frequency of Watching TV							
	Every day X±SD	1-2 days a week X±SD	3-4 days a week X±SD	Only at weekends X±SD	1-2 times a month X±SD	KW	р
State Anxiety	35.04±6.24	36.15±6.50	34.64±3.91	35.82±4.58	36.17±5.49	4.85	.303
Trait Anxiety	33.36±6.75	32.71±6.72	31.47±6.04	32.79±7.55	37.00±8.94	6.03	.197
Tendency to Violence	37.01±11.01	34.20±11.60	32.85±7.48	32.53±9.81	30.50±11.08	15.15	.004

Table 4. Comparison of the state and trait anxiety and tendency to violence based on the frequency of children to watch TV

Table 5. Comparison of the state and trait anxiety and tendency to violence based on children's daily duration to watch TV

Daily Duration of Watching TV					
	0-1 hour X±SD	2-3 hours X±SD	4 hours and above X±SD	F	р
State Anxiety	35.92±5.41	35.04±5.29	33,90±8.15	2.09	.126
Trait Anxiety	32.34±7.08	32.55±6.28	36.33±7.12	5.90	.003
Tendency to Violence	33.59±10.84	35.48±9.75	38.95±12.24	4.08	.018

watching it 1-2 times a month. Mean scores of tendency towards violence proportionally increased with the increase in the frequency of TV watching.

In order to find the reason for the difference in terms of the tendencies towards violence, the Dunnet T3 post hoc test was performed and it was determined that children who watched TV every day had higher scores of tendency towards violence compared to those watching 3-4 days a week (Table 4).

Comparison of the state and trait anxiety and tendency to violence based on children's daily duration to watch TV

Upon examination of Table 5, it was determined that there was a significant difference between mean scores of trait anxiety and violence tendency based on children's duration of TV watching (p<0.05).

Also, there was an insignificant difference between the state anxiety mean scores based on children's duration of TV watching (p>0.05).

In order to determine the reason for the difference in terms of trait anxiety and tendencies toward violence, the LSD post hoc test was performed and consequently it was determined that the difference in terms of scores of the trait anxiety and tendencies towards violence was caused by watching TV for 4 hours a day or more. Furthermore, while children watching TV for 4 hours a day or more had higher scores of trait anxiety compared to those watching TV for 0-1 hour and 2-3 hours a day, children watching TV for 4 hours a day or more had higher scores of tendency towards violence compared to those watching TV for 0-1 hour a day (Table 5).

Comparison of the state and trait anxiety and tendency to violence based on the state of watching violent tv programs

It was determined that children had statistically significant mean scores of state anxiety and tendency towards violence according to their states of watching violent TV programs (p<0.05). The mean score of children watching violent TV programs was 30.34 ± 6.13 in state anxiety and 35.54 ± 10.60 in the tendency towards violence (Table 6).

Comparison of the state and trait anxiety and tendency to violence based on the states of children to desire to be like characters on the TV

A significant difference was determined between groups in terms of mean scores of state and trait anxiety according to children's states of desiring to be like the characters on TV (p<0.05). Children who desired to be like the characters

0 1 0				
	Watching X±SD	Not watching X±SD	U	р
State Anxiety	30.34±6.13	27.32±4.47	2241.50	.024
Trait Anxiety	32.99±6.65	31.05±8.28	2740.50	.258
Tendency to Violence	35.54±10.60	29.21±6.43	2032.00	.006

Table 6. Comparison of the state and trait anxiety and tendency to violence based on the state of watching violent tv programs

Table 7. Comparison of the state and trait anxiety and tendency to violence based on the states of children to desire to be like characters on the TV

	State of desir	ing to be like charact			
	Yes X±SD	No X±SD	Sometimes X±SD	F	р
State Anxiety	36.69±7.14	35.29±5.24	34.07±4.61	6.37	.002
Trait Anxiety	33.86±6.52	30.95±7.13	33.83±6.25	7.59	.001
Tendency to Violence	36.30±10.81	34.57±12.11	34.93±8.67	.82	.440

on TV had higher mean scores of state anxiety (36.69 ± 7.14) compared to children who did not (35.29 ± 5.24) . The mean score of trait anxiety was 33.86 ± 6.52 in children who desired to be like the characters on TV. There was a statistically insignificant difference between mean scores of tendency towards violence based on children's desire to be like the characters on TV (p>0.05) (Table 7).

