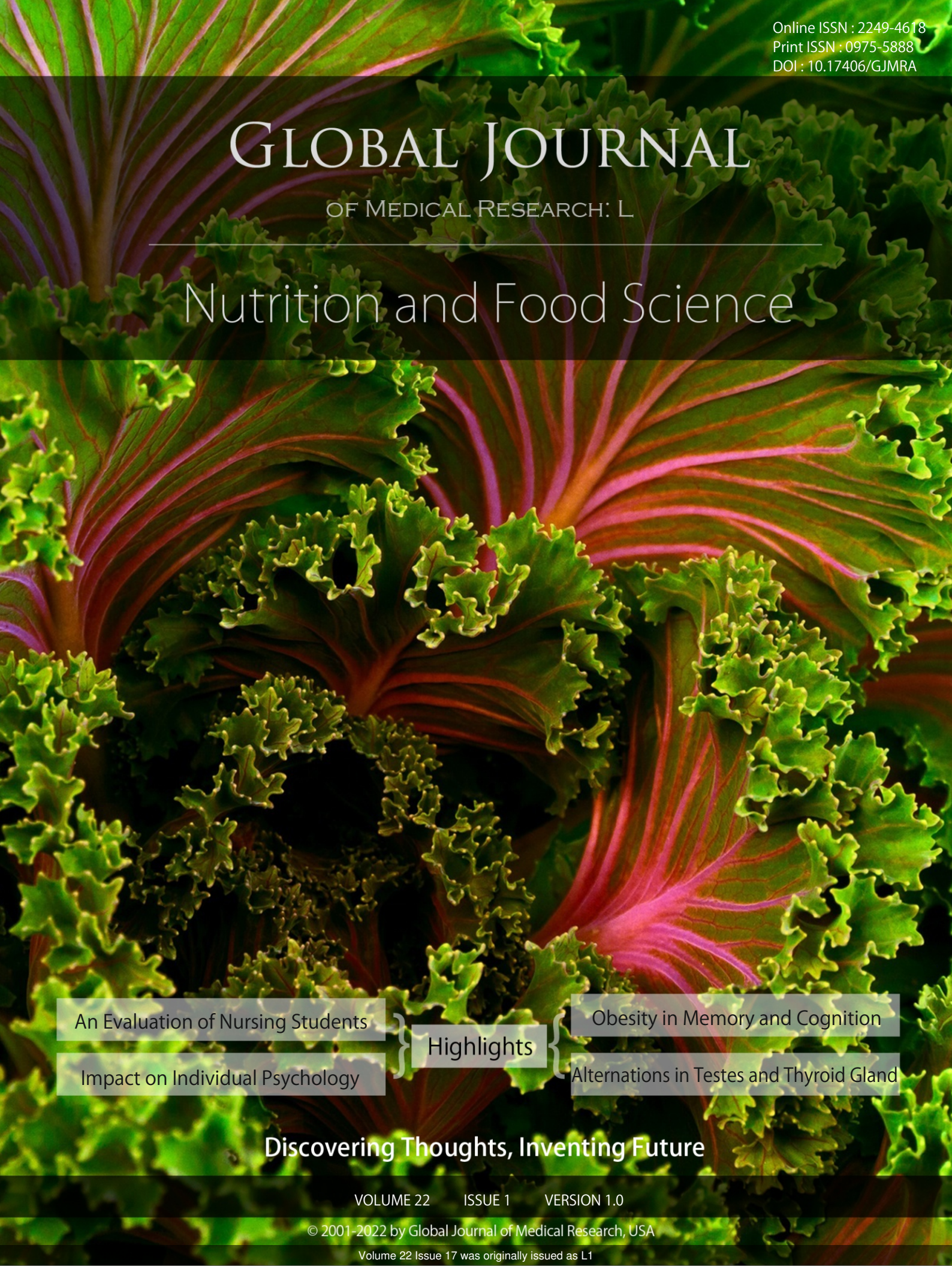
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Nutrition and Food Science



An Evaluation of Nursing Students Impact on Individual Psychology

Highlights

Obesity in Memory and Cognition

Alternations in Testes and Thyroid Gland

Discovering Thoughts, Inventing Future

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An Evaluation of Nursing Students' Food Neophobia and Diet Quality

By Dr. Ayse Gumusler Basaran & Yagmur Demırel Ozbek

Recep Tayyip Erdogan University

Abstract- Food neophobia affects food choice and is thought to have an effect on the healthy eating index. The purpose of this study is to evaluate food neophobia of nursing students and to determine whether it affects diet quality. In addition, it aims to examine the effect of changing demographics on food neophobia. The study was consisted of 155 nursing students. The data were collected online using the sociodemographic information form, the Food Neophobia Scale and the Healthy Eating Index-2015. In the analysis of the data, percentage, mean, Student's t test, Mann Whitney U, Anova and Kruskal Wallis tests and Spearman correlation analysis were used. 72.3% of the students participating in the study are women. 58.7% of them have poor diet quality and 32.3% of them need to improve their diet quality. The mean score of food neophobia is 37.31±10.39, and 13.5% of them are neophobic. Food neophobia was found to be significantly higher in those who do not work and those living in rural areas. It was determined that there is a statistically and significantly weak negative correlation between age and food neophobia, and weak positive correlation between age and the healthy eating index. The result of the study reveals that food neophobia varies with demographic conditions. When evaluated in terms of diet quality, it is seen that the diets of the students are weak or needed to be improved.

Keywords: *food neophobia, diet, student, nursing.*

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An Evaluation of Nursing Students' Food Neophobia and Diet Quality

Dr. Ayse Gumusler Basaran [α] & Yagmur Demırel Ozbek [σ]

Abstract- Food neophobia affects food choice and is thought to have an effect on the healthy eating index. The purpose of this study is to evaluate food neophobia of nursing students and to determine whether it affects diet quality. In addition, it aims to examine the effect of changing demographics on food neophobia. The study was consisted of 155 nursing students. The data were collected online using the sociodemographic information form, the Food Neophobia Scale and the Healthy Eating Index-2015. In the analysis of the data, percentage, mean, Student's t test, Mann Whitney U, Anova and Kruskal Wallis tests and Spearman correlation analysis were used. 72.3% of the students participating in the study are women. 58.7% of them have poor diet quality and 32.3% of them need to improve their diet quality. The mean score of food neophobia is 37.31±10.39, and 13.5% of them are neophobic. Food neophobia was found to be significantly higher in those who do not work and those living in rural areas. It was determined that there is a statistically and significantly weak negative correlation between age and food neophobia, and weak positive correlation between age and the healthy eating index. The result of the study reveals that food neophobia varies with demographic conditions. When evaluated in terms of diet quality, it is seen that the diets of the students are weak or needed to be improved.

Keywords: food neophobia, diet, student, nursing.

I. Introduction

Healthy eating habits are considered important in human life, and it has been reported to reduce the risk of some types of cancer, coronary heart disease, stroke, cataract, and hypertension. Nutritional behavior can be determined not only by the mechanism of hunger and satiety but also by patterns such as food neophobia or selective eating (Galloway et al., 2003). Food neophobia, defined as "reluctance to eat or avoidance of unfamiliar food" by Pliner and Hobden (1992), is a significant feature that affects people's daily food choices. It is a known fact that individuals have a protective mechanism that prevents them from consuming potentially toxic foods (Roßbach et al., 2016). Among the factors affecting the food neophobia is age, gender, education level, place of residence, gastrointestinal system diseases, and food allergies (Muhammad et al., 2015; Staples & Gibson, 2008; Soucier et al., 2019; Schnettler et al., 2017; Olabi et al., 2020; Shim et al., 2011). Food neophobia, which emerges with the transition to the complementary food period, is at its lowest level in early childhood (under 24 months) and the highest level in the 2-6 age range. This may be due to the refusal of unfamiliar food by children to demonstrate their autonomy during this period, which is probably their first year of independence (Muhammad et al., 2015; Staples & Gibson, 2008). Food neophobia decreases with increasing age in later ages, adolescents, and adults. However, it has been reported that food neophobia increases in adults aged ≥65 years (Soucier et al., 2019), and the average score of food neophobiain the 66-80 age group is the highest compared to other age groups. In terms of gender, food neophobiais higher in men than women (Olabi et al., 2020). Food neophobia is at a high level in individuals who are in the potential risk group for gastrointestinal system diseases and food allergy(Shim et al., 2011).It has been observed that it differs among those living in the city or the countryside and decreases as the individuals' education levels increase. Increasing the level of nutrition knowledge may affect food neophobia (Schnettler et al., 2017).

In recent years, research has been made on food neophobia due to its potential to affect nutritional preferences. Food neophobia can influence food choices and the quality and variety of the diet. As reported in the literature, food neophobia restricts dietary diversity (Previato et al., 2015). It can restrict not only the variety of the diet but also the quantity and thus the energy content, resulting in a diet pattern with lower diet quality (Knaapila et al., 2014). Diet quality means nutritional diversity as well as energy and nutrient adequacy. The increase in food diversity provides an increase in the index and supports the protection and improvement of the health of individuals by affecting the diet quality (Uçar, 2018). The aim of this study is to evaluate nursing students' food neophobia, determine whether it affects diet quality, and examine the effect of changing demographic characteristics on food neophobia.

II. Method

a) Population and Sample of the Research

The research is a descriptive cross-sectional study conducted in April-May 2021. The population consisted of 414 students in Rize Recep Tayyip Erdogan

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University, Faculty of Health Sciences, Nursing Department. The incidence of the event was taken as 20%. Considering the number of students required for the study as p: 0.20, t:5, d:0.05, it was calculated that n: 155. Calculations were made using the Roasoft Sample Size Calculator program. The research link was sent to the corporate e-mails of the students using social media tools.

b) Data Collection Tools

The data were collected with the sociodemographic information form developed by the researcher, the Food Neophobia Scale, and the Healthy Eating Index-2015.

i. *The Sociodemographic Information Form:* The form includes general information about the participants like age, gender, marital status, working status, smoking and alcohol consumption, number of meals, the place of residence, and type of high school they graduated from.

ii. *The Food Neophobia Scale:* The Food Neophobia Scale (FNS) was used to evaluate the tendency of individuals to reject or try unfamiliar. The Turkish validity and reliability of the scale, developed by Pliner and Hobden (1992), was performed by Uçar (2018). The 7-point Likert-type scale consisting of ten items has a score range of 10-70, and high scores indicate fear of unfamiliar foods, and low scores indicate enjoying trying them. Individuals with a food neophobia scale score $<\bar{X}\pm SS$ were classified as neophiliac, $\bar{X}\pm SS$ neutral, and $>\bar{X}\pm SS$ neophobic. The Cronbach's alpha value for food neophobia was found to be .806 in the study.

iii. *The Healthy Eating Index (HEI)-2015:* The Healthy Eating Index scores were calculated by considering 24-hour retrospective food consumption records of individuals. The HEI was developed based on the American Dietary Guidelines. The guide is updated every 5 years to reflect current data. The HEI, which was first created in 1995, is revised according to the regularly updated American dietary guidelines. The United States Department of Agriculture (USDA) expert panel reviews the latest updates on nutrition and develops new recommendations.

The HEI-2015 includes13 dietary groups. Of these groups, 9 indicate adequacy components and 4 moderation components. Foods that should be included in the diet adequately are total fruits, whole fruits, total vegetables, greens and beans, whole grains, dairy products, total protein, seafood and plant proteins, and fatty acids. Foods that should be consumed sparingly are refined grains, sodium, added sugars, and saturated fats. The highest and lowest scores on the scale are 100 and 0. The healthy eating index is evaluated in three categories (Panizza et al., 2018): 0-50=malnutrition, 51-80=nutrition that needs to be improved, and 81-100: healthy nutrition.

c) Statistical evaluation of data

SPSS 22 package program was used for statistical analysis of the data. Descriptive data were presented as percentage, mean, and standard deviation, and conformity of quantitative data to normal distribution was evaluated with the Shapiro-Wilk test. Student's t-test and One Way ANOVA analysis were used for normally distributed data, and Mann Whitney U test and Kruskal Wallis analysis were used for data without normal distribution. Spearman correlation analysis was performed. In the correlation analysis, 0-0.39 was accepted as weak correlation, 0.40-0.69 moderate correlation, 0.70-0.89 strong correlation, 0.90-1.00 very strong correlation. The significance value was accepted as $p<0.05$.

d) Ethical aspect: Ethics committee approval numbered 2021/91, and institutional permission of the university was obtained to collect the data.

III. Results

72.3% of the students in the study were female, and 27.7% were male, and their mean age was 20.76±3.07. All the students were single, and 25.2% were first-year students, 29.7% were in the second year, 22.6% were in the third year, 22.6% were in the fourth year.20% graduated from medical vocational high schools, 5.2% were working, and 66.2% lived in an urban area. %9 smoked, and %5.8 drank alcohol. %17 ate 2 main meals a day. The mean score of the Healthy Eating Index was 45.32±14.19. 58.7% had poor quality diet, and 32.3% needed to improve their diet quality. There were no students with a high-qualitydiet.9% did not respond. Descriptive data of the participants are shown in Table 1.

Table 1: Descriptive Data of Participants

Independent Variables		n	%
Gender	F	112	72.3
	M	43	27.7
Class	1	39	25.2
	2	46	29.7
	3	35	22.6
	4	35	22.6
Marital status	Single	155	100
	Married	0	0

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High School	Medical Vocational High Schools	31	20.0
	Others	124	80.0
Working status	Yes	8	5.2
	No	147	94.8
Place of residence	Rural	52	33.8
	Urban	102	66.2
Smoking	Yes	14	9.0
	No	136	87.7
	Quitted	5	3.2
Use of alcohol	Yes	9	5.8
	No	145	94.2
Number of meals per day*	2 main meals	27	17.4
	3 main meals	23	14.8
	2 main meals 1 snack	25	16.1
	2 main meals 2 snacks	23	14.8
	2 main meals 3 snacks	6	3.9
	3 main meals 1 snack	17	11.0
	3 main meals 2 snacks	17	11.0
	3 main meals 3 snacks	10	6.5
Quality of diet **	Poor	91	58.7
	Needs improvement	50	32.3
	High	0	0
Food neophobia	Neophiliac Neutral Neophobic	21	13.5
	Neutral	113	72.9
	Neophobic	21	13.5

**7 (%4.5) participants did not respond. **14 participants (%9) did not respond.*

The mean score of the food neophobia scale was 37.31±10.39. The rate of neophiliac students was 13.5%, the rate of neutrality was 72.9%, and the rate of neophobia was 13.5%. The Food Neophobia and the Healthy Eating Index scores according to the characteristics of the participants are presented in Table 2, and their comparisons with the independent variables are in Table 3.

Table 2: The Mean Scores the Food Neophobia Scale and the Healthy Food Index Scale

Scales	n	Min-Max	χ	Sd
Food Neophobia Scale	155	10-66	37.31	10.39
Healthy Food Index Scale*	141	15-70	45.32	14.19

**Calculated with the number of respondents.*

Table 3: Comparisons of Food Neophobiaby Some Characteristics of Participants

Independent Variables		N	Food Neophobia	P	N*	Healthy Food Index Scale	P
			X̄±SS			Rank Mean	
Gender	F	112	37.66±10.71	.499	102	72.84	.383
	M	43	36.40±9.55		39	66.18	
			t= .678			U= 1801.00, Z= -.873	
High school	Health	31	34.74±10.33	.124	27	82.02	.116
	Others	124	37.95±10.34		114	68.39	
			t= -1.545			U= 1241.50, Z= -1.571	
Working status	Yes	8	28.13±11.38	**.010**	8	95.19	.082
	No	147	37.81±10.13		133	69.55	
			t= -2.616			U= 338.50, Z= -1.738	

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Place of residence	Rural	52	41.00±9.46	**.001**	46	72.10	.823
	Urban	103	35.45±10.38		95	70.47	
			t= 3.237			U=2134.50, Z= -.224	
Alcohol	Yes	10	36.00±13.22	.682	10	56.90	.254
	No	145	37.40±10.21		131	72.08	
			t= -.411			U= 514.00, Z= -1.141	
Class	1	39	38.44±9.04	.497	37	62.84	**.036**
	2	46	37.87±10.71		37	60.51	
	3	35	34.97±10.02		33	83.83	
	4	35	37.66±11.73		34	78.84	
			F= .798			KW X^2= 8.554	
Smoking	Yes	14	37.14±13.67	.998	13	51.77	.132
	No	136	37.33±10.12		124	73.54	
	Quitted	5	37.20±9.33		4	54.75	
			F=.002			KW X^2= 4.055	
Number of meals **	2 main meals	27	39.11±10.27	.066	26	66.60	**.016**
	3 main meals	23	39.96±7.24		21	63.93	
	2 main 1 snack	25	31.12±11.85		25	65.98	
	2 main 2 snacks	23	39.17±10.06		23	70.17	
	2 main 3 snacks	6	41.00±13.64		6	26.42	
	3 main 1 snacks	17	37.41±9.02		17	91.91	
	3 main 2 snacks	17	34.65±8.83		14	76.75	
	3 main 3 snacks	10	37.70±11.73		9	97.56	
			F=1.952			KW X^2=17.263	

**The Healthy Eating Index was analyzed with the number of respondents*

Table 3 shows that food neophobia levels were significantly higher in those who did not work and those living in rural areas (p=.010,p=.001).Gender, type of high school, smoking, alcohol consumption, class, and the number of meals did not cause a significant difference (p=.499, p=.124, p=.998, p=.682, p=.497, p=.066).

In terms of the Healthy Eating Index, the classes of the participants and the number of meals made a significant difference. The healthy eating index score was significantly higher in the 3rd year students than those of 1st and 2nd year students, and it was significantly lower in those consuming 2 main meals+3 snacks than those consuming 3 main meals+1 snack and 3 main+ 3 snacks (p=.036, p=.016). Gender, type of high school, working status, place of residence, smoking, and alcohol consumption did not differ significantly (p=.383, p=.116, p=.082, p=.823, p=.132, p=.254).

In the correlation analysis, a negative correlation was found between age and food neophobia, and a weak positive correlation between age and healthy eating index (r= -.184, r= .0172). There was no significant relationship between food neophobia and the Healthy Eating Index (Table 4)

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Table 4: Correlation Coefficients between Age, the Food Neophobia, and the Healthy Eating Index (Spearman).

		Age	Food Neophobia	Healthy Eating Index
Age	r p	1	-.184* .023	.172* .043
Food Neophobia	r p		1	-.059 .488
Healthy Eating Indexr	r p			1

*$p<0.05$

IV. Discussion

The concept of food neophobia, which many studies have focused on in recent years, is defined as the tendency to avoid new or unfamiliar foods to varying degrees and deals with the approach of individuals to foods and evaluates their eating habits (Soucieret al., 2019). Food neophobia symbolizes the unknown, harmful-beneficial anxiety and dislike (Pliner & Salvy, 2006). In the present study, the mean food neophobia score of the students was found to be 37.31±10.39. The mean food neophobia score was determined as 32.7±12.26 in a study conducted with academicians in Turkey (Kolve Ok, 2020), 41,3±10,93 in another study (Ucar & Kizil, 2018), and 31.2±11.9 in young people (Knaapilaet al., 2011).It was reported to be 36.4±9.8 and 29.8±11.7 in Lebanese and American university students, respectively (Olabi et al., 2009). Adolescents' food neophobia score was reported as 32.96±10.1 in Korea (Cho et al., 2014), 32.83±9.08 in Chinese people, and 36.33±7.85 in Indian people (Muhammad et al., 2015).In our study, 13.5% of the students were found to have food neophobia which is consistent with the ratio of 11.5% in the study with Brazilian young adults (de Andrade Previato et al., 2015).Considering the results, it can be said that the results of this study are compatible with other studies, but the food neophobiais less in America. This may be due to the diversity of food and cultural diversity resulting from the presence of people from different countries.

Food neophobia was found to be significantly higher in unemployed participants in the study, which is because working individuals have to eat out, interact with more different cultures, and have higher income levels. In the literature, food neophobia is reported to decrease with increasing income status in various countries(Jaeger et al., 2017; Meiselman et al., 2010).

The place of residence is effective on food neophobia. It has been determined that the students living in the city in Australia have a lower food neophobia. The fact that individuals living in rural areas are less exposed to cultural differences, and those living in urban areas have a higher chance of trying different foods affects food neophobia (Flight et al., 2003; Olabi et al., 2009). In this study, food neophobia was found to be higher in individuals living in rural areas. In our country, easy access to different foods by those living in urban areas and high cultural diversity can cause individuals living in urban areas to be more open to new foods.

