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ABOUT THE JOURNAL

About the Health Sci. Q.

Health Sciences Quarterly (Health Sci. Q.) journal as known by the name of "Journal of Scientific Perspectives" until April 2021 which has been published since 2017 is an international peer-reviewed journal of HOLISTENCE ACADEMY. It is published quarterly in January, April, July, and October. All manuscripts submitted for publication are evaluated by the editor-in-chief, section editor, editorial board, and referees. In addition, the journal provides a medium for highlighting selected articles reporting highly significant original findings, as Editor's Choice Manuscripts.

Aims and Scope

Health Sciences Quarterly (Health Sci. Q.) is an open-access journal that publishes original research papers, case reports, and reviews, clinical studies covering a wide range of subjects in life sciences and medicine as well as clinical and experimental investigations only in English.

Researchers in health sciences will find much of great use and interest in the Health Sci. Q.

HSQ aims to supply scientists of health with resources in order to provide the scientific knowledge through the publication of peer-reviewed, high quality, scientific papers and other material on all topics related to Medicine, Pharmacy and pharmaceutical sciences, Dentistry, Nursing, Bioethics, History of medicine, Health economics, Pharmacoeconomics, Medical education, Public health, and Epidemiology.

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EDITORIAL

Dear Colleagues,

The Sun is shining, and spring is in the air nowadays. In this beautiful spring, we continue to work hard and try to publish qualified, scientific, and academic articles in the journal Health Sciences Quarterly (Health Sci Q).

In this April issue, we have five original articles and a case report. Migration, which affected all countries in the world, is directly connected with the social, cultural, economic, and political structure of the society and is a concept that shapes social life and has a great impact on individuals' health. The first article is considerable research about the acculturation strategies, risk factors, and health perceptions of Syrian asylum seekers in Turkey. The second article is about the current pandemic and the relation between gender, education, professional level, hospital stay, and the symptom and severity of COVID 19 in permanent residents of Dhaka city. The third article is about bioethics, and the author argues for composite tissue transplantation in the context of integrity and human dignity. The other articles are about the interaction between GSK-3β and β-catenin to maintain cell survival in hepatocytes under high-fructose treatments, and biochemical parameters in stable asthma patients, respectively. The last article is an interesting case report about vocal cord hemangioma.

Health Sci Q (formerly Journal of Scientific Perspectives) is an open-access, peer-reviewed journal dedicate to delivering leading-edge research in all disciplines of health sciences to publish. Health Sci Q encourages researchers all around the world to share their original studies in the form of original research, review, mini-review, case report, letter to the editor, commentary, news and views, as well as meeting reports. Moreover, full texts of all published articles can be downloaded for free from our website.

Herein, we again would like to thank all the authors, the referees, and everyone (also every life forms) who contributed to these ideas/studies/articles.

Hope to meet in the upcoming issues.

Kind regards.

Hasan Erbay MD, PhD, MBGPH

Editor-in-Chief

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ORIGINAL ARTICLE

A qualitative research on the acculturation strategies, risk factors and health perceptions of Syrian asylum seekers

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Abstract

The internal turmoil, that broke out in Syria, started a mass migration movement towards Turkey in 2011. This migration movement, which proved to be an important social phenomenon, individuals from many different cultures have experienced coexistence for compulsory reasons. On top of that experience they were subjected to, the addition of a highly complicated process of acculturation, and the risk factors which immigrants and ethnic minority groups faced caused them to classify as vulnurable regarding health. The aim of this study is to assess how the preferred acculturation strategy of Syrian asylum seekers, who found themselves living along with different cultures, their negative or positive experiences and the risk factors they face affects their health, and health perceptions. The research was designed as a phenomenological research. In-depth interviews were conducted with 24 participants, who were included in the study, using the purposive sampling strategies, homogeneous case sampling and criterion sampling technique. In addition to the usage of code book obtained from the literary works related to the field using the deductive method, the data recorded by observing and the notes from interviews were reduced to themes, categories and codes using the inductive method. The study is grouped under three main themes, namely acculturation strategy of Syrian asylum seekers, risk factors affecting the healths of Syrian asylum seekers and health perception of Syrian asylum seekers. Statistical analysis of the data was carried out by using descriptive analysis and content analysis provided in the MAXQDA 2020 pro-package program. Although the participants heavily express their opinions in favor of seperationg strategy, which is one of the acculturation strategies, this is followed by an integration strategy. Furthermore, the participants were observed to have been subjected to discrimination and rejection, and in this process, facing risk factors mainly social, psychological, environmental, physical and barriers affecting healthcare procurement. Multiple relational analysis show that an intense relationship was found between the participants who preferred the separatist strategy and the risk factors affecting their health. It was observed that the participants who reported good health perception before migrating; due to the most reported social risk factor, economic barriers, reported negative health perception after migrating. The majority of participants who preferred the integration strategy reported good health perception both before and after migration.

Keywords: Immigration, nursing, acculturation strategy, perception of health, Syrian asylum seekers, risk factors

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Introduction

Migration, which affected all countries in the world, especially in the second half of the 20th century, appeared as mass migrations. And this situation caused a rapid acceleration of the increase in the immigrant population in the last half century. *"According to United Nations datas, if it continues with the speed which it has been going fort he last 20 years, the number of international immigrants in the world is expected to reach 405 million in 2050."* [1]. Despite being regarded as an event of displacement of individuals from one place to another, Migration is directly connected [2] with the social, cultural, economic and political structure of the society and is a concept that shapes social life and has a great impact on individuals [3]. Although the mass migration, occuring with or against people's wills, had an effect on individuals' lives at first, in later phases, it more than likely leads to them facing problems about nourishment, shelter and most importantly, health and education [2]. One of the fundamental reasons of this is the cultural differences between the host and the immigrant. This situation has revealed the importance of intercultural interactions [4]. It used to be possible to have societies consisting of only one culture; but, it is no longer possible to characterize a whole nation based on a single culture, language, religion, or identity [5,6]. Keeping in mind that almost all the countries have multicultural structure [7], both migration and culture are the subjects of many research papers [8].