Discussion

It was determined that 62.8% of children included in this study liked watching TV. As a result of their study, Eraslan and Demir (33) determined that 33% of children partially liked watching the TV, 26% liked it very much, 23% liked it a little and 18% liked it a great deal.

It was determined that 53.3% of children who were included in this study watched TV every day, and more than half of children (54.4%) watched TV for 2-3 hours a day. In their study, Belviranli et al. (20) determined that 62.8% of children watched TV for 2 hours or more and 22.3% watched for 4 hours or more. According to a study conducted by Eraslan and Demir (33) 73% of children watched TV for 2 hours or more every day. According to a research conducted by the Radio and TV High Council (34) 28.4% of children watched TV for 5 hours per day or more, 20.8% for 2 hours and 18.1% for 3 hours. In their study, Yalçin et al. (35) determined that 62% of children watched TV for two hours or more every day and 8.3% for more than four hours every day. A study conducted in the United States revealed that children watched TV for an average of 21-28 hours a week (36). According to a study conducted by Braithwaite et al. (37) daily television viewing in excess of one hour was reported in 89% of adolescents and 79% of children. In their study, Tandon et al. (38) determined that children's daily screen time varied from 1.7 hours/day in high socioeconomic status to 2.4 in low socioeconomic status families. According to the literature, children start to watch TV from the ages of 3-4 and watch TV for (on average) at least 1-2 hours a day until the ages of 12-13 (39). The study results showed a parallelism with the literature. According to the literature, there is a negative relationship between the duration of watching the TV and the intelligence level of children. It is stated that with the decrease of hours allocated for watching the TV, the intelligence level of children increases (40, 41). In this case, it could be thought that students' increased frequency of TV watching may adversely affect them in all aspects.

When children included in the study were asked whether or not they desired to be like the characters on TV, 28.6% answered "yes" and 38.3% answered "sometimes".

The state anxiety scores of children included in the study varied between 25 and 60, and the mean score was 35.22 ± 5.72 . The trait anxiety scores of children varied between 20 and 53, and the mean score was 32.89 ± 6.75 . Considering the score interval of the state and trait anxiety scale, it could be asserted that children showed a mild level of anxiety (Table 2). The results obtained from the study that was conducted by Turan Cebeci (42) with 100 students receiving education in the 1st and 5th grades revealed that the trait anxiety scores of children varied between 20 and 59, and the mean score was 36.66 ± 7.34 . The state anxiety scores of children ranged from 22 to 50, and the mean score was 32.72 ± 7.35 . Our study results were in line with literature.

The score interval of tendency toward violence in children included in this study varied between 22 and 75, and the mean score was 32.20 ± 10.51 . Taking the score interval of the violence tendency scale into consideration, it could be asserted that children overall showed a mild level of tendency towards violence (Table 2). According to the study conducted by Özgür et al. (43) the mean score of violence tendency level in students was 44.08±12.48. Considering the maximum score of 80, it could be stated that students did not have a high level of tendency to violence; considering the percentages, on the other hand, 53.6% of students had high levels of tendency to violence (or above "moderate"). The research conducted by the T.R. Turkish Institution of Family Research (44) demonstrated that 35% of children in the age group of 7-14 years had "lower" scores of tendency toward violence (40 points) and 2% had "higher" scores of tendency toward violence (60 points and above). In the study conducted by Uysal (19) 57.8% of students showed low levels of tendency toward violence, 37.9% showed "high" and 2.9% showed "very high".

While the difference between the mean scores of children included in the study was significant in terms of how much they liked watching TV, the difference between their mean scores of state and trait anxieties was insignificant. Children who liked watching TV had higher scores of tendency towards violence compared to those who did not (Table 3). According to this result, it could be thought that children who like watching TV may watch it with more frequency, and they may watch all kinds of TV programs.