In the study, gender did not make a significant difference in terms of food neophobia, like other studies in Turkey (Kol& Ok, 2020; Doğdubay & Yiğit, 2017).

Dematte et al. found the level of food neophobiato be insignificantly higher in smokers in Italy and showed the appetite suppressing effect of nicotine as the reason (Dematte et al., 2013). However, in this study, smoking did not make a significant difference in food neophobia, which may be due to the low rate of smokers involved in the study.

It is known that age is a significant determinant of food neophobia. Especially in adolescence, food neophobiais quite high and decreases with age (Rodríguez-Tadeo et al., 2018). Similarly, in this study, food neophobia decreased with increasing age.

Diet quality is a frequently mentioned topic to lead a healthy life and optimal well-being. The healthy eating index reflects diet quality and diversity (Kral, 2018). Tek et al. conducted a study with 1104 individuals and reported that the diet of 42.8% of the individuals was of poor quality and the diet of 57.2% should be improved (Teket al., 2011). In another study with 498 university students, about 80% participants needed to improve their diet quality, and no student had a high-quality diet (Erçim, 2014). In this study, 58.7% of the students had a poor-quality diet, 32.3% of them needed to improve their diet, and they were not students with a high-quality diet. As a result of these studies conducted with university students, it is clear that the diet quality of the students is quite low. The reason for this situation may be the obligation of students to comply with mealtimes in the places where they live and in schools, their reluctance to eat the meals offered every day, their preference for fast food, and financial difficulties. In addition, it should not be forgotten that eating disorders can be seen frequently in university students.

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Our study showed that 3rd-year students had higher healthy eating index scores than 1stand 2nd-year students. It can be thought that with the increase in their education level, their knowledge about foods increases and they pay more attention to nutrition (Meiselman et al., 2010). Also, the Principles of Nutrition course given in the 2nd year can increase the healthy eating index, so the increase in age may have been caused by this situation.

Diet quality decreased as the level of food neophobia increased in preschool children in the USA (Johnson et al., 2015), adults and the elderly in Finland (Knaapila et al., 2015), adolescents in Korea (Choe & Cho, 2011), children and adults in Spain (Maiz & Balluerka, 2016) and children in Norway (Helland et al., 2017). However, no significant difference was found between the food neophobia and the healthy eating index score in this study, which may be because the diet quality of the students in the study was generally poor or needed to be improved, and no one had a high-quality diet.

V. Conclusion

In this study, in which food neophobia level and diet quality were investigated, food neophobia level was found to be higher in those living in rural areas and those who did not work. Diet quality was found to be better in those who consumed 3 main meals and in 3rd - year students. There was a weak negative correlation between age and food neophobia. Food neophobiais at high levels and varies due to demographic conditions. The place where the individual was born and lived shapes his eating habits and his/her opinion about new foods. In the study, students' diets were poor or needed to be improved. To reduce food neophobia and improve diet quality, it is recommended to conduct informative studies about the content of foods and seek counseling from knowledgeable people about nutrition.

Limitations

The main limitations of the study are that the study was carried out only with the students of the nursing department, a 1-day food consumption record was used to evaluate dietary diversity, and since data were collected online anthropometric measurements such as weight and height could not be evaluated using the same measurement tool.

Declarations of interest: None

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Authors contribution
Ayse Gümüsler Basaran: Methodology, Analysis, Writing –review and editing
Yagmur Demirel Ozbek: Conceptualization, Writing, Resources

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Biochemical Changes of Mancozeb-Induced Alternations in Testes and Thyroid Gland of Male Rats

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Abstract- Mancozeb manganese ethylene bis dithiocarbamate polymeric complex – with zinc salts is a very important protective non-systemic fungicide, classified as an ethylene bis dithio-carbamate fungicide. Mancozeb used for controlling fungal diseases for a wide variety of crops because of its broad-spectrum as fungicidal effects and high compatibility with agrochemicals. The objective of this study was to investigate the results of the fungicide mancozeb at different doses on some biochemical parameters, reproductive performance, and histological changes in testes and thyroid gland. The low amount equals 1/7 of LD_{50} manczeb-d_1, and the high amount equals 1/3.5 of LD_{50} mancozeb-d_1. Amounts of mancozeb (mancozeb-d1 and mancozeb-d_2) adjusted according to the rat's body weights. The results showed that mancozeb decreased plasma testosterone level, sperm count, viability, motility, and significantly ($P<0.05$) increased abnormal sperms, altered acrosome, and abnormal DNA. Treatment of rats with manczeb-d_1 and mancozeb-d_2 significantly ($P<0.05$) decreased T3.

Keywords: *mancozeb, rats, thyroid glands, testes, histology.*

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Biochemical Changes of Mancozeb-Induced Alternations in Testes and Thyroid Gland of Male Rats

Ahmed Abdelrafea Mohamed Anwar [α], Prof. Hesham Zaki Ibrahim [σ] & Prof. Sabah Gaber El –Banna [ρ]

Abstract- Mancozeb manganese ethylene bis dithiocarbamate polymeric complex – with zinc salts is a very important protective non-systemic fungicide, classified as an ethylene bis dithio-carbamate fungicide. Mancozeb used for controlling fungal diseases for a wide variety of crops because of its broad-spectrum as fungicidal effects and high compatibility with agrochemicals. The objective of this study was to investigate the results of the fungicide mancozeb at different doses on some biochemical parameters, reproductive performance, and histological changes in testes and thyroid gland. The low amount equals 1/7 of LD_{50} manczeb-d_1, and the high amount equals 1/3.5 of LD_{50} mancozeb-d_1. Amounts of mancozeb (mancozeb-d1 and mancozeb-d_2) adjusted according to the rat's body weights. The results showed that mancozeb decreased plasma testosterone level, sperm count, viability, motility, and significantly ($P<0.05$) increased abnormal sperms, altered acrosome, and abnormal DNA. Treatment of rats with manczeb-d_1 and mancozeb-d_2 significantly ($P<0.05$) decreased T3. Also, T4 significantly ($P<0.05$) fell in the group treated with mancozeb-d_2. Treatment of rats with mancozeb-d1, and mancozeb-d_2 significantly ($P<0.05$) increased TSH. Furthermore, the histological study showed that exposure to mancozeb reduced the number of mature spermatozoa, necrosis, and basal vacuoles observed in some tubules. Also, mancozeb reduces colloid in most follicles resulting in desquamation of the follicular epithelium into the lumen of the thyroid follicles. In conclusion, despite mancozeb exhibiting low acute toxicity, it has been shown to cause detrimental effects on reproduction, thyroid gland, and its secretion. For this reason, it is necessary to be careful when using mancozeb in agricultural areas and should take precautions.

Keywords: mancozeb, rats, thyroid glands, testes, histology.

I. Introduction

Mancozeb manganese ethylene bis dithio-carbamate polymeric complex with zinc salts is a very important protective non-systemic fungicide, classified as an ethylene bis dithio -carbamate fungicide. Ethylene bis (dithio-carbamate)s (EBDCs) are the most widely used classes of organic fungicides in the world because it can effect on abroad types of fungus, and high compatibility with agrochemicals[1]. The EBDCs registered for food uses in the United States are mancozeb, and zineb. They were first introduced during the 1940s are widely used. These compounds have low water solubility, which results in remaining on the surface of treated crops as superficial deposits[2]. Mancozeb consists of a zinc-rich shell surrounding a central nucleus of polymer-structured EBDC. This structure is highly stable, and the low solubility of the zinc shell means EBDC can pass through this layer and be deposited on the leaf surface[3]. Mancozeb is unstable in water and decomposed by light, heat, and moisture-producing; ethylene thiourea (ETU) and ethylene bis (isothiocyanate) sulphide (EBIS) and other degradation products such as glycine and ethylene urea (EU), which is further to CO_2 under aerobic conditions. ETU is relatively stable and has a high solubility in water, so it can contaminate groundwater. ETU and EBIS are the main responsible compounds for the toxic effects linked to this fungicide group. ETU has teratogenic, carcinogenic, immunotoxic, and mutagenic effects, and EBIS is toxic and causes peripheral paralysis and thyroid dysfunction[4].

Ethylene bis isothiocyanate sulfide (EBIS), converted to ethylene bis isothiocyanate (EBI) by UV light. Both EBIS and EBI are active toxicants and can interfere with and inactivate sulphydryl groups in enzymes and amino acids, leading to enzymatic disruptions, and inhibition of spore germination[3, 5].

Mancozeb and its metabolites are widespread in the environment and have toxic effects due to their ingestion, inhalation, and percutaneous absorption by non- target organisms. Exposures to mancozeb are associated with a neurotoxic, developmental disability, immunotoxic, and carcinogenic effects in humans and experimental animals. Recent toxicological evidence has shown an endocrine- disruptive effect of mancozeb. It can disrupt the pituitary gland leading to decreasing the release of stimulating thyroid hormone (TSH) and thyroid hormones triiodothyronine and tetraiodothyronine. Moreover, it decreases thyroid hormone synthesis or action by directly interacting with nuclear hormone

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receptors, inhibiting thyroid peroxidase, and inhibiting iodine uptake. Also, it has toxic effects on endocrine systems, ovary, testes, and epididymis[6].

Experiments conducted on rodents have established that mancozeb and ETU can cross the placental barrier with significant potential to disrupt reproductive performance, cause DNA damage, and initiate tumors in fetal cells[7].

II. Materials and Methods

a) Animals, experimental design and sampling

This study was approved by the Ethical Committee of the Institutional Animals Care and Use, Alexandria, Egypt, and met all guidelines for their use.

Mancozeb (85%) was obtained from the central agriculture pesticide laboratory. Eighteen healthy adult male rats *(Rattus norvegicus)* with an average weight of (180±10)g were obtained from animal house, Faculty of Medicine, Alexandria University, and acclimated for two weeks before the experiment. They were assigned to 3 groups and housed in Universal galvanized wire cages at room temperature (22-25 °C) and in a photoperiod of 12h/day. Animals have been provided with a balanced commercial diet containing, 18% crude protein, 14% crude fiber, 2% fat, and 2600 Kcal DE/Kg feed.

Animals were divided randomly into three groups (6 animals each). Animals were maintained on food and water *ad libitum*. Doses of mancozeb have been prepared by dissolving in carboxy methylcellulose and adjusted according to the rat's body weights and given orally by gavages approximately at the same time each morning, three times per weekday after day for four weeks. Group I (control) was orally administered with carboxy methyl cellulose. Group II was orally administered with a dose equal to 700 mg/Kg body weight of mancozeb (1/7 LD50). Group III was orally administered with an amount equivelent to 1400 mg/Kg body weight of mancozeb (1/3.5 LD50).

The doses were chosen based on the previous study [8]. At the end of the treatment period, rats were sacrificed, blood was collected from the heart venacava, in heparinized tubes, and was centrifuged at 1,000xg for 15 min. Blood plasma was separated in Eppendorf tubes and stored at -80˚C till further investigations. Testes were isolated, weighed, then washed with saline and preserved at -80 ˚C for further biochemical studies. Parts of testes and thyroid glands used for histological studies kept in formalin (10%). The crude homogenates of the testes were prepared according to Greer [9].

b) Testes homogenate biochemical assay and blood plasma enzymes and hormonal assay

Acid phosphatase (ACP; EC 3.1.3.2) was determined according to Daniel[10], Fructose was determined according to Foreman[11]. Enzyme-linked immunosorbent assay (ELISA) of testosterone was determined according to Nash[12], while T3 and T4 were determined according to Thakur[13] and TSH was determined according to Liu[14]. Biochemicals and hormonal kits have been purchased from BioSystems Company.

c) Sperm collection and analysis

Immediately after decapitation, the rat's testes and epididymis were removed, cleaned from accessory tissues, and sperm collection was performed according to Trošić[15]. Sperm viability has been assessed by the eosin Y stain and the motility of sperm was assayed by the number of sperm that could move in a line. The percentage of viable sperm and the motility of sperm were calculated according to Wyrobek and Bruce[16]. The integrity of the acrosome was assessed using the Tejada acridine orange method[17, 18].

d) Histological examination

Parts of testes and thyroid glands were fixed in 10 % formalin solution, embedded in paraffin wax, and cut with a microtome for 5µ thick sections. The sections were stained by Hematoxylin and Eosin (H&E) stains and microscopically studied to evaluate their morphology[19].

e) Statistical Analysis

The data were analyzed using a one-way analysis of variance (ANOVA) followed by Duncan's multiple comparisons. $P<0.05$ was statically significant according to Norušis[20].

III. Results

a) Effects of Mancozeb on acid phosphatase (ACP) in blood plasma and testes homogenate and fructose level in testes homogenate of male rat

The present study showed that, treatment of rats with mancozeb-d_1 increased ACP activity in blood plasma when compared to the control group, while in the group treated with Mancozeb-d_2, ACP activity decreased when compared to control. Furthermore, in testes, homogenate treatment of rats with Mancozeb-d_1 and Mancozeb-d_2 decreased ACP activity and fructose level when compared to the control group (Table1).

b) Effects of Mancozeb on testosterone and sperm quality

Treatment of rats with Mancozeb decreased testosterone when compared to the control group. Also, Mancozeb decreased sperm motility, viability, and increased the number of total abnormal sperm, altered acrosome, and abnormal DNA when compared to the control group (Table 2).

c) Effects of Mancozeb on thyroid hormones in blood plasma

Results presented in Table 3 showed that, treatment of rats with Mancozeb-d_1 and Mancozeb-d_2 decreased T3 and T4 when compared to the control group. Treatment of rats with Mancozeb-d_2 decreased

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TSH when compared to the control group, while treatment with Mancozeb-d1 increased TSH when compared to the control group.

Table 1: Effects of Mancozeb on acid phosphatase (ACP) in blood plasma and testes homogenate and fructose level in testes homogenate of male rat

Parameters	Groups		
	Control	Mancozeb-d_1	Mancozeb-d_2
ACP (IU/L)	70.54 ± 1.15^{b}	76.60 ± 2.17^{a}	57.54 ± 1.54^{c}
ACP (IU/g tissue)	172.37 ± 5.81^{a}	160.39 ± 10.60^{b}	134.93 ± 4.26^{c}
Fructose (mg/g tissue)	151.95 ± 2.65^{a}	120.97 ± 3.88^{b}	122.91 ± 4.90^{b}

Results expressed as Mean ± SE, n=6
In Tables, the values denoted by different letters within the same row represent significant differences (P<0.05).
Mancozeb dose-1 (700mg/Kg) and Mancozeb dose-2 (1400mg/Kg), respectively

Table 2: Effects of Mancozeb on testosterone in blood plasma and sperm quality

Parameters	Groups		
	Control	Mancozeb-d_1	Mancozeb-d_2
Testosterone (μg/dL)	3.93 ± 0.114^{a}	3.20 ± 0.093^{b}	3.03 ± 0.088^{b}
Motility (%)	76.20 ± 0.583^{a}	66.70 ± 2.12^{b}	60.40 ± 2.56^{c}
Viability (%)	71.00 ± 0.548^{a}	61.00 ± 2.074^{b}	54.00 ± 2.793^{c}
Abnormal sperms(%)	5.30 ± 0.2^{b}	7.20 ± 0.490^{a}	8.20 ± 0.583^{a}
Altered acrosome(%)	5.40 ± 0.245^{b}	7.40 ± 0.510^{a}	7.20 ± 0.374^{a}
Abnormal DNA(%)	6.20 ± 0.583^{b}	7.20 ± 0.374^{b}	11.20 ± 0.490^{a}

Results expressed as Mean ± SE, n=6
In Tables, the values denoted by different letters within the same row represent significant differences (P<0.05).
Mancozeb dose-1 (700mg/Kg) and Mancozeb dose-2 (1400mg/Kg), respectively

Table 3: Effects of Mancozeb on thyroid hormones in blood plasma

Parameters	Groups		
	Control	Mancozeb-d_1	Mancozeb -d_2
T3 (μg/dL)	619.8 ± 18.04^{a}	490.00 ± 14.26^{b}	481.0 ± 14.00^{b}
T4 (μg/dL)	0.530 ± 0.015^{a}	0.214 ± 0.006^{b}	0.235 ± 0.007^{b}
TSH (μg/dL)	0.466 ± 0.014^{b}	0.807 ± 0.024^{a}	0.415 ± 0.012^{c}

Results expressed as Mean ± SE, n=6
In Tables, the values denoted by different letters within thesame row represent significant differences (P<0.05).
Mancozeb dose-1 (700mg/Kg) and Mancozeb dose-2 (1400mg/Kg), respectively

d) Effects of Mancozeb on histological changes in testes

Microscopic examination of control testes of male rats showed; typical testicular structure, normal spermatogonium cells (Spg) with its regular basophilic differentiated nuclei cells, normal spermatogenic (Figure 1). On the other hand, testes tissue of male rats treated with Mancozeb-d_1 (700 mg/kg); revealed large basal vacuoles in the cytoplasm cells, necrotic (N) spermatocytes (SPC) reduced volume of mature spermatozoa (SP) in some tubules. Necrosis was observed in some tubules (N)(Figure 2). Meanwhile, treatment rats with Mancozeb-d_2 (1400mg/kg) showed, dispatching of the tubular epithelium from primary spermatogonial (PSG) layer and reduction of the primary (PSP) and secondary (SSP) spermatids, with the presence of basal vacuoles (BV) (Figure 3).

e) Effects of mancozeb on histological changes in the thyroid gland

Microscopic examination of the control thyroid gland of male rats showed; typical architecture with follicular cells (F) with colloid (C), parafollicular cells (C-cells) (Figure 4). Meanwhile, the thyroid gland of male rats treated with Mancoeb-d_1 (700 mg/kg); showed vacuoles (V) in follicular epithelium, the follicular appeared flattened with flattened nuclei, reduction of colloid is evident; hyperplasia of parafollicular cells (C-

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Cells). Moreover, desquamation (d) of the follicular epithelium into the lumen of the thyroid follicles (Figure 5). On the other hand, treatment of rats with Mancozeb-d_2 (1400mg/kg) showed interstitial edema (O), vacuolated erythrocytes (V), with variable size strands with irregular contours of the follicles (F), reduction of colloid in most follicles, hyperplasia of the follicular epithelium (Figure 6).