Migration happens for the reasons like colonialism, war, seeking job etc. And as a result, countries become multicultural. Thus, people who have different cultural backgrounds come together on a different society and as a result of the interactions between those two cultures, comes a phenomenon that we call 'acculturation'. The definition of acculturation is, a binary cultural and psychological alteration process of two or more cultural groups and their individual members [5,9-11]. At group level; It includes changes in social structures, institutions, cultural practices while also including changes behavior at the individual level [11]. Acculturation; when it first came out with the respresentation of Gordon [12], had been known as 'assimilation model', its basic assumption was the immigrant inevitably getting assimilated by the host culture [13]. Afterwards, under Berry's guidance, 'bidimensional model of acculturation' came out [3]. According to Berry, every individual in a group experiences this process in different ways. The important factor in order to understand these individual differences is how the people direct themselves through this process. To understand these varying behaviors, 'acculturation strategies' are recommended. As they consist of attitudes and behaviors (meaning it includes both preference and the action) exhibited in daily intercultural encounters, they are called strategies rather than attitudes [14]. Eight acculturation strategies which are presented in Berry's model (1980), are now reduces to four by him [10]. Those are; assimilation, integration, separation and marginalization [9,13,15,16]. These strategies have different names depending on which group (dominant/host or non-dominant/immigrant) is being assessed. From the perspective of immigrant groups, individuals adopt the assimilation strategy when they are not interested in preserving their own cultural identities and are in search of daily interactions with other cultural groups [5,9,16]. On the other hand, individuals adopt separation strategy when they want to preserve their own culture and avoid interactions with others [5,9,10,13,16,17]. Integration strategy emerges if one is interested in maintaining their own culture as well as daily interactions with other groups [5,9,10,13,16,17]. Lastly, if the individual has little interest in protecting their culture (usually caused by cultural loss), and/or in interaction with others (usually caused by discrimination), marginalization happen [5,9,10,16]. Besides, both groups are affected by this process that alters not only the immigrant, but also the host [3].

Participants of this research who were forced to leave their country and seek asylum in Turkey were Syrian asylum seeker. At first, there were uncertainties about the status of Syrians who came to Turkey in result of mass migration [18], and temporary protection status was given with the Temporary Protection Regulation published

in the official newspaper No. 29153, carried out by the Foreigners and International Protection Law (YUKK) No. 6458, in 22 October 2014 [19]. It is regulated that foreigners be provided with education, access to the labor market, social assistance and services, interpreting and similar services, and especially health services [20].

In addition to these uncertainties, cultural issues and traumatic war experience they had since the beginning of the migration process, Syrian asylum seekers, who had to leave their place unwillingly and unprepared, are categorized as sensitive groups. These risk factors can very well cause drastic changes in their health as well as their perception of health.

Perception of health, being a subjective concept, nowadays has become the focal point of numerous studies and researchs. Especially health sociologists, epidemiologists and public health specialists are take up the subject in detail about the sociocultural aspects [22]. Perception of health, being an important criteria about the individual's assessment of their health and their quality of life [23], may also be defined as how the individual views their own health. It is known that health perception is a strong indicator of mortality rates [24,25], and it can be used to track risk groups and as a useful endpoint for clinical studies [24]. Perception of health is a very beneficial method as it can indicate some symptoms of diseases that can't be detected through examination or that are not considered to be part of examination [25].

To think of individuals as separate from the society they are a part of, is in conflicts with the acceptance of health being as a whole. Being healthy may vary from person to person, society to society and time period to time period [21]. Hence, traditions and the cultural structure of a society is affecting individual's perception of health [27,28]. For example; not being healthy. While one society may accept the seriousness of a disease, it can be different for societies that have different cultures. Culture is an important factor in determining of access to the health system by influencing individuals' perception and interpretation of disease symptoms, help-seeking behavior, decision-making, expectations from the role of the patient, their way of coping and communication with health providers [29]. Despite the prominence of cultural communication on its effects on health, the observation was that there were not enough qualitative researches on that field. Yet qualitative research; is crucial for nurses, whose field of study is people, to be able to understand and interpret human behavior with all its intricacies [30]. The main reason for phenomenological research in this field is that the acculturation process is specific to each individual and the results of most studies can't be generalized on the society that exhibits that culture. Every individual's experiences and the effects of those experiences are different in this process.

Considering all these things, health care providers paying attention to these differences in health services, establishing effective and on point communication and planning health care accordingly, will reduce the difficulties faced in this regard [31]. For all the asylum seekers who experience this process intricately with all its dimensions, it is very important to plan nursing care with a multidisciplinary approach. This study will be a guide in revealing the effect of this multicultural environment, which deeply affects the health of the society and the individual, on physical and psychological health, how the individual perceives it and their experiences in the process. The intention is that this study will make a conceptual contribution to studies in different disciplines such as public health, nursing, psychology, and social work.

The aim of this study is to reveal the impact of the acculturation strategy preferred by Syrian asylum seekers who coexist among different cultures, and the risk factors they face from their positive or negative experiences in the process, on health and health perceptions.

Materials and Methods

Ethical aspect of the research

Ethical permission was obtained from Ege University Medical Research Ethics Committee (38-2009), and written permissions were obtained from the Provincial Immigration Administration and the Association for Solidarity with Asylum

Seekers and Immigrants in order to carry out the study. In addition, a written and verbal consent of the individuals included in the study was obtained for their participation.

Designing of the research

Study was carried out with one of the scientific research methods the qualitative research. The phenomenology design was chosen in order to reveal the opinions they expressed on this subject and the meanings they attributed to the events in detail.

Determination of participants

The research area consists of Syrian nationals between the ages of 18-65 living in İzmir and the working group, was chosen by purposive sampling method, from individuals who applied to the Association for Solidarity with Asylum Seekers and Migrants (ASAM) for health counseling and Syrian translators working in the institution.

In this study, from purposive sampling strategies, homogenous case sampling and criterion sampling were used. The process of data collection has ended in the research when the data was seen in the saturation point. Purposeful sampling criterias are to be living in Turkey for at least one year, to have no chronic disease, and to be between the ages of 18-65. A total of 24 participants were included in the study. Participants were numbered as K1-K24. Later, two of the participants haven't been able to be included in the study due to the having chronical diseases and being unfit to the measurement criteria.

17 of the participants are women and 7 of them are men. 2 between the ages of 18-25, 13 of them between 26-35, 7 between 36-45, and the remaining 2 of them are between 46-65. 1 of them is single while other 23 are married. 3 of the participants never finished any schools, 4 graduated primary school, 6 elementary school, 7 highschool, 3 university, and finally 1 of them is postgraduate. Among the participants, 5 of which are living with their extended family, while 19 of them are living with nuclear family. And, 1 is in the host country for 0-1 year, 16 of them are in for 2-5 years, and 7 between 6-10 years.