It was determined that among children included in this study, the frequency with which they watched TV had an effect on their tendency towards violence; however, their state and trait anxiety was not affected by the frequency of watching TV. Children who watched TV every day had higher scores of tendency towards violence compared to those who watched TV for 3-4 days a week (Table 4). It was determined that the mean scores of the violence tendency scale increased with the increase in children's TV watching frequency. The study conducted by Tokdemir et al. (8) revealed that students who watched highly violent TV programs applied physical violence in their own lives at a greater rate. The study conducted by Kelishadi et al. (45) prolonged screen time is associated with violent and aggressive behaviour in children and adolescents. According to a study conducted by Glymour et al. (46) revealed that exposure to media violence causes aggression. The study results showed a parallelism with literature in this regard.

There was a significant difference between mean scores of trait anxiety and tendency towards violence according to the duration of watching TV in children included in the study. On the other hand, there was an insignificant difference between mean scores of state anxiety based on the duration of watching TV. Children who watched TV for 4 hours or more a day had higher scores of trait anxiety compared to those who watched for 0-1 hour and 2-3 hours a day. Furthermore, children who watched TV for 4 hours or more a day had higher scores of tendency toward violence compared to those who watched for 0-1 hour a day (Table 5). These results demonstrated that children who watched TV for longer durations showed higher levels of trait anxiety and tendency toward violence. According to the study conducted by Akçay and Özcebe (47) it was determined that the increase of children's duration of watching TV on weekdays decreased their prosocial behaviours and increased their physical and relational aggression, and similarly, the increase of children's duration of watching TV on weekends decreased their prosocial behaviours and increased their physical aggression. According to the study conducted by Maras et al. (48) screen time is associated with anxiety. According to the study conducted by Teychenne et al. (49) sedentary behaviour is associated with risk of anxiety. According to the literature, with the increase in children's and adolescents' duration of watching TV, their nightmares, fears, anxieties and tensions increased in a directly proportional way (14,16).

Children watching violent TV programs had higher scores of tendency towards violence compared to those not watching violent TV programs (Table 6). According to the literature, violent media can increase aggression (2, 50). As a result of their study, Kronenberger et al. (51) and Cardwell (52) detected a relationship between the aggressive behaviours of adolescents and the violent scenes in video games and on TV. Studies conducted by Gentile et al. (53), Rothenberg (54), Coker et al. (55) and Coyne (56) determined a positive relationship between watching violence in the media and aggressive behaviours. In their study, Tokdemir et al. (8) revealed that students watching highly violent programs applied physical violence in their daily lives at a greater rate. These study results were in line with the literature.

It was determined that the state of children included in the study to watch violent TV programs affected their state anxiety and did not affect the trait anxiety (Table 6). According to the literature, children are affected by violence in the media (17, 52, 57). Violence on TV may cause anxiety (17, 18). According to the literature, 92% of children and adolescents who apply to clinics due to fear, anxiety or nightmares are mainly afraid of what they watch on TV (14). The study results showed a parallelism with the literature.

A significant difference was determined between the state and trait anxiety based on the children's desire to be like the characters on TV. Children who desired to be like the characters on TV showed higher mean scores of state anxiety (36.69 ± 7.14) compared to those who did not (35.29 ± 5.24). The mean score of trait anxiety in children who desired to be like the characters on TV was 33.86 ± 6.52 . There was a statistically insignificant difference between mean scores of tendency to violence according to children's states of desiring to be like the characters on TV (Table 7). According to the literature, when children take a figure from violent films as a model, it may cause tragic results (39).

Limitations

The data of the study are limited, as it consisted of a total of 360 (n=360) students receiving education in the 5th, 6th, 7th, and 8th grades of 3 elementary schools in a city centre of Turkey.

Conclusions

It was determined that children showed mild levels of anxiety and tendency towards violence. Moreover, children's daily duration of TV watching, as well as their desire to be like the characters on TV and watching violent TV programs affected their anxiety levels and tendency toward violence. On the other hand, the extent to which they liked watching TV and the frequency of watching TV only affected the tendency towards violence.