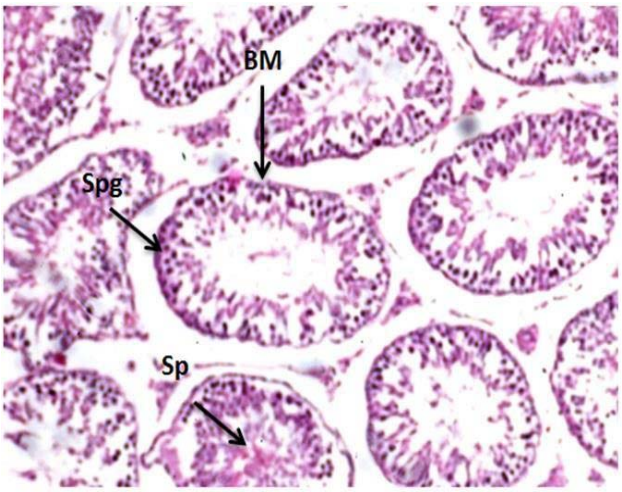


Figure (1): Photomicrographs of testes section of male rats control group *(H&EX200)*

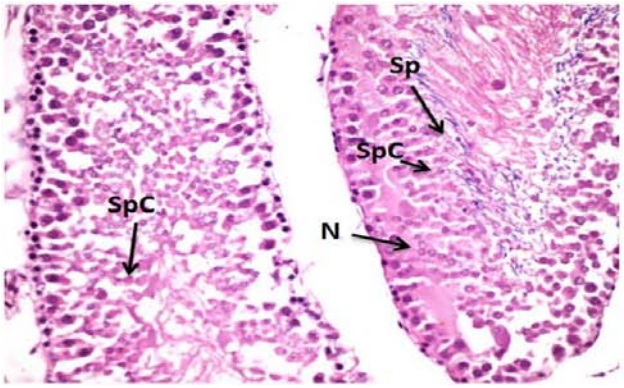


Figure (2): Photomicrographs of testes section of male rats treated with Manc-d1 (H&EX400)

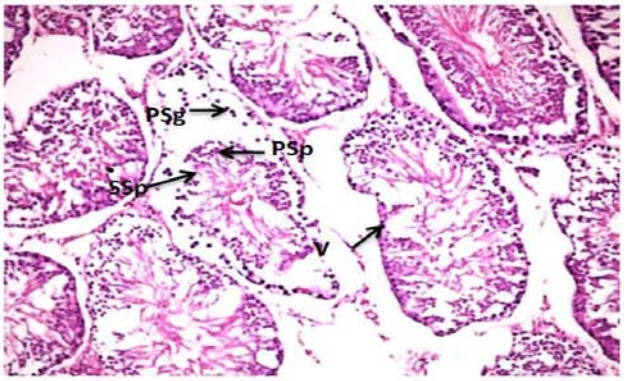


Figure (3): Photomicrographs of testes section of male rats treated with Manc-d2 (H&EX200)

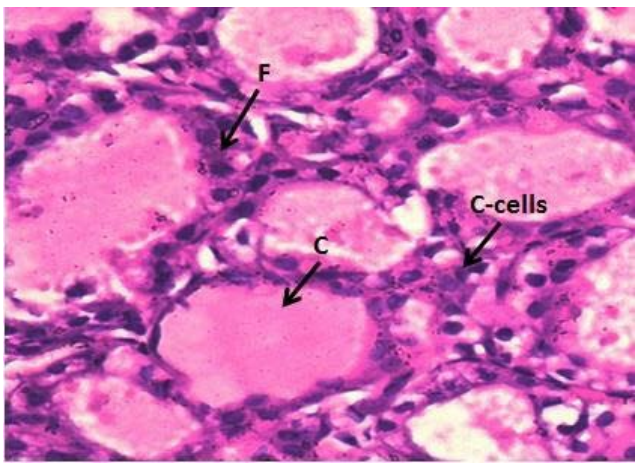


Figure (4): Photomicrographs of thyroid gland section of male rats control group *(H&EX400)*

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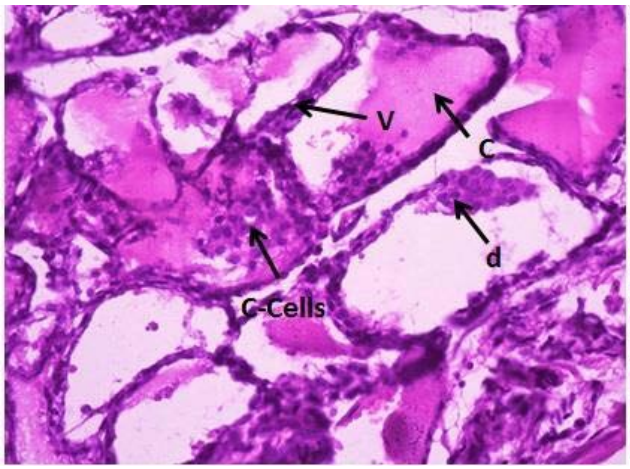


Figure (5): Photomicrographs of thyroid gland section of male rats treated with Manc-d1 (H&EX400)

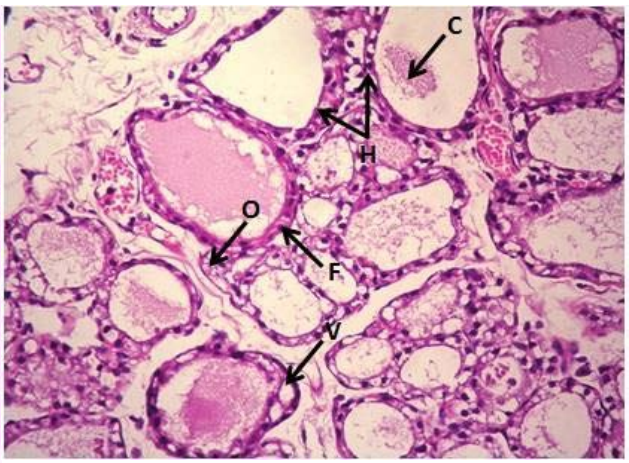


Figure (6): Photomicrographs of thyroid section of male rats treated with Manc-d2 (H&EX400)

IV. Discussion

Fructose has been used to indicate the seminal vesicle function, obstructive azoospermia, and inflammation of male accessory glands [21].

Increases in sperm concentration are often accompanied by a decrease in fructose level in seminal plasma, because sperm use fructose as the primary source of energy. However, other studies have also shown that fructose concentrations in seminal plasma of patients with oligozoospermia and azoospermia did not decrease as compared to ordinary men[22]. Fructose is produced endogenously within the human brain from glucose by the polyol pathway[23].

So, the present results revealed that, the decrease in fructose level means depression in the polyol pathway (fructose formation) and inactivity in cells due to treatment with mancozeb (manc).

Ananthan and Kumaran[24] showed that Mancozeb treatment (300 mg/kg body weight/day) for 60 days caused a significant increase in acid phosphatase in the testicular tissue of rats and increased activities in the serum. The decrease in acid phosphatase activity in the testes following the administration of Mancozeb could be attributed to either leakage of the enzyme into the extracellular fluid as a result of the disruption of the ordered lipid bilayer of the membrane or inhibition of the enzyme activity by this fungicide corresponding with the present results [24, 25, 26].

The decrease of testosterone might be responsible for the decreased sperm counts and motility and also morphological abnormality of testes. The insecticides may cause mitochondrial membrane impairment in Leydig cells and disrupt testosterone biosynthesis by diminishing the delivery of cholesterol into the mitochondria and decreasing the conversion of cholesterol to testosterone.

Acetamiprid-fed rats had fewer Leydig cells than regular diet-fed rats which may have been contributed to the reduction in testosterone biosynthesis[27].

Mancozeb and it's metabolites disturb endocrine gland action and its hormone secretion [6]. Treatment with mancozeb also changes the biochemical parameters of the reproductive tract. A fall in glycogen level may be due to interference in glucose metabolism. Fungicides induce inhibition of glycolytic enzymes, which affect the spermatozoa maturation and sperm motility. Inhibition of glycogen synthesis results in decreasing spermatogenesis process and reduction in serum testosterone[28].

Mancozeb has blocked the conversion of iodide to iodine. Inhibition in the iodide trapping and oxidizing process can lead to microscopic changes in the thyroid follicular cells and a reduced level of T4 [29]

The plasma TSH levels were increased upon chronic exposure to Mancozeb, indicating the usual negative feedback mechanism of the hypothalamus-pituitary- thyroid axis to low plasma T4 concentration. Chronic exposure to mancozeb has also been shown to reduce the synthesis and action of thyroid hormone through directly interacting with nuclear hormone receptors and inhibiting thyroid peroxidase and iodine uptake[6].

V. Conclusion

Mancozeb has adverse effects on the hormonal system, showing thyroid hormones disruption and decreased testosterone level resulting in abnormal sperms, thus reducing fertility, also exposure to mancozeb causes histological changes in the testes and thyroid gland.

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In the name of “Allah” the most beneficent and the most merciful, who gave me strength and knowledge to complete this dissertation

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Long-Term Follow-Up of Standard and Small-Diameter Implantable Cardioverter Leads

By Paolo Zappulla, MD, Antonio Greco, MD, Enrico Bertagnin, MD, Daniela Dugo, MD, Angelo Di Grazia MD & Valeria Calvi, MD

University of Catania

Abstract- *Background:* Small-diameter implantable cardioverter-defibrillator (ICD) leads have been introduced into clinical practice to facilitate the implantation procedure. Despite their expected benefits, the reliability of these leads has proven to be questionable. The main purpose of our study is to investigate the impact of ICD lead diameter (≤8 F versus > 8 F) on long-term lead durability.

Methods: Overall, 206 consecutive patients implanted with a right ventricular ICD lead in the Electrophysiology and Cardiac Pacing Unit of our department from January 2008 to December 2013 were included in this analysis. ICD leads were defined, according to their diameter, as small (≤8 F) and standard (>8 F). The small-diameter leads (n=106) included Linox (Biotronik; n=58) and Durata (St. Jude Medical/Abbot; n=48). The standard-diameter ICD leads (n=100) consisted of Sprint Quattro (Medtronic; n=64) and Endotak (Boston Scientific; n=36).

Keywords: *implantable cardioverter-defibrillator, lead failure, linox, durata.*

GJMR-L Classification: *DDC Code: 617.4120645 LCC Code: RC684.P3*



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Long-Term Follow-Up of Standard and Small-Diameter Implantable Cardioverter Leads

Comparison of Different Size ICD Leads

Paolo Zappulla, MD [α], Antonio Greco, MD [σ], Enrico Bertagnin, MD [ρ], Daniela Dugo, MD [ω], Angelo Di Grazia MD [¥] & Valeria Calvi, MD [§]

Abstract- ***Background:*** Small-diameter implantable cardioverter-defibrillator (ICD) leads have been introduced into clinical practice to facilitate the implantation procedure. Despite their expected benefits, the reliability of these leads has proven to be questionable. The main purpose of our study is to investigate the impact of ICD lead diameter (≤8 F versus > 8 F) on long-term lead durability.

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Results: After a median follow-up of 7.3 years, lead failure rate was significantly increased for small-diameter leads compared with standard-diameter leads (6.6% vs 1%; P =0.035). No difference in lead survival probability has been observed between Linox and Durata small-diameter leads (93% vs 92.7%; P =0.71). The majority of lead failures presented as noise (87.5%), without detectable abnormalities on fluoroscopic evaluation.

Conclusions: Our single-centre study showed that both Linox and Durata small-diameter ICD are associated to be more susceptible to a greater risk of lead failure as compared to standard-diameter ICD leads. In this perspective, a comprehensive vigilance strategy including home monitoring is warranted for early detection of lead failure.

Keywords: implantable cardioverter-defibrillator, lead failure, linox, durata.

I. Introduction

Implantable cardioverter-defibrillator (ICD) devices have been broadly shown to be efficacious for sudden cardiac death prevention [1, 2] and are nowadays recommended in high-risk subsets, either in primary or secondary prevention setting. The main structural weakness of an ICD system lies in the leads. The anticipated lead failure rate increases with age, reaching up to 20% in at least 10-year old leads [3]. Lead technology evolution has followed in a decreased annual failure rate, approximately from 4 % to 0,3% [4]. Small-diameter ICD leads have been introduced into clinical practice to improve the implantation procedure and to reduce the odds of subclavian vein thrombosis. Although their expected benefits, the long-term performance of these leads is still an area of uncertainty [5-7]. Two high-profile safety alerts were conducted in October 2007 (Sprint Fidelis, Medtronic) and December 2011 (Riata, St. Jude Medical). For Sprint Fidelis, in 2007, an increased early failure rate mainly due to conductor fracture was observed [8] and, in subsequent years, failure rates of 2.8 - 3.8% per patient/year were reported [7, 9]. On the other hand, Riata leads showed conductor externalization [10] that may remain electrically silent for longer periods. Prospective screening of Riata leads by high-resolution fluoroscopic imaging found a 15% prevalence rate of externalized conductors after a mean follow-up of 4 years [11]. Afterward new small-diameter ICD leads, Durata, St Jude Medical now Abbot and Linox, Biotronik, has been introduced into the market.

The main purpose of our study is to investigate the impact of ICD lead diameter (£8 F versus > 8 F) on long-term lead durability among patients who underwent ICD leads implantation at our centre.

II. Materials and Methods

a) Patient selection and implantation procedure

For the purpose of the current analysis, 206 consecutive patients in whom a right ventricular ICD lead had been implanted in the Electrophysiology and Cardiac Pacing Unit of our cardiology department from January 2008 to December 2013 were included. According to their diameters, ICD leads were categorized as small-diameter (£8 F; n= 106) or standard-diameter (>8 F; n = 100). The small-diameter leads were Biotronik Linox (model S and SD; n= 58) and St Jude Medical/Abbot Durata (model 7122 and 7170; n= 48). The standard-diameter ICD leads were Medtronic Sprint Quattro (model 6947 and 6935; n= 64) and Boston Scientific Endotak (model 0148, 0155, 0295 and 0296; n= 36). At the time of implantation, baseline ICD leads characteristics were collected in a dedicated

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database, including electrical parameters (e.g. R-wave amplitude, capture threshold, and pacing and high-voltage impedances), type of lead fixation, number of shock coils and lead model. All implantations procedures were carried out by interventional cardiologists with great experience on electrophysiology and cardiac pacing. Venous access for lead insertion was the subclavian vein in all cases.

b) Definition of lead failure

Lead failure was relied on one or more of the following features: recurrent non-physiological high-rate sensing (electrical noise) without any explanation; a sudden pace/sense or high-voltage impedance change (>100% increase or >50% decrease) or values outside the interval of 200-1500 Ω or 20-200 Ω, respectively; a sudden increase in right ventricular threshold; unexplained loss of sensing accompanied by R-wave amplitude decrease.

c) Follow-up

Patients were usually discharged from hospital the day after the implantation procedure and were followed-up at the ICD outpatient clinic at 1 month, every 6 months thereafter, and whenever an ICD shock or a device alert occurred. At each visit, electrical ICD parameters were analysed and recorded in the ICD database.

d) Statistical analysis

Categorical variables are expressed as numbers and percentages, while continuous variables are reported as either mean and standard deviation (SD) or median and interquartile range (IQR), as appropriate. Student's t-test was used for comparison of continuous data and analysis of variance, and chi-squared test was used for comparison of categorical data. A P-value <0.05 was considered statistically significant. Cox regression analysis was used to identify predictors of lead failure. Survival was analyzed by the Kaplan-Meier method, and between-groups differences by log-rank tests. All statistics were performed using SPSS 20 (IBM, Armonk, NY).

III. Results

a) Baseline patient characteristics

Overall, 206 patients underwent ICD implantation at our hospital from January 2008 to December 2013. There were no between-groups differences with regards to several baseline patients' characteristic, including age, sex, left ventricular ejection fraction and body mass index *(Table 1).*

Primary prevention indication (75% vs 89.6%; P = 0.006) and septum as pacing site (8% vs 24.5%; P= 0.001) were significantly associated with small-diameter leads usage *(Table 1).*

Notably, the median follow-up duration was significantly longer for standard-diameter leads as compared to small-diameter leads (90.4 months, IQR 72.3-96.5 vs 80.7 months, IQR 72.3-95.5; P =0.003), due to a change in lead procurement and use throughout the study period.

Table 1: Baseline patients' characteristics

Variables	Standard diameter	Small-diameter	P-value
Age at implantation (years)	66 (57-62)	62 (55-68)	0.62
Female sex	14 (14%)	23 (21.7%)	0.15
BMI (kg/m^2)	28.4 (4.3)	28.1 (6.1)	0.3
LVEF (%)	32 (8)	31 (10)	0.25
CAD	58 (58%)	63 (59.4%)	0.83
Primary prevention	75 (75%)	95 (89.6%)	**0.006**
Secondary prevention	24 (25%)	11 (10.4%)	**0.01**
Single-chamber	42 (42%)	42 (39.6%)	0.73
Pacing site • Apex • Septum	 92 (92%) 8 (8%)	 80 (75.5%) 26 (24.5%)	 **0.003** **0.001**
Follow-up (months)	90.4 (72.3-96.5)	80.7 (72.3-95.5)	**0.003**

Abbreviations: BMI= Body Mass Index; CAD=Coronary Artery Disease; LVEF= Left Ventricular Ejection Fraction.

b) Clinical outcomes

During a median follow-up of 7.3 years, lead failure occurred in 7 (6.6 %) small-diameter leads (4 Linox and 3 Durata) and in 1 (1%) standard-diameter lead (Endotak).

Seven-year lead survival rates were 92% for small-diameter leads and 99% for standard-diameter leads *(Figure a).* Accordingly, the log-rank test showed a significantly decreased lead survival among small-diameter leads (P =0.035).

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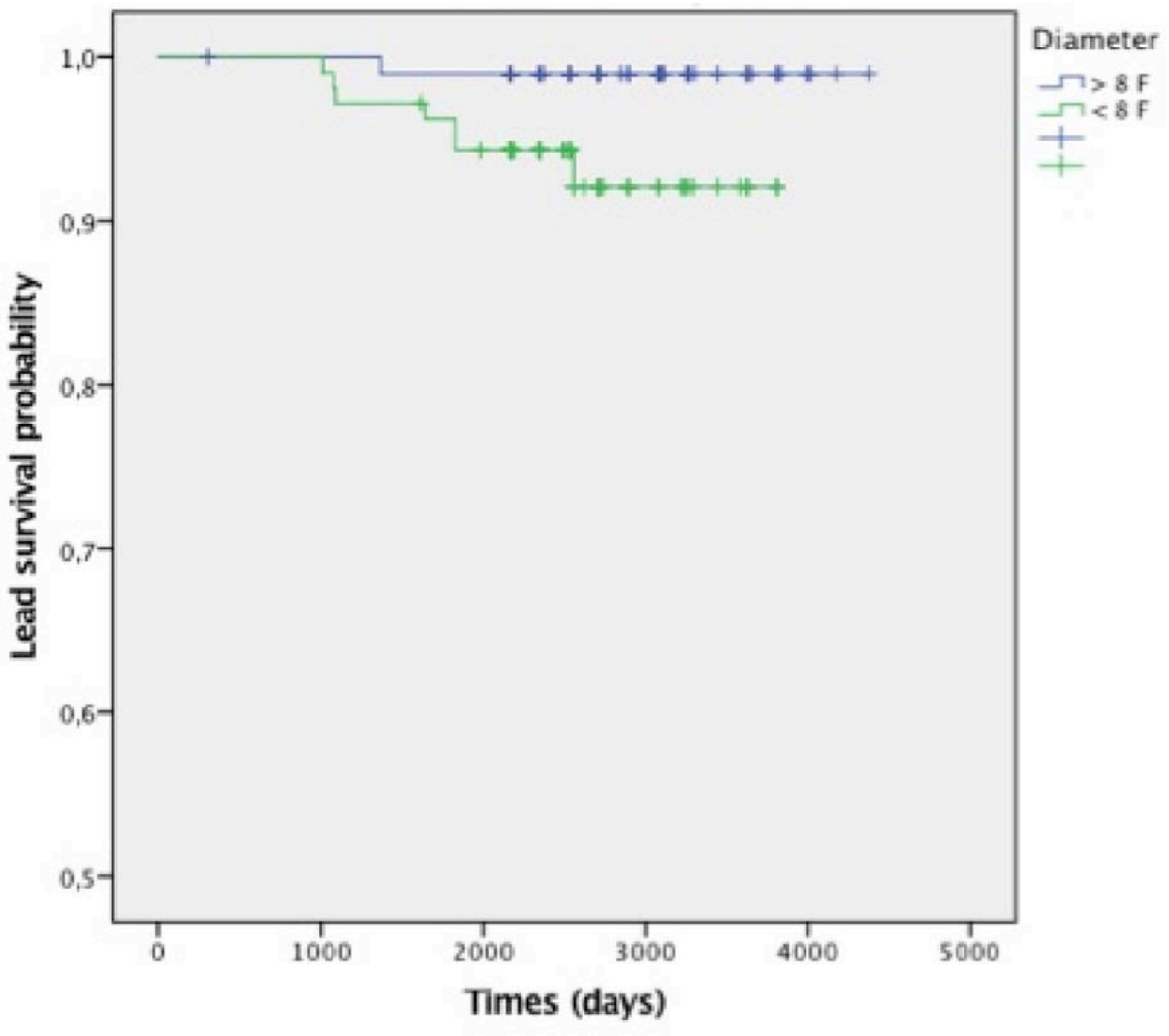


Figure a: Kaplan-Meier survival curves for small-diameter and standard-diameter leads. Abbreviations: F= French gauge

No difference in lead survival rate arose between small-diameter Linox and Durata leads (93% vs 93.7%; P = 0.71) *(Figure b).*

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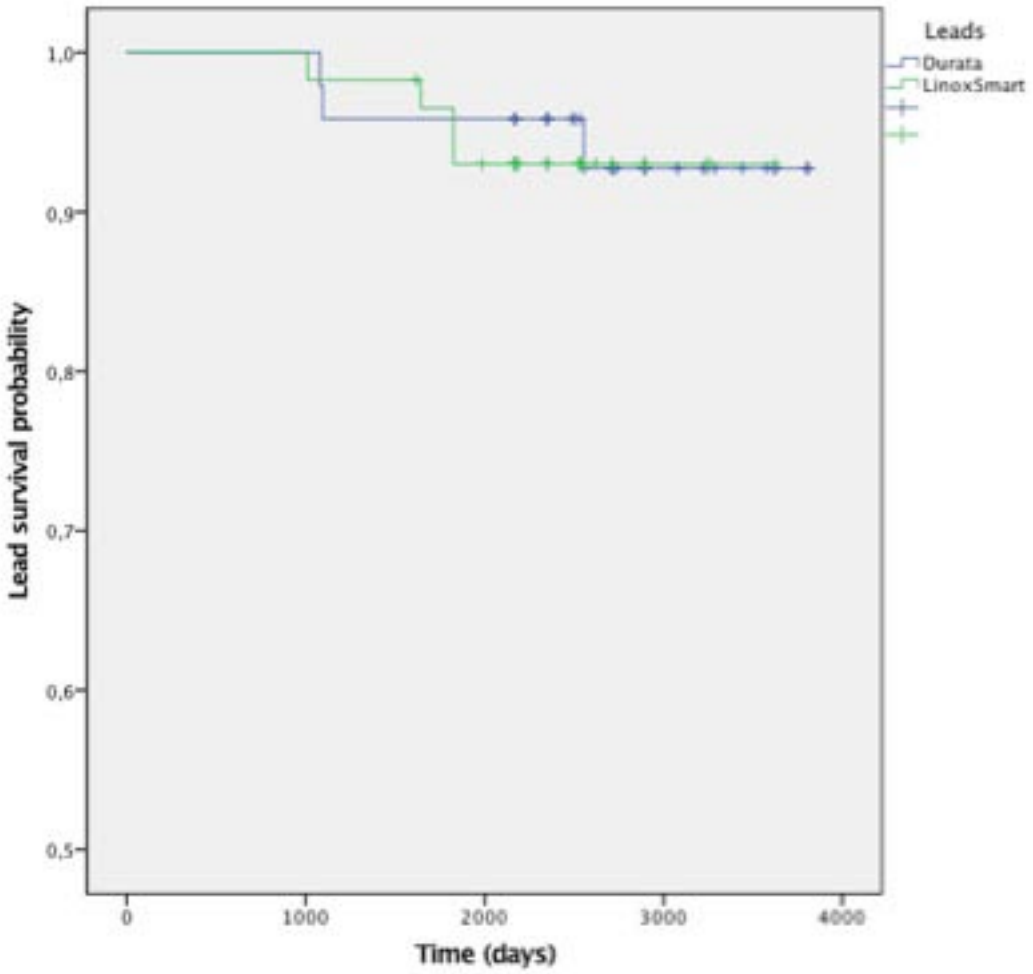


Figure b: Kaplan-Meier survival curve for Linox and Durata leads.