Process of data collection

To collect data in the research, demographic questions and semi-structured interview form, created by the researcher and included introductory information about the participants, were used. In-depth individual interviews were conducted with the participants within the framework of this interview form. While preparing the interview questions, studies and scales related to the subject were used. In addition, the form containing demographic information and questions in the interviews were translated into Arabic by an expert. After the translation, the interview questions were pre-tested with two participants in order to evaluate its intelligibility. After the arrangements made, the interview form took its final form and the negotiations started. The questions asked to the participants in the semi-structured interview forms were grouped under 3 subtitle. In order to question the acculturation experiences of Syrian asylum seekers in the process of migration and the acculturation strategies they prefer in the process; Some questions were asked, such as: "What does it feel like to be Syrian living in Turkey?", "Can you tell us about the migration and your experiences in this process?", "Can you tell us about the place and the conditions you are living in?", "Can you tell us a little about your family and close circle?", "Which language do you prefer to use the most at home and what are the reasons of this prefence?"

Some more questions were directed to them to find out if the status of Syrian asylum seekers are benefiting from health services in the acculturation process; "What do you think about Turkey's health services?", "What did you encounter in the health institutions you applied to?", "Can you explain your experiences about it with their positive and negative aspects?", "Can you talk about the importance of having healthcare professionals with a different culture?"

In the interviews in Arabic, one of the translators translated while the interview continued,

while another interpreter only took notes in detail about the statements of the participant's, thus, ensuring that no data was lost during the interview. The interviewer also took notes of his own and recorded her observations about the participants. After the interview, necessary notes were taken and summarized to the participants for approval. All these notes were included in the analysis as the primary data of the research.

The interviews were held between December 2019 and March 2020. With the choice of participants, 6 of the interviews started in Turkish, 17 in Arabic and one also in Turkish, but due to the participant having trouble whit the usage of language, it was continued in Arabic with the assistance of a translator. The notes taken in parallel with the interviews were studied alongside translators and completed. Then the data was arranged properly and saved as Word text. To be able to organize and obtain the raw data, the notes taken were examined in detail again, and the coding process started. A code book was created with the deductive method from similar studies and the inductive method from the data obtained. The codes obtained were combined under categories and themes according to their common characteristics.

Data analysis strategy

Descriptive (thematic) analysis and content analysis were used as research analysis methods. In the descriptive analysis, the data obtained as a result of the interviews and observations are reduced to the previously revealed themes, summarized and interpreted according to these themes [32]. One of the content analysis types, relational analysis, was also used. Qualitative content analysis involves breaking the data into small sections, coding these units according to the contents they represent, and grouping the coded materials according to the contents they represent [33]. Coding and data analysis of the study were carried out by the researchers using the MAXQDA 2020 package program. Frequency numbers (f) were used in the presentation of the findings. The obtained diversity and density of the themes were interpreted and reported along with various examples.

Validity and reliability

In order to establish convincibility, the interviewer working in the Association for Solidarity with Asylum Seekers and Migrants helped to eliminate biases as well as having better communication throughout the whole process. At the end of the interview, the data obtained regarding the contents of the interview were briefly summarized and the participant's consent was taken. In addition, at every stage of the study, support was received from experts who had minimum amount of contact with the participants (to eliminate bias) and had sufficient knowledge on qualitative research and the subject of research, and the data have been evaluated objectively from an unbiased point of view. In order to ensure transferability, all stages of the research were explained to the participants in detail and the research was carried out in accordance with every step of the process. It was emphasized that the findings of the research reflect the sample group and cannot be generalized to the population. To ensure reliability, the relevant literary works was scanned and the process was examined in similar studies. The obtained data was coded by a second researcher, and similar results came up. For the reassurance of confirmability, the raw data (opinions of the participants, observation by the researcher) were appropriately recorded, and frequent quotations from the participants' statements about each topic were included in the findings section.

Results

The research is grouped under 3 main themes as seen in Figure 1. Theme tags; Acculturation strategy of Syrian asylum seekers, risk factors affecting the health of Syrian asylum seekers, health perception of Syrian asylum seekers.

Acculturation strategies of Syrian asylum seekers

In line with the statements of the participants, the acculturation strategies theme of the Syrian asylum seekers was defined in 4 different categories. Those are; separation, integration, marginalization, assimilation strategies.

It was observed that the participants expressed their views intensely in favor of separation strategy regarding the themes of acculturation strategies of Syrian asylum seekers. In this matter, most claim to prefer to maintain their own culture and habits (language, eating habits etc.), communicate with people from their own nation and use their own language. Participants stated their fear of their children forgetting their mother tongue, and that they feel more comfortable when they use Arabic in daily life, and as a consequence, had difficulty learning Turkish. Statements of K8 and K18;

> *"We are Syrians and we are guests in this country. We cannot do anything, we cannot speak. I cannot speak Turkish… I do not know how to speak Turkish with Turks … I don't know Turkish food, I do not know how to cook. Until now, we only cook syrian dishes. (K8), "I can get along with Syrians. They understand me, I understand them. But Turkish is difficult." (K18)*

After the separation strategy, integration strategy was the most preferred among the participants, and expressed their opinions in this direction. They mentioned that they communicated with the host society (neighbor, colleague, etc.) with this code, and their changes in behavior because of it. Yet those participants were observed not fully giving up on the characteristics of their own culture and continued to communicate with individuals close to their own culture. The participants expressed these views as belonging to both cultures; they explained it with behavioral changes such as consumption of food, use of media, and use of language. Opinions of K5 and K26;

> *"We are used to these since childhood, consuming them. There are some Turkish dishes that we have started to eat here… For example, chickpea soup is delicious. Also 'çiğköfte' and it is also delicious. On the contrary, we make* çiğköfte *as they are made here now..."(K5), "Our neighborhood is beautiful. Turks and Syrians live in our neighborhood." (K26)*