Families, legislators have important responsibilities to protect children from the negative effects of TV. Thus, children's TV watching should be restricted to 1-2 hours a day and their attitudes and behaviours towards their environment while and/or after watching the TV should be observed. Furthermore, paediatricians should inform parents, educators, policy makers, and broadcasters about the potentially harmful effects of violent programming on children's emotions.

The guideline published by the American Academy of Pediatrics in 2002 suggested to prevent children from watching the TV for more than 2 hours a day, and especially prevent children younger than 2 from watching the TV. Additionally, it indicates that children should watch TV under the supervision of parents, who should direct them towards social activities rather than TV. For their part, networks should produce more educational programming for children and adolescents, and ensure that the programming they produce is of higher quality, with less content that is gratuitously violent, sexually suggestive, or drug oriented and fund ongoing annual research, such as the National TV Violence Study on the effects of TV on children and adolescents, particularly in the area of sex and sexuality (22).

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The incidence of operated children with Meningomyelomeningocele

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Abstract

Meningo/myelomeningocele is the most common malformation of medulla spinalis, which is also called Spina Bifida Aperta, Spina Bifida Cystica or in most cases open neural tube defect. When people talk for Spina Bifida, often they refer as myelomeningocele, which is known as the most serious form.

Research objectives: Our research is the creation of some statistics for the incidence of children operated with meningo/myelomeningocele, gender, age, place of residence, and the incidence of complicated cases in Hydrocephaly, in the period from 2010 to April 2014.

Hypotheses

H1. The incidence of children operated with meningo/myelomeningocele.

H2. Complications of meningo/myelomeningocele accompanied with Hydrocephaly.

Purpose: The aim of this study is to raise health commitment, public attention for patients affected by meningo/myelomeningocele, to analyze the incidence of these children who have been operated to us, also treatment and postoperative complications.

Material and Methods: In the study, we have used extracts from the protocol block of neurosurgical operative hall in UCCK in Pristina. Is a retrospective study on the incidence of operated children with Meningo/Myelomeningocele. We have analyzed in a retrospective form all clinical data.

The sample comprises 75 children operated with neural tube defects, meningo/myelomeningocele in the hall of Neurosurgery at UCCK in Pristina, during the period from 2010 to April 2014.

Results: The general number of born children with defects and different pathologies of neural tube from 2010 to April 2014 is 133. The incidence

of operated children with Meningo/Myelomeningocele, in the period from 2010 to April 2014 in the hall of neurosurgery at UCCK in Pristina is 75 cases, of which 48 (64%) are diagnosed with Meningocele (DS=5.31), 27 (36%) are diagnosed with Myelomeningocele (DS=1.94).

From these cases, 31 (38%) were registered from urban areas (r=.371,p<0.01), 44 (62%) were registered from rural areas (r=.536,p<0.01), 48(67%) cases were females, while 27(33%) were males. Out of the 75 children operated with Meningo/ Myelomeningocele 10(14%) cases have suffered complications accompanied with Hydrocephaly (DS=1.22). The average age of operated children was 4-5 days. By making correlation analysis, it was found a significant rapport in the structure of operated children with meningo/Myelomeningocele, and the incidence of children with complications accompanied with hydrocephaly.

Conclusion: Out of 75 operated children with Meningo/myelomeningocele, 10 cases have suffered complications accompanied with Hydrocephaly; time of intervention was after 7-20 days. 3 (30%) cases were from urban areas, 7(70%) cases were from rural areas. 7(70%) cases were females and 3(30%) were males.

By making correlation analysis and standard deviation, we have reached the following values:

The incidence of operated children with Meningocele: DS=5.31,

The incidence of operated children: DS=1.94

The incidence with complications in Hydrocephaly: DS=1.22, r=.961, p=.009 (p<0.01)

Complications according to residence: DS= .707 Village: DS= 1.14, r=.539,p<.0.01

City: DS=.894, r=.371,p<0.01

Complications according to gender: r=.920, p<0.01

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Based on these statistical analyses we see the interrelation of these data and that they are significant.