Clinical features and device data for lead failure cases are shown in *Table 2.* The larger number of lead failures (87.5%) showed up as non-physiological high rate signals (noise), resulting in shocks in 2 patients.There were three cases of increased pacing threshold and one case of increased impedance without any evidence of non-physiologic noise. The fluoroscopic evaluation of all failed leads was normal. Lead extraction was executed successfully in two patients (Patients 4 and 7) and the extracted leads were not submitted to the manufacturer for further testing. Furthermore, all lead failure were confirmed by manufacturers' engineers, who analysed all intracardiac electrograms and fluoroscopic evaluation.

No independent predictors of lead failure were detected by Cox regression model.

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Table 2: Patient and device features of high-voltage lead failure cases.
Abbreviations: DCM= Dilated Cardiomyopathy.

Case	Age at implantation (years)	Underlying aetiology	ICD indication	Lead Model	Lead Age (months)	Presentation	Inappropriate Shock
1	69	Idiopathic DCM	Primary prevention	Endotak Reliance 0155	45.6	Noise	No
2	55	Ischemic DCM	Primary prevention	Linox Smart SD 65/16	54.7	Noise and increased pacing threshold (3.5 V/1.5 ms)	Yes
3	64	Ischemic DCM	Primary prevention	Linox Smart SD 65/16	60.8	Noise	Yes
4	63	Ischemic DCM	Secondary prevention	Linox Smart SD 65/16	60.0	Noise	No
5	58	Ischemic DCM	Primary prevention	Linox Smart SD 65/16	33.7	Noise and increased pacing threshold (3 V/1 ms)	No
6	67	Idiopathic DCM	Primary prevention	Durata 7120	36.0	Increased pacing or shock impedance (> 1500 Ω)	Yes
7	65	Ischemic DCM	Primary prevention	Durata 7120	85.2	Noise and increased pacing threshold (4.8 V/1.5 ms)	No
8	77	Idiopathic DCM	Primary prevention	Durata 7120	36.5	Noise	No

IV. Discussion

The results of this single-centre observational retrospective study reveal a higher incidence of lead failure among small-diameter leads. Linox and Durata leads were the small-diameter leads implanted at our centre. Seven-year lead survival rates were 93% and 93.7% for Linox and Durata, respectively. The incidence of Linox and Durata leads dysfunction still remains controversial. Linox S (single-coil) and Linox SD (dual-coil) leads, as 8-F silicone-insulated ICD leads, were released in April 2006 and February 2007, respectively. Moreover, the Linox series have not long been marketed and have been substitute by the Linox Smart series. These leads are covered with an additional Silglide® surface coating, further evolved into the Linox Smart ProMRI and the Linox Smart DX series.

A product performance report by Biotronik indicated a cumulative lead survival of 95.2% at 7 years for the Linox S and 95.0% at 9 years for the Linox SD [12], almost several single-centre [13-15] and multicentre [16] studies have suggested high rates of lead failure, contradicting the self-reported data from the manufacturer. These studies have reported 5-year Linox lead survival rates ranging between 85.3% and 93.6%, which are similar to our findings. Furthermore, the results of the Biotronik Galaxy and Celestial registries [12], with a mean follow-up of 2.3 years for Linox Smart leads, report a lead failure rate of 2.2% at 3 years, which likely underestimates the true performance of these leads in terms of over sensing development. In our study, the electrical noise mostly develops from the third year onward, beginning with 1- or 2-second episodes, which became more frequent and prolonged, leading to suspicion of progressive deterioration of lead integrity. The exact mechanism of Linox Smart lead failure is unknown, but, given the structural similarities with the Riata lead (St. Jude Medical/Abbott), we believe that it could be due to silicone abrasion due to movement of the internal conductors, sometimes followed by conductor externalization.

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The 6.8-F Durata (model 7122, single-coil) was released in September 2007. Unlike the Linox and Endotak leads, the Durata lead is coated with an additional protective sheath of a polyurethane-silicone co-polymer (OptimTM) with an abrasion resistance 50 times greater than silicone.

Several changes were made in the structure of the Durata leads compared to RiataTM/Riata STTM leads, to prevent lead malfunction. The inner central lumen was reduced, the wall thickness form cable to the outer edge of the lead was increased by 50%, the lead body size was increased from 6.3 to 6.8-F, the shock coil became slightly curved and low titanium material was added to remove structural defects for a better fatigue life. St. Jude/Abbott, in their product performance report in an "Update on Durata lead performance," also stresses that Optim-covered leads show very low rates of abrasion in actively monitored registries. Survival probabilities after 5 years are between 97.4 and 98.0% for the various models of Durata [17]. In our study the survival was 98.5% after 5 years but decreased after 7 years to 92.3 %. It is useful to compare the results of the current study to previous analyses of Durata performance. A search of the MAUDE database by Shah et al. [18] for abrasion reports on Durata, Endotak, and Sprint Quattro showed a significantly higher incidence of lead failure for Durata than for the other two leads. They observed that 69.5% of the reported Durata insulation failures were identified to be the result of interaction between the lead and the ICD generator, indicating a possible time dependency for abrasion risk. Hauser et al. [19] found Durata ICD leads are susceptible to internal insulation gapes that may follow in failure to treat ventricular arrhytmias or in noise/oversensing with unsuitable therapy. In our study, there was only two case of inappropriate shock and two cases of oversensing. To explain the underlying mechanism, the incessant movement of the redundant conductor cables touching the lumen's siliconewas hypothesized [19-21]. In the long time, the inner silicone is abraded from the inside-out beneath a rigid shocking coil. When ethylene tetrafluoroethylene (ETFE) isharmed, the exposed conductor cable contacts the coil. The effect depends on the cable exposed: if it isa sensing cable, noise is the most presumable consequence; if it is a high-voltage cable, a low impedance pathway shorts the cable to the coil and avoids the delivery of a shock. There is not Durata's Optim outer insulation under the shocking coils and thus does not insulate or restrain cable movement in these locations. In this feature, Durata is such like to non-Optim Riata and Riata ST leads.

This study is affected by several limitations. The study design was a single-centre retrospective cohort analysis and an underestimation of lead failure cannot be excluded. The exact mechanism of lead failure was not confirmed by manufacturers' structural and functional analyses, mainly due to the clinical chose whether to extract or leave the lead. In the study all the leads were implanted with the subclavian technique. Subclavian puncture is known to have a higher lead complication rate [22] and might have led to an increased incidence of insulation failure caused by subclavian crush syndrome. The number of implanted leads was too low to warrant any definite conclusion on the long-term performance of this group of leads.

V. Conclusion

Our study showed that small-diameter ICDs are associated to a greater risk of lead failure. Although the exact mechanism by which leads fail has not been fully explained so far, abnormal electrical parameters were present in the majority of cases. In this perspective, a comprehensive vigilance strategy including home monitoring is warranted for early detection of lead failure. Furthermore, a multicentre study including a large number of patients should be conducted, and further data are required to inform future guidelines for the management of patients with Linox and Durata leads.

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Effect of Obesity in Memory and Cognition

By Amina Khatun, Kuntal Ghosh, Shrabani Pradhan & Sudipta Chakrabarti

Abstract- Presently a day's obesity is one of the significant public issues worldwide among kids, teenagers, just as in grown-ups and older people. From the distinctive animal models and clinical trials, it was accounted that natural adequacy related to weight is connected with more regrettable memory function. Evidence recognizes obesity as a significant danger factor for the beginning and progression of a few neurological problems associated with metabolic dysfunction and inflammation, which are related to obesity are owing to consequences for the primarily cognitive impairment. Numerous studies suggest that obesity results in neurological diseases such as Parkinson's disease and Alzheimer's disease, which could be initiated by various metabolic alterations, related to CNS damage as well as cognitive loss or cognitive dysfunction. This review examined whether obesity is associated with cognitive function or cognitive decline and whether obesity confounds the relationship between obesity and cognitive decline. This review approach was employed, using PubMed, and the Google Scholar database. Worse memory function may directly be related to obesity with underlying mechanisms discussed here. However, it is uncertain whether adiposity, itself, is influencing cognitive changes and it drives the obesity-cognitive relationship.

Keywords: *obesity; alzheimer's disease; parkinson's disease; cognitive impairments.*

GJMR-L Classification: *DDC Code: 616.15 LCC Code: RB145*



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Effect of Obesity in Memory and Cognition

Amina Khatun [α], Kuntal Ghosh [σ], Shrabani Pradhan [ρ] & Sudipta Chakrabarti [ω]

Abstract- Presently a day's obesity is one of the significant public issues worldwide among kids, teenagers, just as in grown-ups and older people. From the distinctive animal models and clinical trials, it was accounted that natural adequacy related to weight is connected with more regrettable memory function. Evidence recognizes obesity as a significant danger factor for the beginning and progression of a few neurological problems associated with metabolic dysfunction and inflammation, which are related to obesity are owing to consequences for the primarily cognitive impairment. Numerous studies suggest that obesity results in neurological diseases such as Parkinson's disease and Alzheimer's disease, which could be initiated by various metabolic alterations, related to CNS damage as well as cognitive loss or cognitive dysfunction. This review examined whether obesity is associated with cognitive function or cognitive decline and whether obesity confounds the relationship between obesity and cognitive decline. This review approach was employed, using PubMed, and the Google Scholar database. Worse memory function may directly be related to obesity with underlying mechanisms discussed here. However, it is uncertain whether adiposity, itself, is influencing cognitive changes and it drives the obesity-cognitive relationship.

Keywords: obesity; alzheimer's disease; parkinson's disease; cognitive impairments.

I. Introduction

Obesity is a roaring global concern with a sprouting predominance in children (Ogden, Carroll, Kit, & Flegal, 2014), adolescents, and older people on the earth, especially in a developing country. The number of obese people also has expanded day by day in an epidemic manner throughout the last decade. It was accounted that the prevalence rate of obesity and central obesity varies from 11.8% to 31.3% and 16.9%–36.3%, respectively according to ICMR-INDIAB study 2015, (Ahirwar & Mondal, 2019). Obesity is characterized by the exorbitant gathering of fat, especially adipose tissues, which can adversely influence well-being by expanding the expression of pro-inflammatory markers(Huang, Zhang, & Chen, 2016). Due to the accumulation of excessive adipocytes, various health consequences such as increased heart disease, hypertension, diabetes, inactivity, inflammation, genetic alteration, stroke, and cancer (Aronne, 2001) occur. Some of these medical comorbidities are associated with adverse cognitive effects (Biessels, Deary, & Ryan, 2008). There is a strong correlation between obesity and neurodegenerative diseases, suggesting that obesity might affect the central nervous system, causing neurodegeneration and cognitive decline, as well as causing brain damage (Ashrafian, Harling, Darzi, & Athanasiou, 2013). Neurodegenerative disease (ND) is a significant reason for inability, morbidity, and diminished personal satisfaction, establishing the basis for 12 % of human death internationally (Erkkinen, Kim, & Geschwind, 2018).Investigations have shown that individuals who experience the ill effects of midlife obesity (estimated by BMI) have an expanded danger to building Alzheimer's Disease (AD) and Parkinson's Disease (PD) (Profenno, Porsteinsson, & Faraone, 2010). The role of obesity in memory and cognitive decline has been reviewed in this article.

II. Effect of Obesity on Brain Structure and Cognitive Capacity

a) Brain Structure

Structure alteration in neural architecture due to obesity has been recently reported. For instance, raised BMI is connected to diminished cerebrum volume (Ward, Carlsson, Trivedi, Sager, & Johnson, 2005), the autonomy of age, and morbidity (Gunstad et al., 2008). Expanded BMI is connected with gray matter decay in some specific parts of the brain (Shefer, Marcus, & Stern, 2013), and decreased uprightness of white matter of the brain (Verstynen et al., 2012). Middle-age must be the most critical period for brain aging and at that time, vulnerability to obesity is particularly acute compared with later life (Ronan et al., 2016), and the starting of middle-age, there has been identified white matter atrophy (Fotenos, Snyder, Girton, Morris, & Buckner, 2005) in the brain. Recently, Thompson et al. (2020)conducted a meta-analysis where the connection between obesity (BMI $>$ 30 kg/m^2) and brain structure of 6420 members was studied. Obesity has been shown to be associated with brain structure abnormalities, including a lowered temporal-frontal thickness. Cortical thinning of the brain might be related to decreased microstructural integrity in white matter tracts in obese teenagers (Yau et al., 2014).Further, obesity decreases practical movement in cortical regions that are associated with episodic memory (hippocampus, dorsolateral prefrontal cortex, and angular gyrus) (Cheke, Bonnici, Clayton, & Simons, 2017). Obesity also causes an increase in the amount of glycerol,

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hormones, cytokines, and pro-inflammatory substances involved in developing insulin resistance (Al-Goblan, Al-Alfi, & Khan, 2014). The hippocampus might be especially helpless against the adverse consequences of abnormal glucose tolerance and insulin resistance comparative with other cerebrum districts, a suggestion supported by neurological, structural research associating type 2 diabetes and impaired glucose tolerance (IGT) with hippocampal atrophy (Bruehl et al., 2009; Gold & Shadlen, 2007; Korf, White, Scheltens, & Launer, 2006).Expanded development of harmful glycation end product results in hyperglycemia and type 2 diabetes (Roriz-Filho et al., 2009), this could result in hippocampal volume loss, especially given that the hippocampus is profoundly defenseless against other metabolic affronts (McEwen, 1997; Stranahan et al., 2008). Hippocampus has a high co-restriction of insulin and cortisol receptors (Jacobson & Sapolsky, 1991). It has been guessed that persistently raised corticosteroids related to type 2 diabetes could modify synaptic plasticity and *explicit neurogenesis* in the hippocampus (Magariños & McEwen, 2000).The conceivable clarification could be that peripheral insulin resistance results in expanded hepatic lipid production, especially in ceramides, a product from unsaturated fats and sphingosine and is known to have lipid solvent properties(Tong & de la Monte, 2009). A few studies have shown that ceramide promotes brain insulin resistance through an impaired brain insulin pathway (Arboleda, Morales, Benítez, & Arboleda, 2009), and results in neurodegeneration as a consequence (Arboleda et al., 2009; Sartorius et al., 2014; Tong & de la Monte, 2009). Even though there was no proof that ceramide straightforwardly results in blood-brain barrier disturbance, it is conceivable that a lot of ceramides under obese conditions might be one of the dangerous elements to cause the interruption of the blood-brain barrier. In this way, the blood-brain barrier can be crossed (Fig. 1).

b) Cognitive and memory impairment

After different longitudinal and cross-sectional investigations, researchers considered that obesity in early adulthood or middle age could extend one's risk of later-life cognitive inability. People who had higher BMI in midlife displayed shortages in an assortment of mental spaces, including long-and short memory, psychomotor speed, verbal capacity, and spatial capacity, this led to more fast destruction of cognition (Hassing, Dahl, Pedersen, & Johansson, 2010). An increased BMI, as well as increased energy metabolites (Roriz-Filho et al., 2009), result in worse memory performance by causing hypertonicity and neuroinflammation (Gonzales et al., 2012). Numerous studies have shown that the "Western diet", which is high in saturated fats and simple sugars, impairs learning and memory in people who are obese (Beilharz, Maniam, & Morris, 2015; Loprinzi, Frith, Edwards, Sng, & Ashpole, 2018).It is associated with decreased neurogenesis and increased inflammatory responses. As it is also shown, diet plays a vital role in such memory impairments, as opposed to being caused by adipose changes, and the brain's working memory and negative outcome learning capacity are hampered due to adaptations in the dopamine system due to obesity-induced overeating. (Coppin, Nolan-Poupart, Jones-Gotman, & Small, 2014).

BBB is mainly made up of endothelial cells. However, obesity is a cause of endothelial brokenness, adding to BBB deterioration through some mechanisms (Wardlaw et al., 2013). This results obesity-related cognitive impairments, initiates neuroinflammation and neurodegeneration. Disturbance in the tight junction of endothelium breakdown the BBB (Zlokovic, 2008)proposes that obesity might trigger tight junction interruption prompting BBB breakdown. The disruption of BBB by lipid-like substances results in microglial activation, decreased endothelial tight junction and protein articulation (Shigemoto-Mogami, Hoshikawa, & Sato, 2018; Sumi et al., 2010), ultimately leading to persistence neuroinflammation (Dalvi et al., 2017; Thaler et al., 2012) and cognitive dysfunction (Kahn & Flier, 2000). In like manner, (Bocarsly et al., 2015) announced that obesity prompted decreases in dendritic spines and led to cognitive decline. It has been shown from different findings that obesity is associated with systemic and central inflammation (Gregor & Hotamisligil, 2011; Miller & Spencer, 2014) and is always hindering memory and cognition by stimulating the production of pro-inflammatory cytokines and adipokines that lead to insulin resistance (Su et al., 2017).De Souza and partners found that high-fat diets or obesity raises the pro-inflammatory cytokines and the pro-inflammatory transcription factor NFjB in the hypothalamus (De Souza et al., 2005). The hippocampus, a significant area in cognitive preparing, learning, and memory, might be especially defenseless against inflammation in obesity, with raised TNF-α and ionized calcium-binding connector particle 1 (Iba1; microglial marker) (Jeon et al., 2012). Hence, this concluded that systemic inflammation and obesity have been recognized as the leading cause of cerebral white matter injuries and cognitive brokenness (T Den Heijer et al., 2005; Viscogliosi, Donfrancesco, Palmieri, & Giampaoli, 2017). In addition, higher plasma levels of interleukin (IL)- 12 and 6 are connected to diminished speed in handling data and a quicker pace of cognitive decay (Marioni et al., 2010; Schram et al., 2007; Trollor et al., 2012). Hypertension expands one's danger of being diagnosed to have mild cognitive impairment (MCI) (Reitz, Tang, Manly, Mayeux, & Luchsinger, 2007). It predicts the degree of weakness seen in these people (Goldstein, Levey, & Steenland, 2013). Obesity-induced hypertension in midlife is conversely identified with

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execution on an assortment of cognitive tests, for example, those verbal surveying memory and executive function during obesity (M. Elias, Elias, Sullivan, Wolf, & D'agostino, 2003; Launer, Masaki, Petrovitch, Foley, & Havlik, 1995). Past research has shown that mitochondria assume a crucial part in cerebrum synaptic transmission and age-related intellectual capacity (A. Cheng, Hou, & Mattson, 2010; Hara et al., 2014; Mattson, Gleichmann, & Cheng, 2008; Raefsky & Mattson, 2017). That study suggested that changes in the shape of mitochondria in presynaptic neurons affected synaptic transmission. Additionally, apoptosomes are formed that activate the caspase cascades and subsequently trigger cell death(Cain, Bratton, & Cohen, 2002). Research has shown increased level of pro-apoptotic proteins (Bax and Bad) in brain tissue from rodents with insulin resistance caused by mitochondrial impairment, along with reduced levels of anti-apoptotic proteins (Bcl-2) (Nuzzo et al., 2015; Sa-Nguanmoo et al., 2017; Sa-Nguanmoo et al., 2016). An increment in pro-apoptotic proteins can prompt cytochrome C release, bringing about cerebrum apoptosis (Gómez-Crisóstomo, López-Marure, Zapata, Zazueta, & Martínez-Abundis, 2013). Also, apoptotic-mediated neuronal passing has been known to be one fundamental component for intellectual weakness and other neurodegenerative infections and cognitive loss (Ghavami et al., 2014).