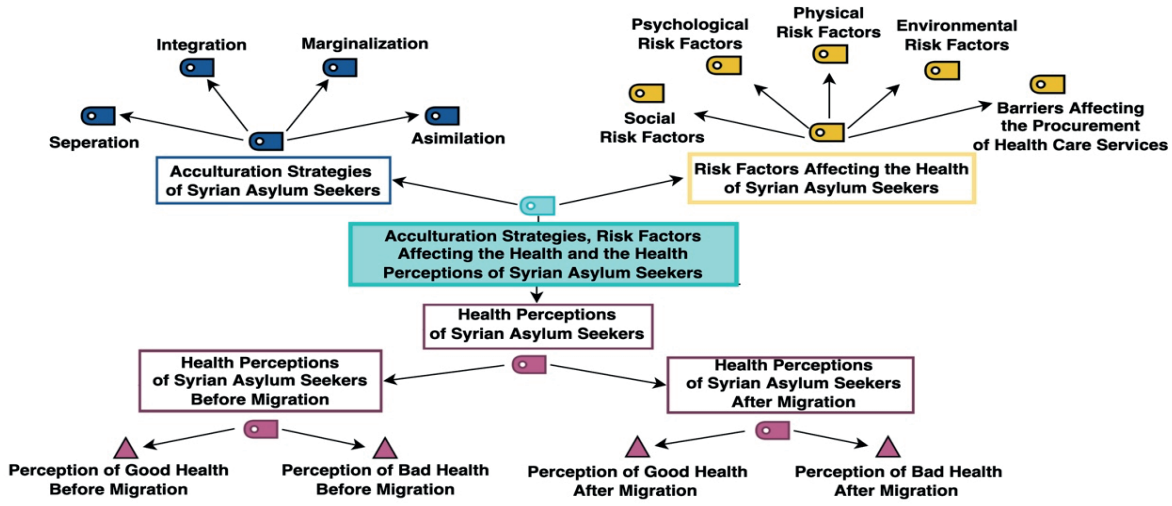

Figure 1. Representation of the themes and categories by the findings of the qualitative analysis regarding the risk factors which affect the healths of Syrian asylum seekers (Concept map)

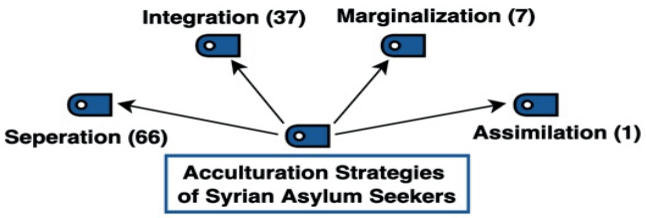

Figure 2. Acculturation strategies of Syrian asylum seekers

In parallel with the results of most studies, the marginalization strategy was not popular among the participants [6]. In this regard, the participants mentioned that they did not feel like they belonged to either culture and that they drifted away from both cultural groups. The thoughts K9;

> *"…I mean, if I could, I would like to speak English…Now we don't know who we can trust. We dont care Syrian or Turk." (K9)*

Only one of the participants was observed to have mentioned the category of the assimilation. Statements of K2 on the subject;

> *"I didn't feel very alienated. I came, shortly after my arrival, met my spouse (Turkish), and got married. I got married about 7-8 months later." (K2)*

Risk factors affecting the health of Syrian asylum seekers

The theme of risk factors affecting the health of individuals was examined under 5 different categories based on similar studies [3] and interview notes. These (Figure 3) are, according to the density of expressed views by the participants, ranked respectively as; social risk factors, barriers affecting the procurement of health care services, psychological risk factors, environmental risk factors and physical risk factors.

Social risk factors

Social risk factors are categorized as 6 different codes. Those being; economic barriers, language barrier, prejudices/ethnic prejudices, lack of social support, loss of social status, lack of education. About the language barrier code, The participants mentioned in 106 different places that they had difficulties in many areas such as finding a job and getting service because they did not know the language. This situation mostly led to not being able to receive salaries, not being able to sufficiently communicate with co-workers, poor neighbor/friendship relations, inadequate access to health services, and disruption in education. Regarding this issue, the participants stated that the language courses provided to them were unhelplful, and they mostly could not attend to it due to work/life conditions (having no one to look after the children, etc.). Statements of K15;

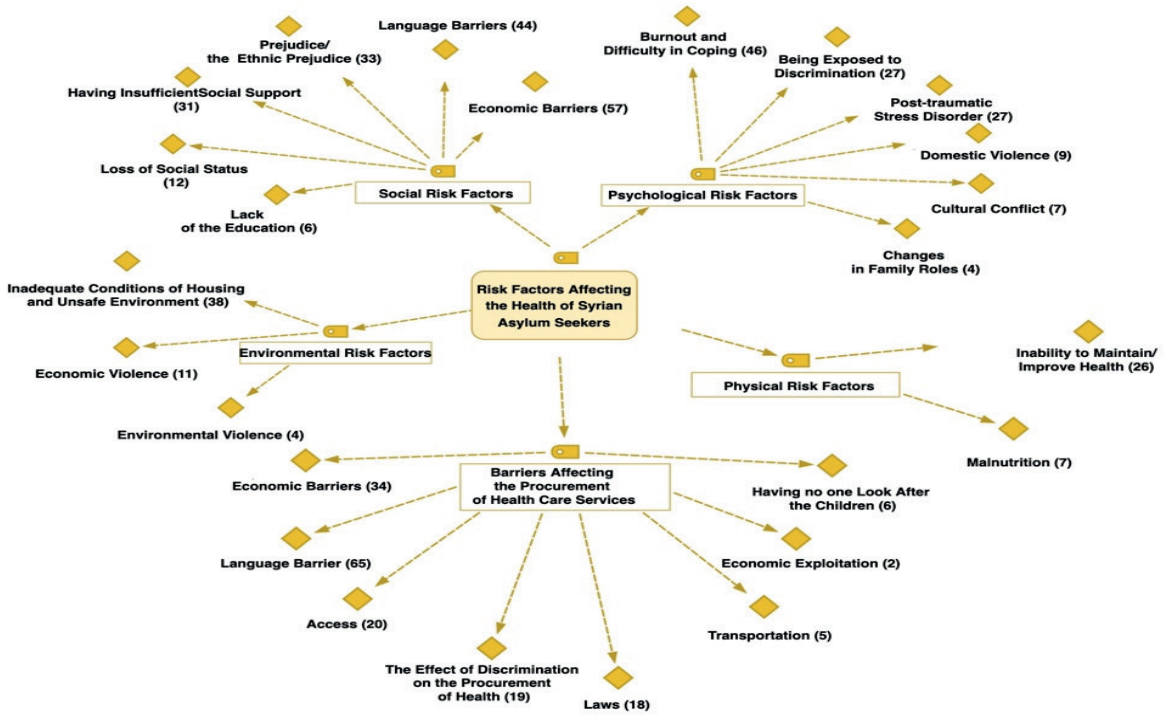

Figure 3. Model of hierarchical codes and sub codes section of risk factors affecting the health of Syrian asylum seekers

"But the main problem is; I don't understand them. We couldn't adapt because of the language problem. The biggest problem for my daughter is… my daughter can't understand. For example, she has a stomachache. She feels like she's going to vomit, but she won't go (to hospital), because she is not able to explain it. I feel sorry for her not being able to explain it..." (K15)

Economic barriers is the code that almost all the participants expressed their views on. About this code; they often emphasized on unemployment, working in irregular jobs, or their income being insufficient to sustain their lives even when they are working. Some participants also stated that they could not pay their rent and got homeless as a result of the economic obstacles they experienced. Having faced economic barriers due to unemployment and temporary jobs, the opinions of participants with the codes of K7 and K10 are as follows:

"It's hard to be in need and being hungry anyway. So we started looking for a job from anywhere we can."(K7) "I have been unemployed for 2 months, I cannot work… We are used to hunger and poverty."(K10)

They talked about the prejudices/ethnic prejudices code, the contempt that syrians face and misconceptions about Syrians and their country. The views of the participant K1 on the subject are:

"…there is something like, everyone is treated the same way. It's as if everyone is the same, those who are educated and those who are not, there is no difference. When they mention a Syrian, people think of beggars." (K1)

The participants mentioned that they could not get enough social support, neither from their families or the people of the country they came from with code of lack of social support. The views of K11;

"No one helps anyone. As I said, isn't my family my life, my blood? I mean, there's no one to knock on your door and ask if you need anything." (K11)

Regarding the loss of social status code, they referred to the pre-war living conditions in their country, saying they were better than in Turkey and the jobs they were working in were more respectable there. The views of K9 about this are as follows:

"My job was good when I was in Syria. It was a profession where I could earn good money. I was a designer. Before I came here, I was not an employee, I was the boss. But i am an employee here."(K9)

Under the lack of education code, the participants stated that they had to take their children off the school due to economic difficulties and discrimination they faced, and they had to put them to work. They also mentioned that they could not send them to school due to the prejudices among the host society and the exclusion they go through. Opinions of K11 and K22;

"...Both (of my children) did not go to school because of discrimination… they never went to school..." (K11) "I'm thinking of taking the youngest sibling off the school now. Because life has become very difficult..." (K18)

Psychological risk factors

The category of psychological risk factors is defined with 6 different codes. Those being; burnout and coping difficulties, exposure to discrimination, post-traumatic stress disorder, domestic violence, cultural conflicts, change of roles family. As seen in Figure 3, in the category of psychological risk factors, the codes which participants expressed the most were burnout and difficulty in coping. The participants talked about the negative experiences they had due to the war in their home country, the discrimination and poverty they experience here, and that they felt burnout because they could no longer cope with them. The statement of K8 on the subject;

"As I said I'm not comfortable, I sleep with the same thoughts, the same exhaustment. So I wake up and hope that maybe I will begin a new life. But nothing changes… I do not want to listen to (music) while there are people who were cut off, people who were shot or died, while my mother, brother and family are far away…" (K8)

The second code on which the participants expressed their opinions intensively was exposure to discrimination. They mentioned that they are discriminated against in many areas and that they are treated differently from Turks. Particularly, the participants emphasized a lot about the discrimination they face in business life. K7's words about the topic:

> *"… 'You just left and fled'. This is what we go through all the time. Some places say 'we do not hire Syrians for employees'. When I work, my normal salary should be at least 3 thousand liras. They only pay 1800 liras at the moment. You have to accept it as a Syrian. If you do not accept, there is no job. They are squeezing this way and that is very difficult for me…"(K7)*

Regarding post-traumatic stress disorder code, the participants talked about the traumas they experienced because of the war in Syria and the negative effects of these traumas on their mental health. The views of the K7 on the subject are:

> *"Because i am depressed... What should I do. Because there was a bomb explosion I left my hometown… My face burned, my mental health got broken… I had a very hard time… While the bombs fell in my country, many of my close friends died. Many people I considered my brothers died. I mean innocent people. How many people died? I mean, children and so on." (K7)*

Under the code of domestic violence, the participants talked about the negative life experiences affected their family life, that there were frequent conflicts in the family and that these conflicts mostly resolved by violence. The statement of the participant K11 on the subject is as follows:

> *"I have never seen the things that I am seeing from my husband 6 years ago. I've been married to him for 15-16 years, I've never seen anything similar to this from him. After I came here, I was subjected to violence and torture. He humiliated me. Why all this? He doesn't work or he doesn't pay for our expenses… All this is happening." (K11)*

With the code; cultural conflict, the participants mentioned that they experience cultural differences, and that they get worse react from the host society as these differences (cultural distance) increase. The views of the participant K3 on the subject are as follows:

> *"... What we preferred in Syria is going to female doctor for pregnancy if you are not in a very difficult situation... But for example, when we go to doctor we say we prefer female doctor. When they say take off your clothes while being examined if there is no need for it, for example, if you are embarrassed and cover it up... they criticize it. They say 'why will the doctor look at you'..." (K3)*

About the code of change in family roles, the participants mentioned that their children also had to start working due to the financial difficulties they experienced here, because of this, there were changes in family roles, and this caused a negative impact on their physical and psychological health. The statements of the participant coded K2 on the subject are as follows:

> *"… When we first came with my brother, we started working. How old he was... Let's say I was 21 when we came. My brother was 4 years younger than me. The other one was 9 years younger than me. All three of us had to work somewhere in a textile shop." (K2)*

Physical risk factors

Physical risk factors are categorized with 2 different codes. These are; Inadequate protection/improvement of health and nutritional deficiency. As can be seen in Figure 3, the code that the participants expressed the most about was inadequacy in the protection/improvement of health. The participants complained that they could not receive health services or protect their health due to poverty, or due to not being able to procure an identity card. The statements of the participant K14 on the subject are as follows:

> *" …you are forced to do it here. We have to do things we cannot do, things that are forbidden for our health, because we have to work." (K14)*

With the code of nutritional deficiency, Participants claimed that they could not eat

adequately and healthily. K23 states that:

> *"…we went through such a time that I deprived my children of many things here. Even if I buy milk for my children from the market, I cannot buy it more than once a month, sometimes even once every two months;"(K23)*

Environmental risk factors

In the category of environmental risk factors, the most emphasized opinions of the participants were inadequate housing conditions and unsafe environment. They mentioned that they had to live in small, humid, old and cheap houses as a crowd due to poverty. The statements of the participant K11 on the subject are as follows:

> *"The house, is like… a small kitchen, It has 2 rooms, and a living room. It's a damp house. The bathroom and the toilet are not seperate. You can't stay in the bathroom without going out 2-3 times, you can't breathe."(K11)*

With the code of economic violence, participants claimed that they were abused economically with very high rents, low salaries among other things. K24 on the subject said:

> *"They wouldn't give us a house. The landlady was a woman with a child, she didn't have much money, she looked at us like we couldn't pay the rent. They started not giving us a house… They started asking for high rents because they knew we had to pay this rent and we had no other choice." (K24)*

Under the environmental violence code, the participants talked about the exclusion and violence they observed in their environment. The views of the K13 on this are as follows:

> *"For example, recently a boy and two girls looked at me laughing and said, "bomb, bomb" in Arabic, and they take an orange and threw it at me." (K13)*

Barriers affecting health care procurement

The category of barriers affecting health care procurement is categorized with 8 different codes: language barrier, economic barriers, access barrier, impact of discrimination on the procurement of services, laws, no one to take care of children, transportation, and economic exploitation. As can be seen in Figure 3, about the category of barriers affecting healthcare procurement, the most common barrier they encountered was their lack of knowledge about the language and the translations being insufficient. The statement of the participant K16 on the subject is as follows:

> *"I don't understand the language here… I don't go to the doctor most of the times. If there is no one to translate for me, if I can't find an interpreter, I don't go. I mean i would be always late for treatment." K16*

With the code of economic barriers, the participants mentioned that they had financial problems due to unemployment, irregular jobs and that they could not procure health services because of those. The views of the participant K12 are:

> *"Most of the time it doesn't compensate. My wife works irregularly and my daughter's physical therapy needs to be paid for. Since we are not Turkish citizens, and we can't afford it in private, my daughter's treatment is disrupted most of the time." (K12)*

Under the access barriers code, the participants mentioned systemic problems such as problems taking appointments, and that they could not access health services because they had difficulty in the hospital processes; especially in the first time, due to having no knowledge about how it works and not getting any help. K12 has put it this way saying:

> *"I don't know anything here; the hospital, or where the right and left of this place are? My daughter was delayed a lot. At first, we didn't know. We learned later but we were late. Because I started my daughter's treatment after 5 years. I had some difficult moments." (K12)*

About the effects of discrimination on service procurement, the participants mentioned that the discrimination they suffered from health care workers as well as other patients negatively affected their health service procurement. The statements of the participant K2 on the subject are as follows:

" …the reactions we got from the doctors… You came to Turkey and you want to choose the hospital and you don't even know how to make an appointment… You came to Turkey and you get paid. Look, these are the doctor's words. You make lots of children… These things affect me too…(K2)

Regarding the code of laws, the participants talked about the systemic problems and unfair laws they encountered. They stated that not having an identity card, being Syrian and their lack of legal rights create obstacles for some treatments. On this topic, participant K21 mentioned:

"It went on like this for 5 years. I couldn't do anything. Because the doctors asked for physical therapy. It's not surgery or anything, it's just physical therapy. The reports we had did not matter. They didn't accept it for physical therapy. Why is it invalid? because we are Syrian citizens..." (K21)

Also, the participants mentioned that there is no one to look after the children when they go to the hospital or when they are hospitalized, because their families are mostly in Syria and social service networks here are insufficient. This situation severely affected their work life and health. Participant K9 expressed:

"…for example, I sometimes stay in the hospital for arouns 2 months, or my wife stays in the hospital for ourchild, my other children stay elsewhere. Go to the hospital, take medicine, go to the other children, I cannot continue to work. I have great difficulties in these matters." (K9)

With the transportation code, the participants mentioned that it is difficult and costly to reach the hospitals.

"Hospitals, go, visits are giving me hard times. Transportation costs are putting me in trouble too much. When we first came here, our child was just born. I did not know any place… " (K21)

Health perceptions of Syrian asylum seekers

The category of health perception of asylum seekers before migration is also defined with 2 different codes (Figure 4): The perception of good health before migration and the perception of bad health before migration. About good health perception; the participants stated that they lived in better conditions in their own country before the migration, that they were in better health, they were able to maintain their health easier, and they ate well. The statements of the participants with the code K14 on the subject are as follows:

"When I was in Syria, I did not complain about anything. My mother and I would wake up in the morning. There is a place close to us in Damascus… It had clean water. We would walk early in the morning, take fresh air, fill some water from there. I had no complaints." (K14)

Under the code of bad health perception, three of the participants mentioned that their health was also bad in their own country before migration. These participants mentioned that they perceived bad health before migration due to the chalky water there and due to weight problems. The views of K4 are:

"The water of the place where we lived in Syria before was chalky. We have been drinking it since we were little, and now I have dental problems because of it." (K4)

Two different codes have been defined regarding the health perception after migration category. These are; The perception of good health after

Figure 4. Health perceptions of Syrian asylum seekers before and after migration

migration and the perception of bad health after migration. The participants who expressed their negative opinions about the perception of bad health after migration mentioned that their health started to deteriorate due to their new life conditions after they migrated. Those conditions are; living in poor houses, terrible work conditions for health, and an abundance of stress. The statements of the participant K3 on the subject are as follows:

> *"Very bad… If I talk about my own health… My heart beat is unstable, my head hurts, my body hurts, I go to the hospital, they say everything is normal. But my body feels like, i am sick-abed who lies in bed for 6-7 days..." (K3)*

Contrary to the participants who claimed to perceived bad health after the migration, few of the participants mentioned that there were no changes in their health after the migration, and some even claimed to have gotten better. The statement of the participant K4 on the subject is:

> *"Thank god I'm in good health. I mean I don't have any problems." (K4)*

Relational analysis

When we examine Figure 5, while individuals who prefer the separation strategy have a good health perception before migration, they stated to have perceived bad health perception after migration. The thickness of the connecting lines indicate the strength of the relationships. Participants who preferred the marginalization strategy also perceived bad health after migration, and good health before it, same with the ones who opt for seperation strategy. Despite some of the participants, who preferred the integration strategy, reporting bad health perception before and after migration, the majority of them had good health perception in both cases. On the other hand, among the individuals who preferred integration reporting good health perception before, some stated to have bad health condition after migration. Participant K4 stated that he preferred the integration strategy. In addition, he made opinions about the perception of good health after migration, which was expressed most commonly. The statements of the participant K4 are as follows:

> *"We mostly speak Arabic at home… My family doesn't speak Turkish very well. They know very little. Our Turkish neighbors and landlords visit us frequently. My wife has learned a little from this. However, it's usually difficult when we talk about something. She can't understand me.", "My health is well thankfully." (K4)*

Participants who preferred the separation strategy mostly stated that they faced economic obstacles, intense burnout and difficulties in coping, lack of social support, prejudice/ethnic prejudice and discrimination. At the same time, same aforementioned participants have bad health perception after migration. The lines marked with red show the relationship between