Key words: meningocele, myelomeningocele, case,children

Introduction

Meningo/myelomeningocele is the most common malformation of medulla spinalis, which is also called Spina Bifida Aperta, Spina Bifida Cystica or in most cases open neural tube defect. When people talk for Spina Bifida, often they refer as myelomeningocele, which is known as the most serious form.

Regarding the forms of Spina Bifida, they are ranked from medium form, soft form, up to its heaviest presentation form. Based in its appearance it is divided into: size and location of the open part of the spine, and how much the backbone and the nerve fibers are affected.

The backbone consists of several bones without regular form, which are called vertebrae. Children have 33-34 vertebrae where during growth the lower vertebrae agglutinate together, whereas an adult has 26 vertebrae. In between vertebrae, there are discs, cartilage, which give elasticity to the backbone for the desirable flexure. In the middle of each vertebra is a large hole where all the vertebrae are connected through the connective tissue, these holes together form a tube in their vertebrae that contains the spinal cord. Spinal cord is part of the central nervous system that sends motor orders from the brain and gives the brain sensory information, namely information that are related with feelings.

Meningocele (without neural elements, nerve fibers)

Is the simplest form of Spina Bifida. Meninges and cerebral fluid do not have neural elements and this space communicates with the spinal canal.

Myelomeningocele (contains nerve fibers)

In this defect besides the cerebral fluid, there are neural elements, which are interpolated in the defect section through the spinal canal. As a result of this defect remains a soft unprotected part which may appear as a bump through the skin in the form of a dark bag. A layer or a thin membrane, which wraps the fluid that protects the brain and the marrow, covers this bag.

Research objectives

Our research is the creation of some statistics for the incidence of children operated with meningo/ myelomeningocele, gender, age, place of residence, and the incidence of complicated cases in Hydrocephaly, in the period from 2010 to April 2014.

Hypotheses

H1. The incidence of children operated with meningo/myelomeningocele.

H2. Complications of meningo/myelomeningocele accompanied with Hydrocephaly.

Purpose

The aim of this study is to raise health commitment, public attention for patients affected by meningo/myelomeningocele, to analyze the incidence of these children who have been operated to us, also treatment and postoperative complications.

Theory and the state of research

Spina bifida refers to any birth defect, which includes the incomplete closure of the backbone.

Most of these are located in lumbar region (the lower part of the backbone), but also in the thoracic and cervical region (the neck).

The number of complications with meningo/ myelomeningocele accompanied with Hydrocephaly is 10 out of 75 operated children in the period from 2010 to April 2014 in the hall of Neurosurgery in UCCK in Pristina. The cause of this malformation, meningo/myelomeningocele is unknown. However, the low level of folic acid in a woman's body before and during pregnancy has an important role in preventing and reducing a birth defect, such as meningo/myelomeningocele. Folic acid (B vitamins or folate) it is important for brain and spinal development.

If a child is born with meningo/myelomeningocele, the next children in that family have a higher risk to be born with such a defect, compared with the general population. However, in many cases, there is no relation with the family.

During the second quarter, pregnant women should repeat blood tests and prenatal controls, which help to diagnose any defect that may occur to the baby. This check up is done for meningo/ myelomeningocele, DS, and other congenital pathology in children. The woman who holds a baby with meningo/myelomeningocele has a higher level than the normal value of a protein called alpha-fetoprotein maternal (AFP).

If the test is positive, further testing is required to confirm the diagnosis. Such tests may include:

- -Ultrasound
- Amniocentesis

Tests that should be done to children born with defects are X-rays, ultrasound, CT or MRI of the spinal area.

Just meningo/myelomeningocele does not create intellectual impairment but if it is not treated well and in time, it can be complicated into hydrocephaly. The most frequent complications that are caused are:

- 1. Urinary infections
- 2. Decubitus or wounds

The born baby with the defect of the backbone (neural tube) needs a specialized examination in many areas. The simplest way of evaluating the movement of your child's feet is by looking each node and seeing if there is any movement or not. Three nodes that you should check are hips, knees, and ankles. After birth, surgery is recommended to repair the defect. Before surgery, baby should be treated carefully to reduce the damage of the exposed spinal cord.