III. Obesity and Dementia

As populaces age, intellectual problems, including dementias, become more normal. The most common form of dementia is Alzheimer's disease (AD), representing somewhere in the range of half and 70% of all dementias. Ongoing efficient reviews and meta-examinations uncover an unpredictable connection between obesity and the possibility of dementias (Anstey, Cherbuin, Budge, & Young, 2011; Beydoun et al., 2011; Gorospe & Dave, 2007). The conviction of dementia being a solitary memory-related confusion of Alzheimer's disease (AD) has tremendously congested. The present comprehension of dementia is a complete loss of memory with diminished mental and scholarly execution because of damaged synapses. The current existing research on BMI and AD is conflicting and consolidating the consequences of many investigations that exhibited a lot of conflicting data. A meta-examination done on 16 articles covering 15 planned investigations showed that underweight, overweight, and obesity in midlife is related to an expanded danger of dementia when contrasted with having normal weight or BMI. Having a raised BMI in midlife altogether expands the danger of dementia perhaps because of expanded inflammation, higher cytokine, and hormone created by fat tissues (Skoog & Gustafson, 2003). Having an expanded BMI can likewise be related to countless morbidities, for example, insulin opposition prompting diabetes, elevated cholesterol, hypertension, and cardiovascular infection (Naderali, Ratcliffe, & Dale, 2009).The vascular impacts may likewise play a part in advancing a quickly developing disease of late-life, Alzheimer's pathology. Additionally, the variables mentioned above and the higher BMI is link with the changes in cerebrum structure, white matter changes, blood-brain obstruction aggravations, and the age-related administrative changes in protein, carbohydrate, and lipid digestion that might trigger dementia pathology. The persistent overconsumption of food sources wealthy in carbohydrates and lipids in obesity can influence insulin emission and fundamentally affects cerebral glucose digestion. The normal intracellular components in type 2 Diabetes Mellitus and AD incorporate variant redox guidelines, oxidative pressure, and dynamic incendiary cycles bringing about disabled insulin emission and signaling pathways(Verdile et al., 2015). Studies have shown that central insulin organization may be powerful in helping people with Alzheimer's to perform cognitively (Claxton et al., 2015; Freiherr et al., 2013; Haj-Ali, Mohaddes, & Babri, 2009).Further evidence suggests insulin may influence AD-related proteins (e.g., APP and tau) and contribute to the progression of AD pathology and cognitive impairment (Ferreira, Clarke, Bomfim, & De Felice, 2014; Steculorum, Solas, & Brüning, 2014; Umegaki, 2014). The T2DM has a particularly damaging effect on the hippocampus - a part of the brain crucial for memory and learning functions (Bruehl et al., 2009; Tom den Heijer et al., 2003; Gold & Shadlen, 2007; Korf et al., 2006). Though diabetes is not just a danger factor for mild cognitive impairment (MCI) and Alzheimer's disorder yet in addition to some other kinds of dementia (G. Cheng, Huang, Deng, & Wang, 2012). Obesity can likewise initiate endothelial brokenness and cause cerebral hypoperfusion and improve the creation of β-amyloid that will general, diminish endothelial capacity further, making an endless loop prompting pathogenic changes of AD. This endothelial brokenness is because of a diminished combination and activities of nitric oxide (NO) from the endothelium and expanding the development of oxidative pressure. Increasing levels of deviated dimethylarginine inhibit NO synthase activity, resulting in cerebral hypoperfusion and mental and neurodegenerative changes in AD (Toda, Ayajiki, & Okamura, 2014).In addition to the Aβ and Tau proteins causing AD, many factors are also a contributing factor to this disease (Alves, Correia, Miguel, Alegria, & Bugalho, 2012)including mitochondrial impairments, ROS generation, oxidative damage, proinflammatory responses, energy utilization impairments, and failure in various neurotransmission systems(Cai, Zhao, & Ratka, 2011; Ferrer et al., 2012).The gut-brain axis, also known as the gut-microbiota interaction, has also been suggested to be important in the utilization of high fat

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diets and other imbalanced eating plans that hinder perception (Solas, Milagro, Ramírez, & Martínez, 2017). Notably, cognitive execution and markers of cerebrum decay like whole brain and hippocampal volumes are amazing indicators of intellectual decrease and dementia in everyone (Amiya et al., 2005; M. F. Elias et al., 2000; Jack et al., 2005). In this manner, obesity-related degradation might intensify the danger for dementia and a cognitive decrease by synergistically associating with the maturing system. Predictable with this idea, higher BMI is associated with cerebrum degradation in patients determined to have AD (Abilés et al., 2010). Besides, there is proof that midlife obesity is related to an expanded pace of aggregate and hippocampal brain degradation and cognitive decrease ten years after the fact (Debette et al., 2011) and finally, cases of neurodegenerative disease. AD and PD are two main neurodegenerative diseases characterized by the accumulation of abnormal protein in the brain, results in a neuronal loss (Gaeta & Hider, 2005) and causes cognitive impairment.

IV. Summary and Conclusion

As a result of the systematic frame introduced in this review, we can now understand how obesity leads to brain changes that can result in cognitive impairment. As In addition to inflammation, hyperinsulinemia/insulin resistance, interruption of oxidative stress, and neurodegenerative diseases, obesity has been associated with cognitive impairment. It can therefore be concluded that obesity-induced structural changes in the brain, impaired mitochondrial function, insulin resistance and blood-brain barrier are major contributors to memory impairment.

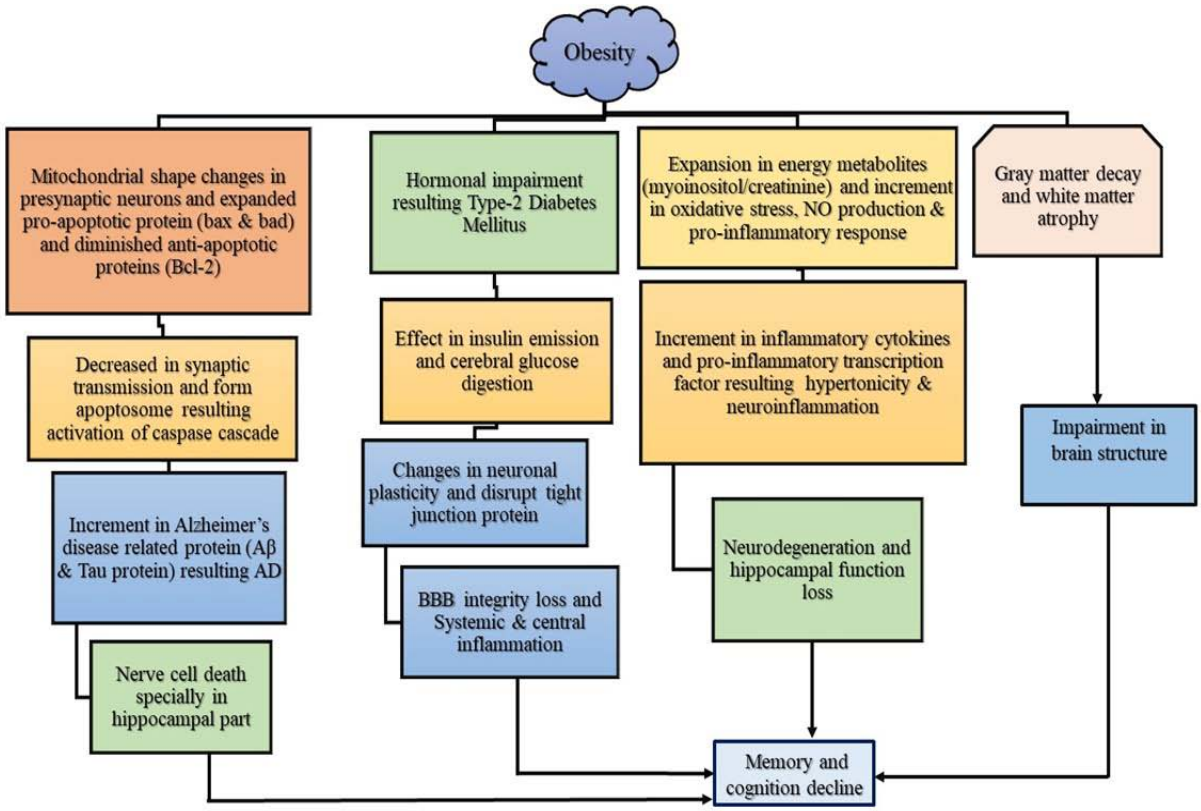


Fig.1: Systemic diagram of obesity-induced cognitive decline.

Abbreviations: AD (Alzheimer's Disease), PD (Parkinson's Disease), ND (neurodegenerative disease), BMI (basal metabolic rate), BBB (blood-brain barrier), T2DM (Type 2 diabetes mellitus), MCI (mild cognitive impairment), NFjB (nuclear factor jB), TNF-α (Tumour Necrosis Factor-α), IL- 12 (interleukin-12), Aβ (amyloid β).

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Comfort Foods and its Impact on Individual Psychology- A Review Article

By Usmaan Topiwala

Introduction- Stress can be considered as feeling when a person believes that demands exceed the personal and social resources the individual is able to mobilize and it affects its homeostasis. Stress on a rise in covid-19 pandemic due to socioeconomic conditions, loss of family members, uncertainty, decreased human interaction, etc [1]. People are increasingly spending more time at home because the educational institutes have turned towards online modes of teaching and many employees have been made to work from home.

Comfort foods can be defined as food to which a person has emotional and nostalgic attachment and have a component of unhealthiness, tastiness and are easy to prepare. It is not necessary that all these characteristics are found in all comfort foods but one of these is usually present.[3]

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Comfort Foods and its Impact on Individual Psychology- A Review Article

Usmaan Topiwala

I. Introduction

Stress can be considered as feeling when a person believes that demands exceed the personal and social resources the individual is able to mobilize and it affects its homeostasis. Stress on a rise in covid-19 pandemic due to socioeconomic conditions, loss of family members, uncertainty, decreased human interaction, etc [1]. People are increasingly spending more time at home because the educational institutes have turned towards online modes of teaching and many employees have been made to work from home.

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This narrative review is meant to review the existing literature on relation between stress and eating of comfort foods. This will help us to arrive at a conclusion whether stress can increase consumption of comfort foods and vice-versa.

Changes in nutritional quality of meals and calorie intake have lead to a dramatic increase obesity over the past 30-40 years in developed and increasingly, in developing countries.[2]

Cognitive functions have been reported to be impaired due to obesity in both people and rodents .It has been observed in rats that exposure to a high fat and high sugar diet for as little as 1 week selectively impaired place recognition [2]. According to American Psychological association, nearly one -third of adults self- report overeating (hyperphagia) when stressed[4]. Eating more comfort foods after stress can be considered self medication for decreasing stress. This would dampen the response of body towards stress and leads to decrease in secretion of cortisol in long terms. This can lead to problems in handling stress in future and addiction to comfort foods.[5] Comfort eating is more likely to occur in women and obese. These groups can also become deficient in certain nutrients due to high consumption of only a certain type of nutrient[6] Also large amount of time is spend at home during the pandemic which would increase accesibility and need for comfort foods.[1] This study will be a great medium to create awareness among the vulnerable section ie women and obese thus decreasing their dependence on comfort foods

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II. Methods

For the purpose of reviewing the literature, search was made on pubmed using keywords “comfort foods” and “stress” during May 2021. 208 results were reported. Studies included were providing a relation between comfort foods and stress on humans. Studies which were performed on animals i.e. rats and those related to heat or cold stress were excluded. 31 studies were identified to be useful for the review.

III. Discussion

Comfort foods are highly idiosyncratic across individuals. The very first taxonomic approach to comfort foods was proposed by Wansink, Cheney, and Chan (2003), and it was based on the physical characteristics of those foods.1 Wansink and colleagues conducted a two-part experiment. In the first study, they mailed a questionnaire to some randomly selected households to collect data on what kinds of foods people find more comforting. in the second study that was conducted over the phone; participants were asked to rate each comfort food identified in the initial study. They were asked if they considered it a comfort food, how guilty they felt after consuming it and how healthy they felt after consuming this food. Although the results suggested potential age and sex differences in comfort foods, this work also indicated the idiosyncratic nature of comfort foodsie comfort foods differ from person to person an would be based on that persons life experiences .

Certain research suggests that they are particularly likely to turn to such foods in times of high emotional arousal, regardless of which foods people choose as comfort foods. (e.g., DubLeBel, & Lu, 2005; Evers, Adriaanse, de Ridder, & de Witt Huberts, 2013). It has been reported that humans use consumption of comfort foods to attempt to distract themselves from, or alleviate, Negative emotions, or on the contrary, heighten the sensation of positive emotions (Dubé et al., 2005; O’Conner, Jones, Conner, McMillan, & Ferguson, 2008).

But people will usually seek Comfort food when they are in a negative affect state of stress. O’Conner Et

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al. (2008) reported that increased consumption of high-fat and high-sugar Foods between meals are Correlated with interpersonal and work related stressors. A recent study also determined that more chocolate was consumed by people with High stress and lower cortisol levels as compared to those with low stress and high cortisol levels in a laboratory Study (Tryon, DeCant, & Laugero, 2013). Further, van Strien, Roelofs, And de Weerth (2013) found that people who scored high on an emotional eating scale combined with a lower (blunted) cortisol response Consumed more food after a stressful task than did those who scored High on an emotional eating scale combined with higher cortisol levels; Participants who scored low on the emotional eating scale did not show These differences.

Similarly, it was found that participants consumed The most of sweet, fat-rich foods when they were stressed when given an option to consume sweet, Salty, or bland foods of varying amounts of fat, (Oliver, Wardle, & Gibson, 2000). One study on contrary found that those who consume Comfort foods when stressed perceived these situations as less stressful When compared to those who did not consume comfort food (Finch & Tomiyama, 2015). This might lead to sense of euphoria about something that does not exist and this might lead to not facing problems.

Additionally, Labroo and Mukhopadhyay (2009) concluded that if people believe their positive mood is short-term, they would consume unhealthy food that will preserve their existing positive mood just the way people abuse drugs. This is the reason that there is a risk of addiction. In contrast, if people Believe their negative mood is short-term, they will consume healthier Food allowing them to focus on long-term needs because the negative Mood will alleviate itself. Similarly, if an emotion is thought to be long-Term, people will consume unhealthy food if they are in a negative mood in order to improve it, whereas they would consume healthy food In a positive mood because they are able to focus on their long-term needs.

Some investigations have focused on comfort food's Nostalgic components. It was found that along with comfort food providing psychological relief, people found it to be Comforting due to the consumption context and experience. (LeBel, Lu, & Dubé, 2008). It has been Suggested that social contexts and childhood experiences are important in The formation of life-long comfort food consumption. Spence (2017) Argues that strongest influence on whether a food will later become a Comfort food is based on past associations (e.g., memories and relationships) with Food. One of investigations in this nostalgia domain has Focused on social surrogacy (e.g., Troisi & Gabriel, 2011).The social surrogacy approach is a blend of Aspects of the emotional and nostalgic approach (Troisi & Gabriel, 2011; Troisi, Gabriel, Derrick, & Geisler, 2015; Troisi & Wright, 2017). Troisi and colleagues claim that the consumption of comfort Food can act as an emotional substitute to counteract loneliness. Each time the Food is consumed, memories of the emotions and inter Personal relationships associated with this food are activated (Ong, IJzerman, & Leung, 2015; Troisi & Gabriel, 2011; Troisi & Wright, 2017).It should be pointed out that one of the major ways of eradicating stress is focusing on building better interpersonal relationships. This need is being replaced by comfort foods thus making people dependent on comfort foods and infesting them with a lack of interest in developing interpersonal relationships.

1. PLS and cognitive restraint enhance the salience of NA as a trigger for stress-eating. Individuals with high chronic and perceived life stress have greater baseline and stress-induced NA [31,54], and show a relationship between stress-induced NA and consuming a larger percentage of portioned snack food [30l
2. Also Van Oudenhove et al. has observed that food intake without awareness (i.e., without visual, taste, and olfactory inputs) can modify emotions (2)
3. Approaches to treating obesity should certainly take the link between stress and food into account; the origin of stress should be identified and dealt with.

For young adult college students who are learning important self-management skills, intake of high-fat, non-nutritious "comfort foods" (e.g. heavy meals, sweets, salty snacks) in response to stress may be especially problematic. This would pave way for lifelong bad habits and obesity. Indeed, diet and other behavioral risk factors for obesity have been shown to remain similar from early life into adulthood (Craigie et al., 2011).

Limitations

Conclusion

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Yacon Flour: A Functional Food Ingredient with an Impact on the Adipose Tissue Remodeling of Obese Rats

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Abstract- *Background:* The increase in the global prevalence of overweight and obesity has prompted a wide range of strategies to reduce its impact on health. Research in the field of nutrition has shown great interest in the potential of functional foods as a non-pharmacological alternative to prevent or counteract obesity. Here we analyzed the effects of *Smallanthus sonchifolius* (yacon) flour on hypoxia, oxidative stress, inflammation, and differentiation of visceral white adipose (WAT) tissue in HFD-fed rats. We also compared these effects with agave inulin supplementation, to better characterize the prebiotic potential of these oligofructans as functional ingredients.

Results: We found that yacon flour mainly exerts comprehensive effects by limiting visceral WAT expansion and downregulating the Hypoxia-inducible transcription factor-1α (HIF-1α) expression, an important regulatory signaling molecule that mediates the inflammatory responses induced by hypoxia.

Keywords: *obesity, high-fat diet, yacon, FOS, inulin, adipose tissue, oxidative stress, hypoxia.*

GJMR-L Classification: *DDC Code: 611.0182 LCC Code: QP88.15*



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Yacon Flour: A Functional Food Ingredient with an Impact on the Adipose Tissue Remodeling of Obese Rats

Maria Virginia Grande [α], Ernesto Nicolás Diaz Miranda [σ], Sara Serafina Sánchez [ρ] & Stella Maris Honoré [ω]

Abstract- Background: The increase in the global prevalence of overweight and obesity has prompted a wide range of strategies to reduce its impact on health. Research in the field of nutrition has shown great interest in the potential of functional foods as a non-pharmacological alternative to prevent or counteract obesity. Here we analyzed the effects of *Smallanthus sonchifolius* (yacon) flour on hypoxia, oxidative stress, inflammation, and differentiation of visceral white adipose (WAT) tissue in HFD-fed rats. We also compared these effects with agave inulin supplementation, to better characterize the prebiotic potential of these oligofructans as functional ingredients.

Results: We found that yacon flour mainly exerts comprehensive effects by limiting visceral WAT expansion and downregulating the Hypoxia-inducible transcription factor-1α (HIF-1α) expression, an important regulatory signaling molecule that mediates the inflammatory responses induced by hypoxia. Also, yacon reduces lipid peroxidation, improves the antioxidant system, and attenuates the expression of pro-inflammatory genes MCP-1, TNF-α, IL-1β and IL-6, and TGF-β1, elevating anti-inflammatory IL-10, in visceral WAT. Further, yacon downregulates Wnt5a and upregulates Wnt3a and SLC2A4 expressions in visceral WAT, ameliorating insulin resistance of HFD rats. Otherwise, agave inulin supplementation can improve visceral WAT pathology, avoiding oxidative stress and inflammation mainly by increasing GSH levels and reducing IL-6 expression. No effect on HIF-1α and Wnt5a gene expression was detected in the visceral WAT of inulin-supplemented rats.