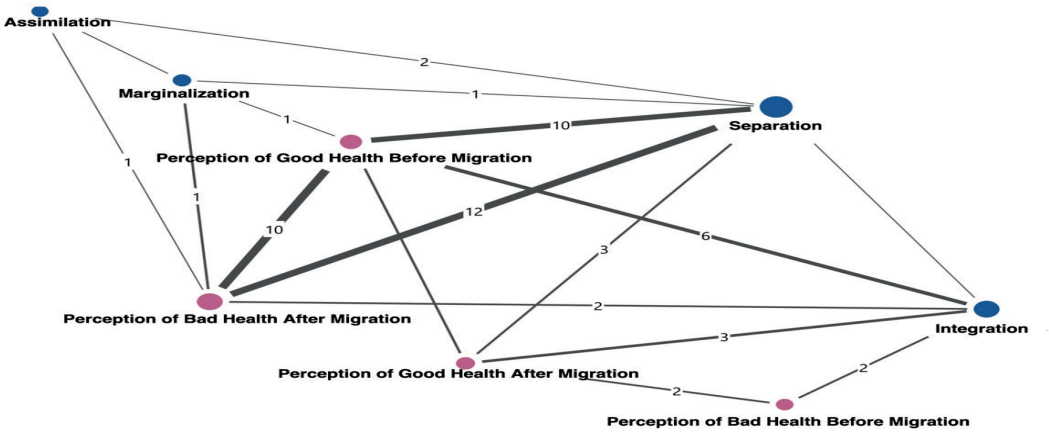

Figure 5. Concept map showing the relationship between the acculturation strategies and the health perceptions of asylum seekers

these codes. In addition, yellow lines indicate the strong connection between the risk factors affecting the health of asylum seekers who prefer the separation strategy, and the relationship between the perception of good health before migration and the perception of bad health after migration. It was observed that the participants who reported good health perception before migration mostly reported bad health perception after migration mainly because of economic barriers they faced. Economic and language barriers under the category of social risk factors, are observed to prevent participants having access to health care services. The turquoise lines on the map show these relationships. The relationship between integration and the good and bad health perception after migration is shown in the previous map. Figure 6 also shows that integration is associated with language barrier as a risk factor. It is suspected that language barrier will affect access to health care and indirectly the perception of health for individuals who had bad health perception and preferred integration. The opinions of the participant K14, who talked about economic barriers, burnout and coping difficulties, and the perception of bad health after migration (dotted lines marked with red on the map) are as follows:

"I am without the majority of my teeth for about a year. I can not eat. Here in Turkey, treatment is paid, public hospitals require an ID card. Also, my wife and I feel psychologically in a dead end. I'm so bored with everything in life. I want to go back to Syria, i mean there is a war and my family is there. We were displaced from where we used to live. Health, income, sadness and grief make a person grow older, he becomes older than his age. Especially what happened to us. Normally i am not allowed to smoke. But lately, I smoke too much…" (K14)

Discussion

In this study, "Berry's Acculturation Model", developed by Berry and his colleagues, was used to interpret the data [34] and the acculturation strategies after migration chosen by the participants were deducted based on experiences. In a study conducted with Syrians migrated to Canada, their access to freedom, equal treatment and immagrant rights by the Canadian system positively affected their cultural integration processes after migration [35], and integration is the most popular acculturation strategy among them [6,36-38]. According to Kılıç, Syrian women are more likely to adopt the integration strategy than the acculturation strategies in Berry's model [39]. However, while in this study, the most preferred acculturation strategy was the

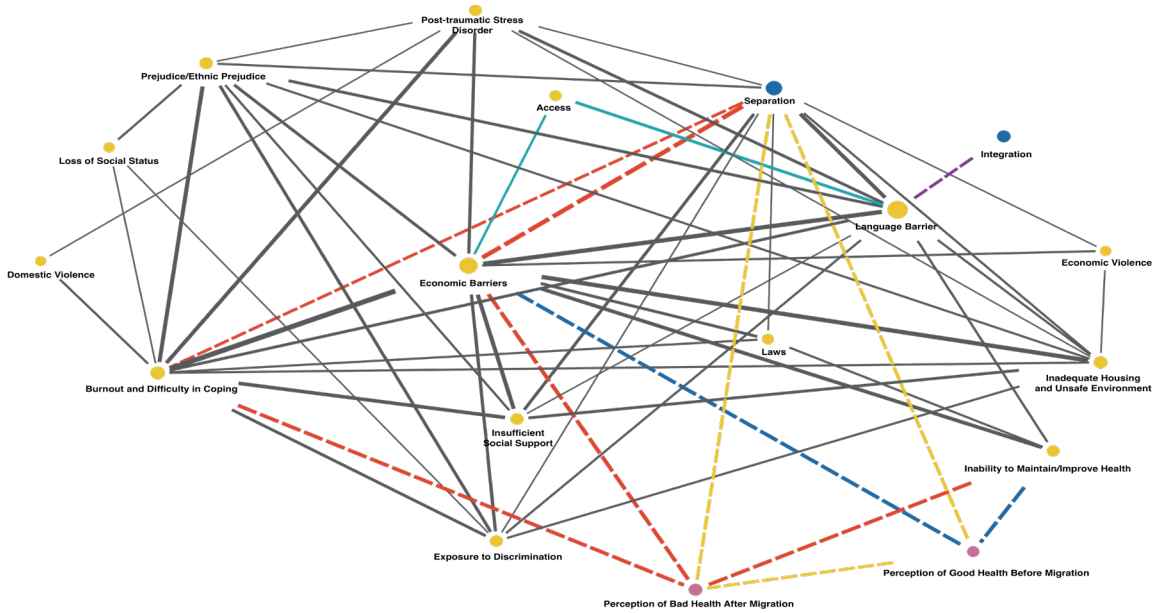

Figure 6. Concept map showing the relationship between health perception of Syrian asylum seekers, risk factors affecting their health and acculturation strategies

separation strategy, it was followed closely by integration. The least preferred strategy among the participants was assimilation, and followed by marginalization.

Migration experience can cause many physical, mental, socioeconomic and cultural problems [40]. The majority of immigrants face traumatic and challenging issues such as unemployment, insufficient support, prejudice, discrimination and abuse [29]. In addition, situations such as very low income, the lack of adequate health institutions in the region, lack of health insurance, language problems, and the multiple families living in the same household negatively affect the health of Syrians [41]. It has also become very difficult to find housing, because of high demand and increasing house rents [18]. It was observed that the employment situation of immigrants has serious effects on the individual and his family, as well as the effects on the economy and social life. This situation proved to be a source stress for both the society and the individuals. Asylum Seekers, who are working in unfair environments, who do not know their rights in cases such as work hazards, who do not want to lose their jobs or be sent back to their country, are unable to pursue their legal rights [42]. Another issue frequently mentioned by the participants in this study is the high rate of discrimination in workplaces, especially in work distribution and salaries. This negatively affects the socio-economic status of individuals. Since socio-economic status creates certain images and obligations on individuals, and in parallel to this, loss of social status makes it that much difficult to maintain a good image and take on important responsibilities [43]. For this reason, it is very important to support vocational education, language education, education programs teaching rights, finding jobs suitable to their abilities and skills, and similar practices in the employment of the individual [42].