Usually surgical treatment is recommended within the first days of life. The main surgical aim in this stage is to put the spinal cord back into the spinal canal, in order to make intervention in the defect of the backbone and to cover the damaged area with healthy and normal skin.

There are two hypotheses when it is the appropriate time for operation:

- First hypothesis: The operation should be done within 36-48 hours after birth.
- Second hypothesis: After 5 days that we are sure that the child is examined correctly and his general condition is stable, also to be sure that parents understand the seriousness of the problem.

Early operative treatment for the newborn is to preserve as much as possible, neural elements, especially those that are functional. If we consider these factors, then the sooner the better because the elimination of the bag defect is done, the coverage of damaged skin with healthy skin, and preservation of neural elements.

In the first days after surgery, it is essential to preserve the integrity of the wound not to have any infection. It is preferable to keep the child facedown; also, it is preferable not to move much with feet, if there is any movement, the skin should not be withdrawn, so the tension on the wound should be very low. Around the 10th day, the condition of the wound is evaluated. To those children to whom Hydrocephaly is developed this usually happens between the 5th-14th days.

The final result is dependent from many factors:

- 1. Size and location of spinal defect.
- 2. The tempo in which Hydrocephaly is developed.
- 3. Infections as a complication.
- 4. Surgery and techniques with which the operation was conducted.
- 5. Rehabilitation and motivation of family.

According to the world literature, mortality of these children in the first decade is quite large in developed countries, in our country there is not any accurate statistic.

The importance of the study

This study for parents and caregivers of children with neural tube defectsprovides some data for the condition of children with congenital problems, which can occur frequently. This study provides information on the treatment and consequences with which children with Meningocele/Myelomeningocele are faced from birth and throughout their lives.

Positive attitude towards these children will motivate them to develop their physical capacities, psychological, and intellectual.

Negative attitude towards them causes complex reactions and addiction. On the other hand, their excessive protection prevents normal development of personality, and physical capacity of these children.

Material and Methods

In the study, we have used extracts from the protocol block of neurosurgical operative hall in

UCCK in Pristina. Is a retrospective study on the incidence of operated children with Meningo/Myelomeningocele. We have analyzed in a retrospective form all clinical data.

The sample comprises 75 children operated with neural tube defects, meningo/myelomeningocele in the hall of Neurosurgery at UCCK in Pristina, during the period from 2010 to April 2014.

Results

The general number of born children with defects and different pathologies of neural tube from 2010 to April 2014 is 133. The incidence of operated children with Meningo/Myelomeningocele, in the period from 2010 to April 2014 in the hall of neurosurgery at UCCK in Pristina is 75 cases, of which 48 (64%) are diagnosed with Meningocele (DS=5.31), 27 (36%) are diagnosed with Myelomeningocele (DS=1.94).

From these cases, 31 (38%) were registered from urban areas (r=.371,p<0.01), 44 (62%) were registered from rural areas (r=.536,p<0.01), 48(67%) cases were females, while 27(33%) were males. Out of the 75 children operated with Meningo/ Myelomeningocele 10(14%) cases have suffered complications accompanied with Hydrocephaly (DS=1.22). The average age of operated children was 4-5 days. By making correlation analysis, it was found a significant rapport in the structure of operated children with meningo/Myelomeningocele, and the incidence of children with complications accompanied with hydrocephaly.

Results of quantitive data

Medical and surgical management of these children during the hospitalization is studied in detail to the default parameters. The average age in intervention time of Meningo/ Myelomeningocele was 4-5 days. Statistical analysis showed that the intervention of the defect Meningo/myelomeningocele before 48 hours has reduced the appearance of complications accompanied with Hydrocephaly. The average time in intervention of complicated cases was 5 days.

This observation is statistically significant and shows that healing factors after intervention of myelomeningocele represent the most important factor of risk for development of complications in Hydrocephaly. In our study, which includes the period from 2010 to April 2014, we have a total of 75 children operated with deformation of the neural tube, of which 48 (64%) with medical diagnosis Meningocele, 27 (36%) with medical diagnosis Myelomeningocele, 10 (14%) of them had complications which are accompanied with Hydrocephaly. Only 41 of them are in average economic situation, while others have certain difficulties, respectively they need help.