Conclusion: Collectively, our data indicate that yacon flour, unlike inulin, produces a selective reduction of HIF-1α that improves adipose tissue remodeling. Our results demonstrate the promising efficacy of yacon as a dietary therapeutic strategy to improve the visceral WAT dysfunction and reduce alterations associated with diet-induced obesity.

Keywords: obesity, high-fat diet, yacon, FOS, inulin, adipose tissue, oxidative stress, hypoxia.

I. Introduction

Obesity is a complex metabolic disorder with a multifactorial origin. Increasing evidence suggests that oxidative stress is a critical factor linking obesity to its metabolic complications [1]. Indeed, excessive accumulation of body white adipose tissue (WAT), particularly visceral WAT, stimulates a prooxidant and proinflammatory state, increasing the risk of a large number of pathological events such as insulin resistance, diabetes, cardiovascular complications, liver failure, sleep disorders and oncological problems [2].

Sustained nutrient overflow, especially in obesity states, can dysregulate adipose tissue storage capacity leading to adipocyte hypertrophy and tissue hypoxia [3]. It has been proposed that a relative oxygen deficit due to reduced blood flow in adipose tissue, contributes to adipocyte dysfunction and may impact systemic metabolic homeostasis [4]. Hypoxia affects several biological functions in adipose tissue, such as adipocyte differentiation, angiogenesis, apoptosis, inflammation, and insulin resistance [5]. Additionally, mitochondrial reactive oxygen species (ROS) production, especially superoxide anions and hydrogen peroxide, have been shown to activate signaling cascades, being responsible for the propagation of the hypoxic signal (Lempesis et al, 2020). Hypoxia-inducible transcription factor-1 (HIF-1) is an important regulatory signaling molecule that mediates the inflammatory responses induced by hypoxia [6]. This transcription factor, a heterodimer formed by an oxygen-sensitive α-subunit and a constitutively expressed β-subunit (HIF-1β), is accumulated during hypoxia resulting in the activation of HIF-1α target genes [7]. The expression of the HIF-1α subunit has been used as a marker of hypoxia states and several studies suggest that HIF-1α inactivation could protect against obesity and insulin resistance [7, 8].

In recent decades, the increase in the global prevalence of overweight and obesity has prompted a wide range of strategies to reduce their impact on health. The development of functional foods represents a valuable opportunity as a non-pharmacological alternative for the prevention and/or treatment of obesity [9]. It involves the discovery of new bioactive compounds, as well as the understanding of the mechanisms by which these food ingredients exert their anti-obesity effects.

Prebiotics are a group of nutrients that selectively stimulate the growth and activity of beneficial bacteria in the human gut [10]. Fructooligosaccharides (FOS) and inulin, two non-digestible fructose polymers with

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different degrees of polymerization, are gaining great importance as functional ingredients given their multiple health benefits and pharmaceutical applications [11]. Due to the presence of a β-(2→1) glycosidic bond, these oligosaccharides resist enzymatic hydrolysis in the mammalian digestive system and are metabolized by the gut microbiota into short-chain fatty acids (SCFAs). The SCFAs influence energy intake and weight gain improving obesity [11, 12].

Most of the commercially available inulin comes from *Cichorium intybus* (chicory) roots, and *Agave tequilana* Weber var. azul stem and leaves [13] FOS are naturally found in *Allium* spp. (onion, garlic, and leek), and *Musa paradisiaca* (banana) [14]. *Smallanthus sonchifolius (Poepp. & Endl.) H. Robinson* (yacon) tubers, native specie of the Andean regions of South America, are another abundant source of FOS with health-promoting benefits [15, 16]. In a previous study, we established that yacon flour restored serum lipid profile and attenuated weight gain in animal models and humans by modulating signaling pathways that regulate adipogenesis [17, 18]. Although the beneficial effects of yacon on metabolism are known, the effects on adipose tissue pathology and its associated parameters are not fully clarified.

In this context, we now analyzed the effects of yacon rich in FOS on hypoxia, oxidative stress, inflammation, and differentiation of visceral WAT in HFD-fed rats. Also, we compared these effects with those from agave inulin, to achieve a better characterization of the prebiotic potential of these oligofructans as functional ingredients.

II. Materials and Methods

a) Plant Material

Smallanthus sonchifolius flour was obtained according to [18]. Briefly, the roots were carefully washed, peeled, sliced, and dried at 60°C in a forced air circulation oven to reduce water content. The dried material was then pulverized to obtain yacon roots flour and stored at 4°C until use. The content of FOS was estimated as previously [17] and daily intake levels of yacon flour were calculated concerning the amount of FOS using a dose equivalent to 680 mg FOS/Kg b.w./day corresponding to 1.57 g of yacon flour/kg b.w./day. To compare the metabolic effects of yacon flour and inulin, Organic Inulin Pure Prebiotic Powder from Blue Agave, was purchased from NOW Foods (USA) and administered to the animals at a dose of 680 mg FOS/Kg b.w./day.

b) Animals, diets, and experimental protocol

Male Wistar rats weighing 180–200 g were obtained from the colony bred at the INSIBIO (CONICET-UNT), Tucumán, Argentina. Rats were kept in a breeding room with a controlled environment (temperature: 23 ± 1°C, relative humidity: 60 ± 5%, and 12 h light-dark cycle). Rats were maintained on a 12-h light-dark cycle with free access to food and water. All experiments were performed following the Guide for the Care and Use of Laboratory Animals (Institute of Laboratory Animal Resources, Commission on Life Sciences, National Research Council, National Academy Press, Washington, DC) and approved by the local Animal Care Committee from the Universidad Nacional de Tucumán (No. 004/2017). The experimental animals were randomly divided into two groups: the control diet group (CD, n=6) was fed a standard chow diet (Asociación Cooperativas Argentinas S.E.N.A.S.A., containing 12.08 kJ/g calories: 69.5% from carbohydrates, 5.6% from fat, and 24.9% from protein) and a high- fat-diet group (HFD, n=18) which have free access to a special diet [18], containing 17.40 kJ/g: 35.0% from carbohydrates, 41.0% from fat, and 24.0% from protein). Both animal groups were maintained on each diet for 12 weeks. Water and solid food were available *ad libitum*. At this time, animals fed HFD reached obesity status.

c) Experimental Groups

After 12 weeks on HFD or standard chow, the animals were randomly divided into the following groups according to the treatment with or without the addition of yacon flour or inulin, as a dietary supplement for 8 weeks.

i. HFDY group (n=6), rats fed a high-fat diet plus a tablet of yacon flour (equivalent to 680mg FOS/kg b. w).
ii. HFDI group (n=6), rats fed a high-fat diet plus a tablet of inulin (680 mg/kg b. w.)
iii. HFD group (n=6), rats fed a high-fat diet.
iv. CD group (n=6), rats fed a standard diet.

Throughout the experimental period, animals were weighed (g) weekly and food intakes were recorded daily. Abdominal circumference (immediately anterior to the forefoot) and thoracic circumference (immediately behind the foreleg), and were determined according to [19]. The body weight and body length (nose–anus length) were used to determine the following morphometric parameters: Body mass index (BMI) = body weight (g)/length^2 (cm^2); Lee index = cube root of body weight (g)/nose-anus length (cm). Nutritional parameters were calculated based on food and energy intake: energy intake (kJ/day) = mean food consumption x dietary metabolizable energy.

d) Tissue Sampling

The animals were sacrificed in the fasted state through cardiac puncture under anesthesia with 1:1 xylazine-ketamine. Collected blood samples were allowed to clot at 37°C and serum was separated by centrifugation at 3000g for 10min. The visceral WAT (mesenteric) was quickly collected and rinsed thoroughly with ice-cold saline, blotted, weighed, and

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fixed in 4% formaldehyde saline for histological analysis. The remaining tissues were frozen immediately and stored at −80°C until analyzed.

e) Biochemical Determinations

Blood glucose was measured using a blood glucometer and strips (Roche Accu-Chek Active, Mannheim, Germany). Serum levels of triglycerides (TG), total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-c) were measured using commercial kits (Wiener lab Group, Argentina) according to the manufacturer's instructions.

f) Oral glucose tolerance test (OGTT) and insulin tolerance test (ITT)

The OGTT and ITT were developed at week 12 (data not shown) and at the end of the experimental period (week 20). For OGTT, baseline blood glucose (time 0) was determined in fasted animals and then a glucose solution (2 g/kg b.w. glucose) was administered via gavage, followed by the determination of blood levels at 15, 30, 60, and 120 min with a Glucometer (Accu-Check; Roche Diagnostics, GmbH, Mannheim, Germany). For ITT the animals were injected intraperitoneally with 0.75 IU/kg b.w. of porcine Insulin (Betasint, BETA laboratory) after a 4-hour fast. Blood glucose concentration was measured with blood from tail-tip bleedings at 0, 15, 30, and 60 min. The areas under the curve of glucose were calculated [18].

g) Histology and immunofluorescence microscopy analysis

Samples from fixed visceral WAT were dehydrated, embedded in paraffin, and cut into 4 µm-thick sections at 50 µm intervals. The sections were stained with hematoxylin and eosin (H&E) for histological study as previously described [18]. Ten randomly selected fields in two slides of each rat were evaluated by two investigators blinded to the origin of the slides. Adipocyte size was determined using ImageJ 1.8.0 software (National Institutes of Health, Bethesda, MD).

Tissue was blocked in 5% goat serum in PBS for 1 h and stained with anti-F4/80 (Abcam, Cambridge, MA) or NF-kB p65 (eBioscience™) antibody overnight at 4°C. After washing with PBS, tissue was incubated with an Alexa 488-conjugated anti-rabbit secondary antibody (Invitrogen) for 1 h at room temperature. The tissue was then imaged at 40× magnification using a Leica DM2500 Microscope and analyzed using ImageJ software. A total number of F4/80-expressing cells was counted in ten randomly selected fields and expressed as positive cells/field.

h) Redox State Markers

Visceral WAT samples were homogenized (1:10 w/v) in a 0.1 M phosphate buffer solution pH 7.4 at 4°C. One part was homogenized to measure the activity levels of antioxidant enzymes and malondialdehyde (MDA). The second part was homogenized in a cold solution of 0.1 M $HClO_4$ 2mM EDTA for reduced glutathione (GSH) estimation.

Lipid peroxidation in WAT was analyzed by determining the formation of MDA [20]. GSH levels were determined through the spectrophotometric method [21]. The enzymatic antioxidant capacity was assayed by estimating superoxide dismutase (SOD) [22], catalase (CAT) [23], and glutathione-S- transferase (GST) [24] activities.

i) RNA Extraction and RT PCR Amplification

RNA from adipose tissue was isolated using Trizol (Thermo Fisher Scientific, Netherlands) followed by purification with an RNeasy Mini Kit (Qiagen, Basel, Switzerland), according to the manufacturer's instruction including a DNase treatment with an RNase-free DNase Set. 0.5 µg of RNA were reverse transcribed into cDNA using M-MLV Reverse Transcriptase (Promega, USA). Gene expression was evaluated using a Mastercycler personal instrument (Eppendorf, Germany) according to [18], with an optimized concentration of primer sets for HIF-1α (NM024359.1) forward primer 5′-CACAGCTGACCAGTTACGATTG-3′ and reverse primer 5′- CACAGACAACAACAACAACTGAAC-3'; TGF-β1 (NM021578.2) forward primer 5′- GTGGCTGA-ACCAAGGAGACG-3′ and reverse primer 5′-GGTGTTGAGCCCTTTCCAGG-3′; MCP-1 (NM0-31530.1) forward primer 5′-TCAACCCTAAGGACTT-CAGCAC-3′ and reverse primer 5′-AGGCAT-CACATTCCAAATCACAC-3'; IL-1β (NM031512.2) forward primer 5′- CACCTCTCAAGCA-GAGCACA-3′ and reverse primer 5′- GACCTGACTT-GGCAGAGGAC-3'; TNF-α (NM012675.3) forward primer 5′-CTCAAGCCCTGGTATGAGCC-3′ and reverse primer 5′-GGCTGGGTAGAGAACGGATG-3'; IL-6 (NM01-2589.2) forward primer 5′-ATTGTATG-AACA-GCGATGATGCAC-3′ and reverse primer 5′-CCAG GTAGAAACGGAACTCCAGA-3'; IL-10 (NM01-2854.2) forward primer 5′-ACTGCAGGACTTTAAGGGTTACTTG-3' and reverse primer 5′-TAGACACCTTTGTCTTGGA GCTTA-3'; Wnt5a (NM022631.2) forward primer 5′-AGGACTTACCTCGGGACTGG-3´and reverse primer 5′-CGACCTGCTT-CATTGTTGTG-3; Scl2a4 (NM012751.1) forward primer 5′-CCTCCAGGATGAAGGAACA-3′ and reverse primer 5′-GGGAGAAAAGCCCATCTAGG-3'; β-actin (NM-007393) forward primer 5′-CCGGCTTCGCGGGCGACG-3′ and reverse primer 5′-TCCCGGCCAGCCAGGTCC-3′. mRNA levels were standardized against β-actin mRNA levels in the same sample. The mean value for the CD was set at 100%.

j) Western Blotting

Protein levels of five Wnt-3a were measured with western blot as described previously [18]. Briefly, 20 µg of total protein per sample was used for SDS-PAGE and transferred to a nitrocellulose membrane (Hybond-C super; Amersham, Buckinghamshire, UK). Blots were blocked with 5% (w/v) fat-free milk dissolved

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in phosphate-buffered saline containing 0.05% (v/v) Tween-20 (TBST), incubated with mouse anti-Wnt3a (1:100 dilution; Cell Signaling Technology Inc. Danvers, USA) as primary antibody and ECL anti-mouse IgG (Thermo Fisher Scientific) as a secondary antibody. Protein levels were detected with a biotin-extrAvidin-peroxidase system (SIGMA Aldrich, USA). Band intensities were quantified by ImageJ software.

k) Statistical Analysis

All results are presented as the mean ± standard deviation and were analyzed with GraphPad Prism®, version 8 (GraphPad Software, Inc., La Jolla, CA, USA). Comparisons of all the variables between the groups of each experiment were performed through the use of unpaired Student's t-tests and by one-way ANOVA followed by Tukey's post-test. A probability level of $p < 0.05$ was considered statistically significant.

III. Results

a) Effects of yacon on morphological and nutritional parameters

As shown in Table 1, animals in the HFD group significantly increased body weight compared to the CD group ($p<0.05$). Supplementation with yacon flour for 8 weeks significantly reduced body weight in obese HFD-fed animals ($p<0.05$). Consistent with these results, yacon or inulin supplementation significantly ($p<0.05$) reduced food intake in HFDY and HFD animals, resulting in lower energy intake ($p<0.05$). A significant ($p<0.05$) improvement in the morphometric parameters of the animals supplemented with each of the prebiotics at the dosetested was also observed. Table 1 also shows the effects of yacon flour on the relative weights of liver, and visceral WAT. HFD-fed rats exhibited an increase in the hepatic index that was reversed by both yacon and inulin supplementation. In addition, yacon supplementation significantly ($p<0.05$) reduced the visceral WAT index promoted by HFD-feeding, especially decreasing the deposition of visceral WAT in the mesenteric pad. However, inulin supplementation showed no difference ($p>0.05$) in adipose tissue deposition.

b) Effects of yacon on adipose tissue hypoxia

During obesity, adipocyte hypertrophy is associated with local adipose tissue hypoxia [25]. According to the above results, H&E staining revealed the presence of a higher number of large adipocytes in the visceral WAT of HFD and HFDI animals, while smaller adipocytes predominated in HFDY supplemented animals (Figure 1A, B). Then, we analyzed the expression of HIF-1α, the inducible subunit of HIF-1, as a key transcription factor mediating hypoxic responses [7]. The results showed that HIF-1α gene expression was significantly ($p<0.05$) higher in the visceral WAT of the HFD group compared to the CD group. Yacon supplement significantly ($p<0.05$) reduced the expression of this factor compared to the HFD group. However, no effect on HIF-1α expression was observed in the visceral WAT of the HFDI group (Figure 1C).

c) Effects of yacon on oxidative stress of adipose tissue

Long-term exposure of fat cells to hypoxia can provoke oxidative stress in human and animal WAT [26]. Indeed, visceral WAT from HFD-rats showed increased levels of MDA and reduced GSH ($p<0.05$). Yacon consumption in HFDY significantly ($p<0.05$) reduced MDA and increased GSH in visceral WAT after an 8-wk feeding (Figure 2A, B). Moreover, yacon increased the GST and CAT enzyme activities in HDFY compared to the HFD group (Figure 2C, D). However, GPx activity did not show a significant difference between both groups ($p>0.05$) (Figure 2E). Inulin supplementation also improved the redox status of visceral WAT (Figure 2A-E), although to a lesser degree, except for GSH levels, where it showed a greater effect (Figure 2B).

d) Effects of yacon on the inflammatory response of adipose tissue

The state of hypoxia promotes inflammation of adipose tissue in obesity through the activation of two main transcription factors, HIF-1α and nuclear factor-kB (NF-κB), which in turn activate the transcription of several angiogenic and/or pro-inflammatory genes [7]. To study the inflammation response in yacon or inulin-supplemented HFD-rats, we quantified inflammation gene expression in visceral WAT (Figure 3). We found that pro-inflammatory adipocytokines were significantly ($p<0.05$) increased in the HFD compared to the CD group ($p<0.05$) (Figure 3A, B). Interestingly, yacon treatment improved the inflammatory status of adipose tissue, reducing the expression of MCP-1, TNF-α, TGF-β1, IL-1β, and IL-6 in the HFDY group ($p<0.05$). The anti-inflammatory cytokine IL-10 was significantly elevated in HFDY rats ($p<0.05$) (Figure 3A, B). Inulin treatment significantly ($p<0.05$) decreased the TGF-β1 and IL-6 expression in the visceral WAT similar to yacon, but increased IL-10 to a lesser extent (Figure 3B). Macrophage infiltration in WAT contributes to inflammation, extracellular matrix remodeling, and obesity-related metabolic dysfunction [27]. Macrophage marker F4/80 staining of visceral WAT sections revealed that macrophage infiltration to WAT decreased significantly ($p<0.05$) in HDFY animals (Figure 3C, D). Consistent with this finding, lower levels of NF-κB p65 in these adipocytes were detected (Figure 3C, E).

e) Effects of yacon on adipogenesis-related genes

Hypertrophic WAT provides an optimal environment for increasing the differentiation rate of adipocyte progenitors, due to a decreased glucose uptake and higher plasma glucose levels [25]. So, we decided to analyze the expression of the paracrine

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factors Wnt3a and Wnt5a involved in adipocyte differentiation, as well as the glucose transporter SCL2A4 in the visceral WAT after an 8-wk HFD feeding. (Figure 4). Western blot assay showed that Wnt3a protein levels were lower in the visceral WAT of HFD-rats. However, yacon significantly ($p<0.05$) increased this paracrine factor in HFD-animals (Figure 4A). In addition, while HFD-feeding up-regulated Wnt5a and down-regulated SCL2A4 mRNA expression in the visceral WAT ($p<0.05$); yacon supplementation restored the expression of both mRNAs to their CD levels ($p<0.05$). Inulin intake up-regulated SCL2A4 mRNAs levels in the visceral WAT showing a similar effect to yacon; however, no effects on SCL2A4 mRNAs expression were observed in these animals. ($p>0.05$) (Figure 4B).

f) Effects of yacon on systemic glucose and lipids homeostasis

To compare the efficacy of both prebiotics on the systemic metabolic and oxidative status, we determined the effects of yacon flour and inulin supplementation on glucose and lipid homeostasis and oxidative stress markers. As shown in Table 2, the HFDY group showed reduced ($p<0.05$) fasting glucose levels and a significant ($p<0.05$) improvement in glycemic response after OGTT and ITT compared to the animals in the HFD group. Similar effects were observed in the group supplemented with inulin. Both yacon and inulin consumption improves the lipid profile of HFD animals. TG levels were similar in both groups, however, the HFDY group showed lower levels of TC and LDLc, compared to HFDI ($p<0.05$). In addition, the animals that consumed yacon showed lower postprandial TG values than inulin ($p<0.05$), but there were no significant differences in postprandial levels of cholesterol in both groups ($p>0.05$). The analysis of the oxidative stress markers MDA and GSH indicated that MDA was lower in the HFDY group compared to the HFDI group, while the level of GSH was further improved after inulin supplementation ($p<0.05$).

IV. Discussion

During the development of obesity, adipose tissue undergoes a remodeling process as a consequence of adipocyte enlargement and recruitment of adipogenic precursor cells, to adjust excess nutrients and avoid peripheral lipotoxicity [28]. Diet modification is one of the most relevant strategies against obesity in the long term management. In this sense, the identification of natural and safe ingredients to incorporate in functional foods destined to reduce weight is necessary. In this work, we analyzed the functional effect of yacon flour in the visceral WAT pathology of HFD-induced obese rats, and compare its efficacy versus commercial agave inulin.

Our results showed that both yacon flour, rich in FOS, and inulin were effective in reducing body weight and improving anthropometric parameters. This could be related to the ability of fructans to modulate gastrointestinal peptides such as ghrelin and peptide YY (PYY), involved in the control of food intake [18, 29]. Furthermore, there is evidence that these oligosaccharides increase the level of GLP-1 in the proximal colon, with an impact on metabolic regulation that contributes to reducing weight in obesity [12, 16, 18].

Overnutrition increases adiposity, leading to an adipocyte dysfunctional phenotype associated with local tissue hypoxia [3]. Growing data suggest that this chronic condition plays a key role in macrophage chemotaxis, adipocytokine dysregulation, and impaired insulin signaling in visceral WAT [4, 27]. Our data thus suggest that yacon supplementation ameliorates WAT tissue oxidative stress and inflammation, by alleviating hypoxia state, and improving visceral fat mass in HFD-fed rats. Indeed, here we show for the first time that HFD-induced overexpression of HIF-1α in visceral WAT was reduced by yacon supplementation. Indeed, here we show for the first time that HFD-induced HIF-1α overexpression in visceral WAT was reduced by yacon supplementation, but not by inulin. The action of yacon on HIF-1α could be related to the general weight loss induced by FOS. However, the absence of an effect on HIF- 1α by inulin allows us to suggest that the differences found could be due to the presence of other components in the yacon flour more than the different degrees of polymerization [30] of the fructans under study. Further studies are needed to clarify this aspect.

HIF-1α factor induction is considered an early initiator for WAT dysfunction and it has been suggested that HIF-1α inhibition could ameliorate the negative effects of fat expansion associated with dietary-induced obesity [31]. So, the yacon flour supplement may constitute an effective food therapeutic option in the context of metabolic dysfunction. HIF-1α is a transcription factor that responds to a low concentration of oxygen [4, 5]. Under hypoxic conditions, mitochondria increase the production of ROS, leading to inhibition of prolyl hydroxylase activity with subsequent stabilization of HIF1-α protein [32]. HIF-1α is then translocated to the nucleus to stimulate the transcription of target genes involved in the regulation of oxygen homeostasis *via* angiogenesis and metabolic reprogramming [6, 33]. In addition, HIF-1α targeted a wide range of cellular functions, including apoptosis, autophagy, redox homeostasis, inflammation, fibrosis, and self-renewal [5, 7]. In line with this, we showed that yacon flour supplementation improved the redox state reducing lipoperoxidation and strongly improving antioxidant enzyme activities in visceral WAT. Moreover, yacon reduced NF-κB p65 signal in visceral WAT, which was related to reduced transcription of inflammatory

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cytokine MCP-1, TNF-α, IL-1β, and IL-6, and is consistent with the reduced macrophage infiltration demonstrated. Some data indicate that TGF-β can increase the HIF-1α gene transcription and promote its accumulation and activity by increasing protein stability [34]. So, the improvement in inflammatory parameters caused by yacon consumption and, particularly, the decrease in TGF-β expression in the visceral WAT could also affect the transcription of the HIF-1α gene and cooperate with the decreased bodyweight to reduce HIF-1α levels. Furthermore, Zhou et al., [32] showed that TGF-β1 could also be a molecular target of HIF-1α and ROS under hypoxic conditions, promoting tissue fibrosis. The authors also reported that suppression of HIF-α prevented upregulation of TGF-β1 mRNA. These data reinforce the extraintestinal effects of yacón by showing action on HIF-1α, ROS, and TGF-β.

TGF-β1 has also been shown to play an important role in adipogenesis during the maturation stage of progenitor cells showing an inhibitory action on adipocyte differentiation [35]. This fact could imply an additional role for yacon in adipogenesis through the modulation of TGF-β1 expression. In addition, Wnt5a, another paracrine factor belonging to the Wingless/Wnt family,is known to activate adipogenesis through a non-canonical pathway, promoting preadipocyte proliferation and PPAR-γ activation [36]. On the other hand, Wnt3a maintains preadipocytes in an undifferentiated state through adipogenic inhibition of C/EBP α and PPAR-γ [37]. Previous results indicated that yacon flour downregulates these key transcription factors, enhancing insulin sensitivity, and lowering blood lipid concentrations [18]. Kang et al. [38] evidenced an antagonistic effect of both factors during adipogenesis. They demonstrated that Wnt3a induction can block Wnt5a expression, inhibiting adipogenesis and restoring adipose tissue function. In concordance, our results showed that yacon down-regulates Wnt5a and up-regulates Wnt3a transcription in visceral WAT, evidencing the participation of Wnt paracrine factors in the effects of yacon on adipose tissue. The role of Wnt5a in promoting inflammation and metabolic dysfunction in obesity has also been described [36]. Previous work has demonstrated that yacon flour can improve glucose tolerance and insulin sensitivity in both animals and humans, modulating adiponectin and leptin levels [18]. Long-term yacon supplementation also improves glucose uptake ameliorating abnormal insulin signaling cascades in the visceral WAT of HFD rats by enhancing the p-Akt/Insulin ratio. Glucose transport in insulin-resistant adipocytes from obese and diabetic subjects correlates with reduced SCL2A4 mRNA and protein expression [39]. Here we demonstrated that both yacon and inulin supplementation induced a robust upregulation of SCL2A4 glucose transporter in visceral WAT of HFD-rats. These data suggest an additional role for both ingredients in maintaining insulin-dependent glucose homeostasis. Moreover, different studies have suggested that enhancement of SLC2A4 gene expression could represent a good effective approach not only to increase plasma membrane GLUT4 and WAT's ability to clear blood glucose [40] but also to improve fasting triglyceridemia [39].

V. Conclusion

Functional ingredients are a trend in the market due to the possibility of manufacturing processed products with greater health benefits and pleasant sensory characteristics, adding value to products. The goal of the present study was to compare yacon flour rich in FOS and agave inulin regarding their effects on the oxidative stress and inflammatory response induced by lipid overload and hypoxia in adipose tissue. Although both fructans show a positive effect on the remodeling of adipose tissue, this research demonstrated new healthy properties of the bioactive compounds present in yacon flour *vs.* inulin, expanding the possibilities of its use by the food industry, in the development of new healthy products (dairy, bakery, meat and beverage products).

Conflicts of Interest

The authors declare that there are no conflicts of interest.

Acknowledgments

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Table 1: Effect of yacon flour intake on anthropometrical and nutritional parameters

Parameters	CD	HFD	HFDY	HFDI
Bodyweight (g)	399.16±38.79	585.55±39.19[a]	514.2±21.19[b]	565.8±20.98 [a,c]
Food intake (g/animal/day)	23.27±0.86	27.01±1.92[a]	22.98±0.31[b]	24.79±1.46[b]
Energy intake (kcal/day)	277.25±7.71	477.91±25.23[a]	426.31±23.17[a,b]	426.64±31.76[a,b]
BMI	94.07±0.04	134.67±3.16[b]	113.74±1.22[a,b]	116.50±15.63[a,b]
Lee index	0.35±0.02	0.39±0.01[a]	0.37±0.01[b]	0.37±0.02[b]
AC	17.33±1.04	20.06±0.30[a]	17.75±0.57[b]	19.88±2.60
AC/TC	1.01±0.02	1.07±0.03[a]	0.98±0.01[b]	1.00±0.01[b]
Total visceral fat (g/100 gb.w.)	2.76±0.75	8.14±1.07[a]	4.31±1.10[a,b]	7.45±0.90[a,c]
Mesenteric fat (g/100 g b.w.)	0.70±0.15	2.39±0.52[a]	1.17±0.41[a,b]	2.20±0.25[a,c]
Liver (g/100 g b.w)	2.66±0.13	3.10±0.18[a]	2.47±0.12[b]	2.48±0.24[b]

BMI: Body mass index at the end of treatment; AC: Abdominal circumference; TC: Thoracic circumference. The data are expressed as mean values ± SD. (n=6/group). One-way ANOVA test (significant $p < 0.05$). [a]$p<0.05$ vs. CD; [b]$p < 0.05$ vs. HFD; [c]$p < 0.05$ vs. HFDY.

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Table 2: Effect of yacon flour intake on glucose and lipids homeostasis

	CD	HFD	HFDY	HFDI
Fasting glucose (mg/dL)	98.0±6.0	129.0±6.0[a]	116.0±3.0[a,b]	116.0±3.0[a,b]
OGTT AUC (mg/dL/min)	17799±457.2	21778±942.5[a]	18519±444.2[b]	18558±837.4[b]
ITT AUC (mg/dL/min)	3574±140.0	5866±570.1[a]	3574±785.6[b]	5324±231.8[a,c]
TG (mg/dL)	32.0±4.3	76.4±3.8[a]	46.8±5.1[b]	41.4±12.6[b]
TC (mg/dL)	63.2±6.9	98.3±11.1[a]	68.8±4.0[b]	81.4±3.4[a]
LDL-c (mg/dL)	25.2±0.9	39.0±4.2[a]	19±2.6[a,b]	29.3±2.1[b,c]
Postprandial TG AUC (mg/dL/min)	5180±227.7	12540±472.2[a]	10189±445.3[a,b]	6540±815.7[a,b,c]
GSH (mg/mL)	0.025±0.0027	0.018±0.0003[a]	0.021±0.0006[a,b]	0.020±0.0001[b]
MDA (nmol/mL)	0.34±0.04	0.90±0.05[a]	0.50±0.02[a,b]	0.65±0.02[a,b,c]

Values are expressed as mean ± SD (n=6/group). The group was compared using a one-way ANOVAtest (significant $p < 0.05$). [a]$p < 0.05$ vs. CD; [b]$p < 0.05$ vs. HFD; [c]$p < 0.05$ vs. HFDY. AUC: area under the curve; ITT:insulin tolerance test; OGTT: oral glucose tolerance test; TG: triglycerides; TC: total cholesterol; LDL-c: low-densitylipoprotein cholesterol; GSH: reduced glutathione; MDA: malondialdehyde.

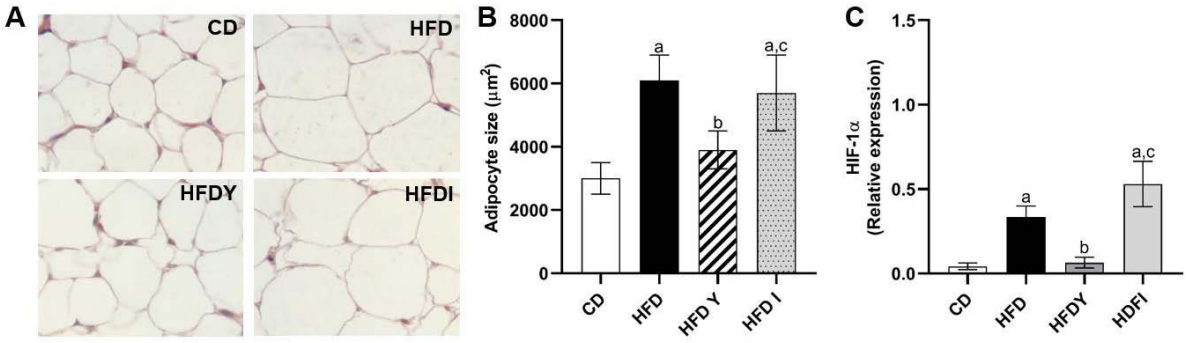


Figure 1: Effects of yacon flour and inulin on visceral adipose tissue remodeling of HFD-fed rats. (**A**) H&E stained sections from visceral WAT (magnification 400x). (**B**) Adipocyte size. (**C**)Relative mRNA expressions of HIF-1α. Data were normalized to Actin mRNA and expressed as fold change over the CD rats. The results are expressed as the mean ± SD of triplicate RT-PCR analysis. (n=6/group). One-way ANOVA test (significant $p < 0.05$). [a] $p<0.05$ vs. CD; [b] $p<0.05$ vs. HFD; [c] $p<0.05$ vs. HFDY

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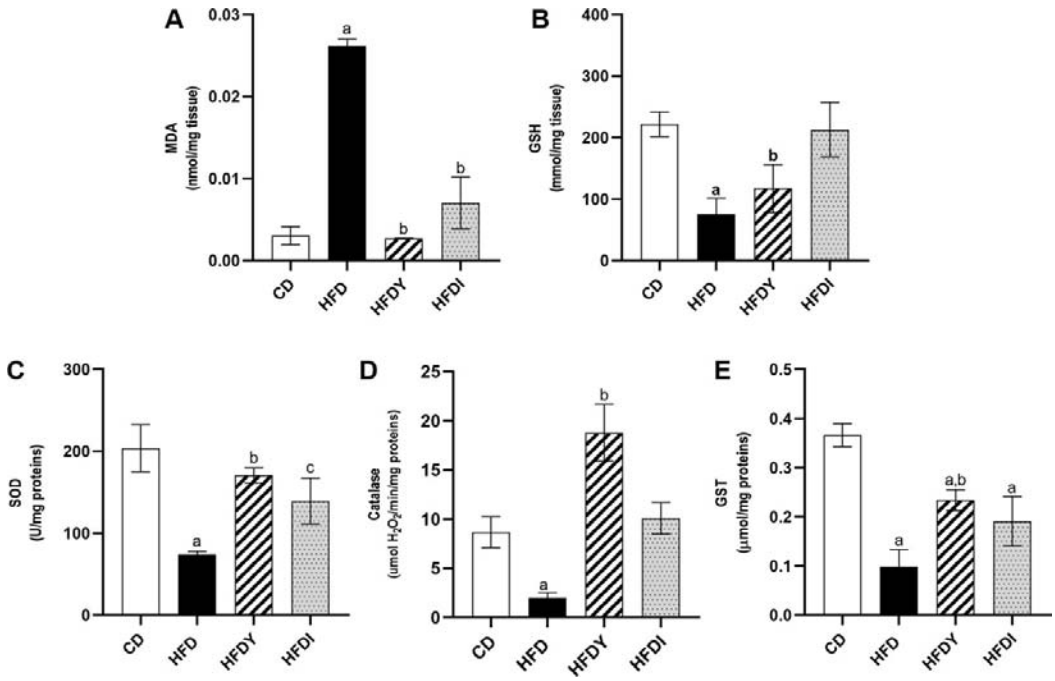


Figure 2: Effects of yacon flour and inulin on oxidative stress markers and antioxidant activity of visceral WAT of HFD-fed rats. (A) Malondialdehyde (MDA) and (B) reduced glutathione (GSH) levels; (C) superoxide dismutase (SOD); (D) catalase, and (E) glutathione S-transferase (GST) activities. The results are expressed as the mean ± SD. (n=6/group). [a] $p<0.05$ vs. CD; [b] $p< 0.05$ vs. HFD; [c] $p<0.05$ vs. HFDY.

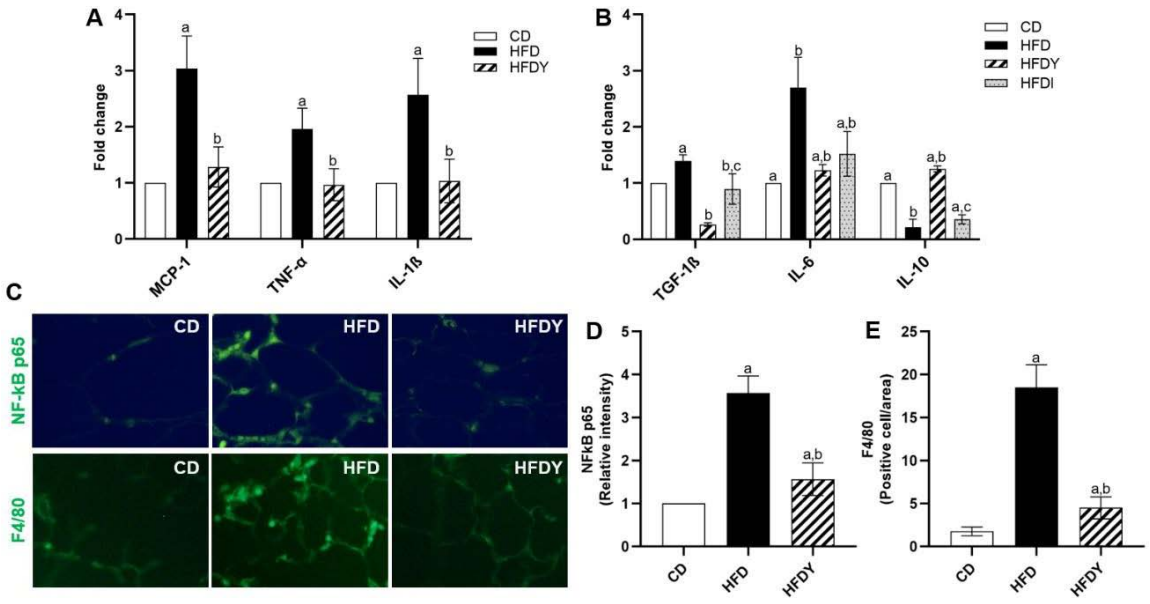


Figure 3: Effects of yacon flour and inulin in visceral adipose tissue inflammation of HFD-fed rats. Relative mRNA expressions of pro-inflammatory and anti-inflammatory cytokines (A) MCP-1, TNF-α, IL-1β, (B) TGF-1β, and IL-6 IL-10. Data were normalized to Actin mRNA and expressed as fold change over the CD rats of triplicate RT-PCR analysis. (C) NF-kB p65 and F4/80 immunostaining in visceral WAT (magnification 400x). (D) NF-kB p65 relative intensity. (E) F4/80 positive cells count in visceral WAT. The results are expressed as the mean ± SD (n=6/group). One-way ANOVA test (significant $p < 0.05$). [a] $p<0.05$ vs. CD; [b] $p< 0.05$ vs. HFD; [c] $p<0.05$ vs. HFDY

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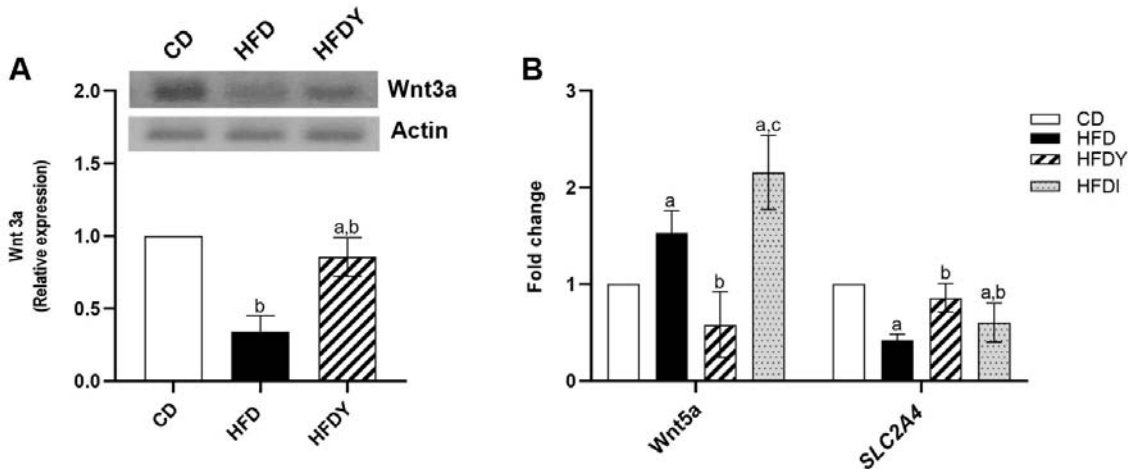


Figure 4: Effects of yacon flour and inulin on adipogenesis-related genes in HFD-fed rats. (**A**) Wnt3a protein expression in visceral fat by western blotting. (**B**) Relative mRNA expressions of Wnt5a paracrine factor and glucose transporter SLC2A4. Data were normalized to Actin mRNA and expressed as fold change over the CD rats. The results are expressed as the mean ± SD deviation of triplicate RT-PCR analysis (n=6/group). One-way ANOVA test (significant $p < 0.05$). [a] $p<0.05$ vs. CD; [b] $p< 0.05$ vs. HFD; [c] $p<0.05$ vs. HFDY

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Acknowledgments

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The following is the official style and template developed for publication of a research paper. Authors are not required to follow this style during the submission of the paper. It is just for reference purposes.