Results of qualitative data

Based on percentage, in tabular and graphical form we have shown the incidence of operated children in the hall of neurosurgery at UCCK in Pristina and complications accompanied in Hydrocephaly during the annual period 2010 to April 2014 (Annex 1 and 4). In the study for presentation of data we have used Microsoft Excel and statistical program SPSS.

In chart (1) is presented the incidence of operated children with Meningo/Myelomeningocele, from 2010 to April 2014. Interventions are presented in percentage, where we can analyze and see that in 2010 from 371 overall cases has been intervened in 42 (12%) cases with different deformities of the neural tube, 25 (60%) are operated with Meningo/ Myelomeningocele. In 2011 from 373 overall cases has been intervened in 25 cases with different deformities of the neural tube, 10 (72%) of the cases are operated with Meningocele, 4(28%) of the cases are operated with Myelomeningocele.

In 2012, from 429 cases, has been intervened in 29 (68%) cases with deformities of the neural tube, 10 (35%) of the cases are operated with Meningocele, 6 (21%) of the cases are operated with Myelomeningocele. In 2013, from 433 operated cases, has been intervened in 26 (6%) cases with deformities of the neural tube, 9 (50%) of the cases are operated with Meningocele. In 2014 (until April), from 106 cases, has been intervened in 10 (10%) cases with different deformities of the neural tube, 5 (50%) of the cases are operated with Meningo/Myelomeningocele. According to the correlational analysis we have significant values to the incidence of children operated with Meningo/Myelomeningocele and the incidence of complications accompanied with Hydrocephaly: r = .961, p = .003 (p< 0.1), DS = 1.58.

Table 1. The incidence of children operated with Meningomyelomeningocele and the incidence of complications

Cases	2010	2011	2012	2013	2014
Anesthesiology and reanimation care clinic Neurosurgery hall	371	373	429	433	104
The incidence of children operated with Meningo/Myelome- ningocele	25	14	16	18	8
The complication of the incidence of children operated with Meningo/Myelomeningocele	16%	7%	7%	6%	12.5%



Graf 1. The incidence of children operated with Meningomyelomeningocele and the incidence of complications

In tabular (Annex 1) and graphical form (1) it is presented the incidence of complicated cases in Hydrocephaly. From 2010 to April 2014, the number of complicated cases was 10(14%) out of 75 interventions with different deformities of the backbone (neural tube). In 2010, the number of complicated cases was 4 (16%) out of 15 general interventions. In 2011, the number of complications was 1 (7.2%) out of 14 interventions with Meningo/Myelomeningocele.



Graf 2. The number of complicated cases



Graf 3. The incidence of children operated with Meningo/Myelomeningocele and the incidence of complicated cases on Hydrocephaly

In 2012, the number of complications was 2 (12.5%) out of 16 general interventions. In 2013, the number of complications was 2 (12%) out of 18 cases of total interventions. In 2014, the number of complications was 1 (10%) out of 5 cases of total

Table 2. The incidence of children operated with Meningo/Myelomeningocele and the incidence of complicated cases on Hydrocephaly

The incidence of children operated with Meningo/Myelomeningocele	2010	2011	2012	2013	2014
Meningocele	17	10	10	9	2
Myelomeningocele	8	4	6	9	6
Hydrocephaly	17	11	13	8	3
% Meningocele	44%	40%	34%	35%	20%
% Myelomeningocele	12%	16%	21%	35%	55%
% Hydroceohaly	44%	44%	45%	31%	25%

interventions. The incidence of complications from 2010 to April 2014 is 10 cases or 14% of interventions in general (Graph 2). According to correlation analysis, the incidence of complicated cases by residence and gender has provided significant values. Gender: DS=1.22, r=.920, p=.-063 (p<0.01) Residence: DS=.707, r=.894, r=1.14 p<0.01

In graphic form (2) we have presented the structure of complicated cases of patients according gender. Based on the retrospective data, the number of female patients is higher comparing with the number of male patients. In 2010 we have 2 (50%) complicated cases of female gender and 2(50%) cases of male gender or 16% of the general number of interventions with congenital defects of neural tube. In 2011, we have 1 (10%) complicated case or 20% from the general number of interventions.