Manuscript Style Instruction (Optional)

- Microsoft Word Document Setting Instructions.
- Font type of all text should be Swis721 Lt BT.
- Page size: 8.27" x 11'", left margin: 0.65, right margin: 0.65, bottom margin: 0.75.
- Paper title should be in one column of font size 24.
- Author name in font size of 11 in one column.
- Abstract: font size 9 with the word "Abstract" in bold italics.
- Main text: font size 10 with two justified columns.
- Two columns with equal column width of 3.38 and spacing of 0.2.
- First character must be three lines drop-capped.
- The paragraph before spacing of 1 pt and after of 0 pt.
- Line spacing of 1 pt.
- Large images must be in one column.
- The names of first main headings (Heading 1) must be in Roman font, capital letters, and font size of 10.
- The names of second main headings (Heading 2) must not include numbers and must be in italics with a font size of 10.

Structure and Format of Manuscript

The recommended size of an original research paper is under 15,000 words and review papers under 7,000 words. Research articles should be less than 10,000 words. Research papers are usually longer than review papers. Review papers are reports of significant research (typically less than 7,000 words, including tables, figures, and references)

A research paper must include:

a) A title which should be relevant to the theme of the paper.
b) A summary, known as an abstract (less than 150 words), containing the major results and conclusions.
c) Up to 10 keywords that precisely identify the paper's subject, purpose, and focus.
d) An introduction, giving fundamental background objectives.
e) Resources and techniques with sufficient complete experimental details (wherever possible by reference) to permit repetition, sources of information must be given, and numerical methods must be specified by reference.
f) Results which should be presented concisely by well-designed tables and figures.
g) Suitable statistical data should also be given.
h) All data must have been gathered with attention to numerical detail in the planning stage.

Design has been recognized to be essential to experiments for a considerable time, and the editor has decided that any paper that appears not to have adequate numerical treatments of the data will be returned unrefereed.

i) Discussion should cover implications and consequences and not just recapitulate the results; conclusions should also be summarized.
j) There should be brief acknowledgments.
k) There ought to be references in the conventional format. Global Journals recommends APA format.

Authors should carefully consider the preparation of papers to ensure that they communicate effectively. Papers are much more likely to be accepted if they are carefully designed and laid out, contain few or no errors, are summarizing, and follow instructions. They will also be published with much fewer delays than those that require much technical and editorial correction.

The Editorial Board reserves the right to make literary corrections and suggestions to improve brevity.



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All manuscripts submitted to Global Journals should include:

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The title page must carry an informative title that reflects the content, a running title (less than 45 characters together with spaces), names of the authors and co-authors, and the place(s) where the work was carried out.

Author details

The full postal address of any related author(s) must be specified.

Abstract

The abstract is the foundation of the research paper. It should be clear and concise and must contain the objective of the paper and inferences drawn. It is advised to not include big mathematical equations or complicated jargon.

Many researchers searching for information online will use search engines such as Google, Yahoo or others. By optimizing your paper for search engines, you will amplify the chance of someone finding it. In turn, this will make it more likely to be viewed and cited in further works. Global Journals has compiled these guidelines to facilitate you to maximize the web-friendliness of the most public part of your paper.

Keywords

A major lynchpin of research work for the writing of research papers is the keyword search, which one will employ to find both library and internet resources. Up to eleven keywords or very brief phrases have to be given to help data retrieval, mining, and indexing.

One must be persistent and creative in using keywords. An effective keyword search requires a strategy: planning of a list of possible keywords and phrases to try.

Choice of the main keywords is the first tool of writing a research paper. Research paper writing is an art. Keyword search should be as strategic as possible.

One should start brainstorming lists of potential keywords before even beginning searching. Think about the most important concepts related to research work. Ask, “What words would a source have to include to be truly valuable in a research paper?” Then consider synonyms for the important words.

It may take the discovery of only one important paper to steer in the right keyword direction because, in most databases, the keywords under which a research paper is abstracted are listed with the paper.

Numerical Methods

Numerical methods used should be transparent and, where appropriate, supported by references.

Abbreviations

Authors must list all the abbreviations used in the paper at the end of the paper or in a separate table before using them.

Formulas and equations

Authors are advised to submit any mathematical equation using either MathJax, KaTeX, or LaTeX, or in a very high-quality image.

Tables, Figures, and Figure Legends

Tables: Tables should be cautiously designed, uncrowned, and include only essential data. Each must have an Arabic number, e.g., Table 4, a self-explanatory caption, and be on a separate sheet. Authors must submit tables in an editable format and not as images. References to these tables (if any) must be mentioned accurately.

Figures

Figures are supposed to be submitted as separate files. Always include a citation in the text for each figure using Arabic numbers, e.g., Fig. 4. Artwork must be submitted online in vector electronic form or by emailing it.

Preparation of Eletronic Figures for Publication

Although low-quality images are sufficient for review purposes, print publication requires high-quality images to prevent the final product being blurred or fuzzy. Submit (possibly by e-mail) EPS (line art) or TIFF (halftone/ photographs) files only. MS PowerPoint and Word Graphics are unsuitable for printed pictures. Avoid using pixel-oriented software. Scans (TIFF only) should have a resolution of at least 350 dpi (halftone) or 700 to 1100 dpi (line drawings). Please give the data for figures in black and white or submit a Color Work Agreement form. EPS files must be saved with fonts embedded (and with a TIFF preview, if possible).

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Tips for writing a good quality Medical Research Paper

1. Choosing the topic: In most cases, the topic is selected by the interests of the author, but it can also be suggested by the guides. You can have several topics, and then judge which you are most comfortable with. This may be done by asking several questions of yourself, like "Will I be able to carry out a search in this area? Will I find all necessary resources to accomplish the search? Will I be able to find all information in this field area?" If the answer to this type of question is "yes," then you ought to choose that topic. In most cases, you may have to conduct surveys and visit several places. Also, you might have to do a lot of work to find all the rises and falls of the various data on that subject. Sometimes, detailed information plays a vital role, instead of short information. Evaluators are human: The first thing to remember is that evaluators are also human beings. They are not only meant for rejecting a paper. They are here to evaluate your paper. So present your best aspect.

2. Think like evaluators: If you are in confusion or getting demotivated because your paper may not be accepted by the evaluators, then think, and try to evaluate your paper like an evaluator. Try to understand what an evaluator wants in your research paper, and you will automatically have your answer. Make blueprints of paper: The outline is the plan or framework that will help you to arrange your thoughts. It will make your paper logical. But remember that all points of your outline must be related to the topic you have chosen.

3. Ask your guides: If you are having any difficulty with your research, then do not hesitate to share your difficulty with your guide (if you have one). They will surely help you out and resolve your doubts. If you can't clarify what exactly you require for your work, then ask your supervisor to help you with an alternative. He or she might also provide you with a list of essential readings.

4. Use of computer is recommended: As you are doing research in the field of medical research then this point is quite obvious. Use right software: Always use good quality software packages. If you are not capable of judging good software, then you can lose the quality of your paper unknowingly. There are various programs available to help you which you can get through the internet.

5. Use the internet for help: An excellent start for your paper is using Google. It is a wondrous search engine, where you can have your doubts resolved. You may also read some answers for the frequent question of how to write your research paper or find a model research paper. You can download books from the internet. If you have all the required books, place importance on reading, selecting, and analyzing the specified information. Then sketch out your research paper. Use big pictures: You may use encyclopedias like Wikipedia to get pictures with the best resolution. At Global Journals, you should strictly follow here.



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6. Bookmarks are useful: When you read any book or magazine, you generally use bookmarks, right? It is a good habit which helps to not lose your continuity. You should always use bookmarks while searching on the internet also, which will make your search easier.

7. Revise what you wrote: When you write anything, always read it, summarize it, and then finalize it.

8. Make every effort: Make every effort to mention what you are going to write in your paper. That means always have a good start. Try to mention everything in the introduction—what is the need for a particular research paper. Polish your work with good writing skills and always give an evaluator what he wants. Make backups: When you are going to do any important thing like making a research paper, you should always have backup copies of it either on your computer or on paper. This protects you from losing any portion of your important data.

9. Produce good diagrams of your own: Always try to include good charts or diagrams in your paper to improve quality. Using several unnecessary diagrams will degrade the quality of your paper by creating a hodgepodge. So always try to include diagrams which were made by you to improve the readability of your paper. Use of direct quotes: When you do research relevant to literature, history, or current affairs, then use of quotes becomes essential, but if the study is relevant to science, use of quotes is not preferable.

10. Use proper verb tense: Use proper verb tenses in your paper. Use past tense to present those events that have happened. Use present tense to indicate events that are going on. Use future tense to indicate events that will happen in the future. Use of wrong tenses will confuse the evaluator. Avoid sentences that are incomplete.

11. Pick a good study spot: Always try to pick a spot for your research which is quiet. Not every spot is good for studying.

12. Know what you know: Always try to know what you know by making objectives, otherwise you will be confused and unable to achieve your target.

13. Use good grammar: Always use good grammar and words that will have a positive impact on the evaluator; use of good vocabulary does not mean using tough words which the evaluator has to find in a dictionary. Do not fragment sentences. Eliminate one-word sentences. Do not ever use a big word when a smaller one would suffice.

Verbs have to be in agreement with their subjects. In a research paper, do not start sentences with conjunctions or finish them with prepositions. When writing formally, it is advisable to never split an infinitive because someone will (wrongly) complain. Avoid clichés like a disease. Always shun irritating alliteration. Use language which is simple and straightforward. Put together a neat summary.

14. Arrangement of information: Each section of the main body should start with an opening sentence, and there should be a changeover at the end of the section. Give only valid and powerful arguments for your topic. You may also maintain your arguments with records.

15. Never start at the last minute: Always allow enough time for research work. Leaving everything to the last minute will degrade your paper and spoil your work.

16. Multitasking in research is not good: Doing several things at the same time is a bad habit in the case of research activity. Research is an area where everything has a particular time slot. Divide your research work into parts, and do a particular part in a particular time slot.

17. Never copy others' work: Never copy others' work and give it your name because if the evaluator has seen it anywhere, you will be in trouble. Take proper rest and food: No matter how many hours you spend on your research activity, if you are not taking care of your health, then all your efforts will have been in vain. For quality research, take proper rest and food.

18. Go to seminars: Attend seminars if the topic is relevant to your research area. Utilize all your resources.

19. Refresh your mind after intervals: Try to give your mind a rest by listening to soft music or sleeping in intervals. This will also improve your memory. Acquire colleagues: Always try to acquire colleagues. No matter how sharp you are, if you acquire colleagues, they can give you ideas which will be helpful to your research.

20. Think technically: Always think technically. If anything happens, search for its reasons, benefits, and demerits. Think and then print: When you go to print your paper, check that tables are not split, headings are not detached from their descriptions, and page sequence is maintained.

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22. Report concluded results: Use concluded results. From raw data, filter the results, and then conclude your studies based on measurements and observations taken. An appropriate number of decimal places should be used. Parenthetical remarks are prohibited here. Proofread carefully at the final stage. At the end, give an outline to your arguments. Spot perspectives of further study of the subject. Justify your conclusion at the bottom sufficiently, which will probably include examples.

23. Upon conclusion: Once you have concluded your research, the next most important step is to present your findings. Presentation is extremely important as it is the definite medium though which your research is going to be in print for the rest of the crowd. Care should be taken to categorize your thoughts well and present them in a logical and neat manner. A good quality research paper format is essential because it serves to highlight your research paper and bring to light all necessary aspects of your research.

Informal Guidelines of Research Paper Writing

Key points to remember:

- Submit all work in its final form.
- Write your paper in the form which is presented in the guidelines using the template.
- Please note the criteria peer reviewers will use for grading the final paper.

Final points:

One purpose of organizing a research paper is to let people interpret your efforts selectively. The journal requires the following sections, submitted in the order listed, with each section starting on a new page:

The introduction: This will be compiled from reference matter and reflect the design processes or outline of basis that directed you to make a study. As you carry out the process of study, the method and process section will be constructed like that. The results segment will show related statistics in nearly sequential order and direct reviewers to similar intellectual paths throughout the data that you gathered to carry out your study.

The discussion section:

This will provide understanding of the data and projections as to the implications of the results. The use of good quality references throughout the paper will give the effort trustworthiness by representing an alertness to prior workings.

Writing a research paper is not an easy job, no matter how trouble-free the actual research or concept. Practice, excellent preparation, and controlled record-keeping are the only means to make straightforward progression.

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Specific editorial column necessities for compliance of a manuscript will always take over from directions in these general guidelines.

To make a paper clear: Adhere to recommended page limits.



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- Submitting a manuscript with pages out of sequence.
- In every section of your document, use standard writing style, including articles ("a" and "the").
- Keep paying attention to the topic of the paper.
- Use paragraphs to split each significant point (excluding the abstract).
- Align the primary line of each section.
- Present your points in sound order.
- Use present tense to report well-accepted matters.
- Use past tense to describe specific results.
- Do not use familiar wording; don't address the reviewer directly. Don't use slang or superlatives.
- Avoid use of extra pictures—include only those figures essential to presenting results.

Title page:

Choose a revealing title. It should be short and include the name(s) and address(es) of all authors. It should not have acronyms or abbreviations or exceed two printed lines.

Abstract: This summary should be two hundred words or less. It should clearly and briefly explain the key findings reported in the manuscript and must have precise statistics. It should not have acronyms or abbreviations. It should be logical in itself. Do not cite references at this point.

An abstract is a brief, distinct paragraph summary of finished work or work in development. In a minute or less, a reviewer can be taught the foundation behind the study, common approaches to the problem, relevant results, and significant conclusions or new questions.

Write your summary when your paper is completed because how can you write the summary of anything which is not yet written? Wealth of terminology is very essential in abstract. Use comprehensive sentences, and do not sacrifice readability for brevity; you can maintain it succinctly by phrasing sentences so that they provide more than a lone rationale. The author can at this moment go straight to shortening the outcome. Sum up the study with the subsequent elements in any summary. Try to limit the initial two items to no more than one line each.

Reason for writing the article—theory, overall issue, purpose.

- Fundamental goal.
- To-the-point depiction of the research.
- Consequences, including definite statistics—if the consequences are quantitative in nature, account for this; results of any numerical analysis should be reported. Significant conclusions or questions that emerge from the research.

Approach:

- Single section and succinct.
- An outline of the job done is always written in past tense.
- Concentrate on shortening results—limit background information to a verdict or two.
- Exact spelling, clarity of sentences and phrases, and appropriate reporting of quantities (proper units, important statistics) are just as significant in an abstract as they are anywhere else.

Introduction:

The introduction should "introduce" the manuscript. The reviewer should be presented with sufficient background information to be capable of comprehending and calculating the purpose of your study without having to refer to other works. The basis for the study should be offered. Give the most important references, but avoid making a comprehensive appraisal of the topic. Describe the problem visibly. If the problem is not acknowledged in a logical, reasonable way, the reviewer will give no attention to your results. Speak in common terms about techniques used to explain the problem, if needed, but do not present any particulars about the protocols here.

The following approach can create a valuable beginning:

- Explain the value (significance) of the study.
- Defend the model—why did you employ this particular system or method? What is its compensation? Remark upon its appropriateness from an abstract point of view as well as pointing out sensible reasons for using it.
- Present a justification. State your particular theory(-ies) or aim(s), and describe the logic that led you to choose them.
- Briefly explain the study's tentative purpose and how it meets the declared objectives.

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Use past tense except for when referring to recognized facts. After all, the manuscript will be submitted after the entire job is done. Sort out your thoughts; manufacture one key point for every section. If you make the four points listed above, you will need at least four paragraphs. Present surrounding information only when it is necessary to support a situation. The reviewer does not desire to read everything you know about a topic. Shape the theory specifically—do not take a broad view.

As always, give awareness to spelling, simplicity, and correctness of sentences and phrases.

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This part is supposed to be the easiest to carve if you have good skills. A soundly written procedures segment allows a capable scientist to replicate your results. Present precise information about your supplies. The suppliers and clarity of reagents can be helpful bits of information. Present methods in sequential order, but linked methodologies can be grouped as a segment. Be concise when relating the protocols. Attempt to give the least amount of information that would permit another capable scientist to replicate your outcome, but be cautious that vital information is integrated. The use of subheadings is suggested and ought to be synchronized with the results section.

When a technique is used that has been well-described in another section, mention the specific item describing the way, but draw the basic principle while stating the situation. The purpose is to show all particular resources and broad procedures so that another person may use some or all of the methods in one more study or referee the scientific value of your work. It is not to be a step-by-step report of the whole thing you did, nor is a methods section a set of orders.

Materials:

Materials may be reported in part of a section or else they may be recognized along with your measures.

Methods:

- Report the method and not the particulars of each process that engaged the same methodology.
- Describe the method entirely.
- To be succinct, present methods under headings dedicated to specific dealings or groups of measures.
- Simplify—detail how procedures were completed, not how they were performed on a particular day.
- If well-known procedures were used, account for the procedure by name, possibly with a reference, and that's all.

Approach:

It is embarrassing to use vigorous voice when documenting methods without using first person, which would focus the reviewer's interest on the researcher rather than the job. As a result, when writing up the methods, most authors use third person passive voice.

Use standard style in this and every other part of the paper—avoid familiar lists, and use full sentences.

What to keep away from:

- Resources and methods are not a set of information.
- Skip all descriptive information and surroundings—save it for the argument.
- Leave out information that is immaterial to a third party.



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Results:

The principle of a results segment is to present and demonstrate your conclusion. Create this part as entirely objective details of the outcome, and save all understanding for the discussion.

The page length of this segment is set by the sum and types of data to be reported. Use statistics and tables, if suitable, to present consequences most efficiently.

You must clearly differentiate material which would usually be incorporated in a study editorial from any unprocessed data or additional appendix matter that would not be available. In fact, such matters should not be submitted at all except if requested by the instructor.

Content:

- Sum up your conclusions in text and demonstrate them, if suitable, with figures and tables.
- In the manuscript, explain each of your consequences, and point the reader to remarks that are most appropriate.
- Present a background, such as by describing the question that was addressed by creation of an exacting study.
- Explain results of control experiments and give remarks that are not accessible in a prescribed figure or table, if appropriate.
- Examine your data, then prepare the analyzed (transformed) data in the form of a figure (graph), table, or manuscript.

What to stay away from:

- Do not discuss or infer your outcome, report surrounding information, or try to explain anything.
- Do not include raw data or intermediate calculations in a research manuscript.
- Do not present similar data more than once.
- A manuscript should complement any figures or tables, not duplicate information.
- Never confuse figures with tables—there is a difference.

Approach:

As always, use past tense when you submit your results, and put the whole thing in a reasonable order.

Put figures and tables, appropriately numbered, in order at the end of the report.

If you desire, you may place your figures and tables properly within the text of your results section.

Figures and tables:

If you put figures and tables at the end of some details, make certain that they are visibly distinguished from any attached appendix materials, such as raw facts. Whatever the position, each table must be titled, numbered one after the other, and include a heading. All figures and tables must be divided from the text.

Discussion:

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Position your understanding of the outcome visibly to lead the reviewer through your conclusions, and then finish the paper with a summing up of the implications of the study. The purpose here is to offer an understanding of your results and support all of your conclusions, using facts from your research and generally accepted information, if suitable. The implication of results should be fully described.

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Research papers are not acknowledged if the work is imperfect. Draw what conclusions you can based upon the results that you have, and take care of the study as a finished work.

- You may propose future guidelines, such as how an experiment might be personalized to accomplish a new idea.
- Give details of all of your remarks as much as possible, focusing on mechanisms.
- Make a decision as to whether the tentative design sufficiently addressed the theory and whether or not it was correctly restricted. Try to present substitute explanations if they are sensible alternatives.
- One piece of research will not counter an overall question, so maintain the large picture in mind. Where do you go next? The best studies unlock new avenues of study. What questions remain?
- Recommendations for detailed papers will offer supplementary suggestions.

Approach:

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References	Complete and correct format, well organized	Beside the point, Incomplete	Wrong format and structuring

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