Graf 4. In graphic form we have presented the structure of complicated cases of patients according gender

In 2012, we have 2 (12.5%) cases of female gender or 3% of the general number of interventions. In 2013, we also have 2 (12%) cases of female gender from the general number of the interventions. In 2014 (until April), we have just one complicated case of male gender of the general number of interventions.

In graphic form (3) we have presented the structure of patients with complicated cases, according to residence. Based on retrospective data we have analyzed and presented these data. In 2010, the number of operated children from rural areas is 14 or 56% of the cases, whereas from urban areas this number is 11 or 44% of the total cases. In 2011, the number of cases from rural areas is 5(35%), whereas from urban areas it is 9(65%). In 2012, the number of cases from rural areas is 11(68%), whereas from urban areas it is 5(32%). In 2013, the number of patients from rural areas is 8(44%), whereas from urban areas it is 10 (56%) and in 2014 the number of patients from rural areas is 7(70%), whereas from urban areas it is 3(30%).



Graf 5. In graphic form we have presented the structure of patients with complicated cases, according to residence

Discussion and recommendation

Problems of the neural tube defects are a major source of disability, despite a significant decline in cases of the incidence. In world countries, it is often diagnosed in prenatal phase, and thus the operation of fetus has been realized. Preliminary studies strongly suggest that at least a part of neurological abnormalities may be developed in the middle of pregnancy. Until now, around 400 operations of fetus have been done in children with Myelomeningocele around the world.

During 12 years of study, the incidence of Myelomeningocele has decreased in a linear rate, for about 4.6 cases per 100.000 births per year. A summary of comparable reports in east in the northeastern region of the United States shows that a relatively stable linear decrease in the incidence of myelomeningocele is continuing at this rate for last 50 years. It is concluded that small local fluctuations and variability in data collection have showed steady decrease in this phenomenon. Significant declines were seen in the rates of incidence in Hydrocephaly, compared to previous reports.

After comparisons of cases committed in the world and to us, we see that in cases with neural tube malformations compared with made research by Handikos, during the period from 2001 -2009, and our research during the period from 2010-2014, there is positive decrease. It is worth noting that we

do not have data for all born children with meningo/myelomeningocele, or with neural tube defect. General data, but incomplete in Kosovo, collected by Handikos, during the period 2001-2009, have 64 people registered with Spina Bifida. (HAN-DIKOS-Spina Bifida in Kosovo, December 2001).

- Gender: 37 are males (58%) whereas 27 are females (42%).
- Age: Under the age of 7 are 13 children, from age 7-17 are 32 children, and from age 18 are 18 children, whereas for one of the cases we do not have information for the age.

From the whole group of 64 persons, 52 of them were registered with paraplegia, 32 are with incontinence because of the damage to the spinal cord, 26 of them are presented in different levels of Hydrocephaly and 10 of them have had surgical intervention.

Conclusion

Out of 75 operated children with Meningo/ myelomeningocele, 10 cases have suffered complications accompanied with Hydrocephaly; time of intervention was after 7-20 days. 3 (30%) cases were from urban areas, 7 (70%) cases were from rural areas. 7 (70%) cases were females and 3 (30%) were males.

By making correlation analysis and standard deviation, we have reached the following values:

The incidence of operated children with Meningocele: DS=5.31,

The incidence of operated children: DS=1.94

The incidence with complications in Hydrocephaly: DS=1.22, r=.961, p=.009 (p<0.01)

- Complications according to residence: DS= .707 Village: DS= 1.14, r=.539,p<.0.01

- City: DS=.894, r=.371,p<0.01
- Complications according to gender: r=.920, p<0.01

Based on these statistical analyses we see the interrelation of these data and that they are significant.

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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

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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.

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