Asylum seekers who experience forced migration have difficulties in various dimensions in different areas, and these difficulties can negatively affect their psychological well-being [44]. Immigrants develop mental disorders, especially due to the extraordinary situations and the violence they experience, and it is also one of the things affecting their health negatively [41]. Prejudices and exposure to discrimination have been a source of serious stress. In a study conducted with Syrian and Yemeni immigrants, it was claimed that there were changes in the family structure of the participants, their family roles, their relations with the family and the environment and so on [45]. In another study conducted with military personnel who served during the Gulf War, post-traumatic stress disorder was found to negatively affect physical health [46]. Also in this study, it was observed that the negative experiences in the war affected both mental and physical health negatively.

Not having Access to enough healthy food to meet the daily needs of individuals has been another issue that is insufficient for asylum seekers [41]. Factors such as nutrition and hygiene problems, the inability to provide clean drinking water and the inability to remove wastes properly affect the health conditions negatively in the regions where the asylum seekers mostly migrated. At the same time, immigrants also face problems such as inadequate and unbalanced eating, and infectious diseases due to nutritional problems during the migration process [41]. The most common difficulties that the asylum seekers face in receiving health care are language, cultural barriers, fear of prejudice, and lack of enough knowledge of the health system [29]. Most of the immigrants cannot speak the language of the country; They do not know where and how to look for solutions for the problems they encounter [18] and they have serious communication problems because of speaking different languages [31]. This situation leads to an increase of discrimination. In parallel with the effect of discrimination on health care procurement, Syrians experience social exclusions such as economic, regional, city-based, educational and health [47].

In this study, the participants stated that they perceived their health well before migration. In the study conducted by Kallas with Syrian immigrants in Canada, he mentioned that the majority of women who immigrated to Canada perceived an improvement in their health status and their health perceptions were generally

more positive in Canada, and mentioned that these developments were generally related to physical health [35]. However, in this study, it was observed that especially social, psychological, environmental and physical risk factors are frequently encountered and these factors are associated with the perception of poor health after migration. Social risk factors; individual unemployment [43], social relations [48] are significantly related to the perception of health, and it was observed that the participants talked about the economic barriers they faced due to unemployment, the inadequacy of their social support, and the same participants mostly reported the perception of bad health.

While it is obvious that the assimilationist policies and practices do not lead to the welfare of immigrants, it is also known that marginalization also causes the most negative consequences [14]. Since the participants did not talk much about the assimilation and marginalization code, there was no significant relationship found between these codes and the health perception code in this study. Discrimination is undoubtedly playing a role in resulting worse health perceptions [49] and observed health results [50]. Lastly, it was observed that the participants who preferred the separation strategy over integration, reported more about bad health perception, and there was a significant relationship between them in relational analysis.

Conclusion

As a result of the traumas and negative experiences they had before migrating, during the war process, Syrian asylum seekers faced a number of risk factors and were evaluated as vulnerable groups in health. In this process, being forced to leave their country, leaving their financial resources, jobs, families and social circles behind are all effective in the emergence of these risk factors. The participants had to work for low wages and without any social security in jobs that are not suitable for health and require physical strength, because of the poverty they face after those losses. The majority of the participants stated that they lived in unsanitary, damp, windowless, and crowded houses. All these can cause many psychological and physiological problems and negatively affect health perceptions. Along with these, priorities of individuals had changed and they put their health after basic necessities to survive such as food, shelter and sustaining life. Participants who encountered a brand new culture had difficulty in learning the characteristics of the new culture, and they had difficulties expressing themselves in many areas, especially due to the language barrier. Besides, some of the participants with the health services, experienced discrimination from employees, patients and their relatives, and it has been observed that this situation has become a source of concern for individuals and causes disruptions in healthcare procurement. Participants have been observed to mostly prefer the separation strategy more than other acculturation strategies. Traumas and negative experiences throughout the migration process; situations such as cultural conflict with the host society in the process of acculturation, mutual prejudices, insufficient social support, loss of social status; Caused the immigrants to face with psychological risk factors like post-traumatic stress disorder, difficulties with coping and burnout. These risk factors have caused changes in the family dynamics of individuals and resulted in violence within the family. It has been faced with situations such as children who need education have to work at an early age and children have to be in the role of parents due to the losses they experience. Participants who claim to have encountered these experiences, especially the ones who preferred seperation strategy, reported perception of good health before migration. Yet, due to the fact that they encountered many of these risk factors after migration, it became increasingly hard to sustain good health and it turned into perception of bad health.

This study may contribute to the completion of gaps in studies in the field of migration and health and also when it comes to planning of different studies. It can strengthen scientific data with qualitative and quantitative approaches carried out in the field of nursing. The main factor in the failure of Syrian asylum seekers communicating with other cultures and the decrease in their communication is the language barrier. The

language barrier, which is not a risk factor to neglect, is negatively affecting social life and access to services such as health and education. With the language courses organized by experts in the field and trained translators working in those services (health institutions, etc.), the negative effects on the physical and mental health of the individuals would be eliminated. Programs built for better mutual communication of ethnic groups, provision of better Access to information and/or programs alleviating the pressure on individuals and making the life easier for them, will undoubtedly maket he acculturation process go smoother. With health service providers, the role of nurses is especially important, who are in contact with people all the time. Awareness of different cultures for nurses should be increased, studies should be carried out on this subject and nursing care suitable for different cultures should be provided. For this reason, it is necessary to revize the education and consultancy services in the field of health. In order to plan appropriate trainings, it is important to enrich the literature on the field and to increase the competencies of health workers in this regard. In nursing, which is the group that has the most direct contact with asylum seekers in health institutions, it should be a priority to include these issues in the education program in university regarding intercultural nursing care as well as planning in-service training on the subject.

Limitations: Although the researcher knew the language well, the interviews in Arabic were conducted with the help of a translator in order to understand the concepts specific to culture correctly. Because of the prohibition to take voice recording by the order of İzmir Provincial Directorate of Migration Management, no voice was recorded in the interviews conducted inside the institution and they were carried out with the presence of two translators, as well as taking notes in detail. Because of the limited conditions in the office, (telephone, traffic of consulters etc.) the interview was done in an available time in terms of intensity.

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ORIGINAL ARTICLE

Prevalence, symptom and severity of COVID 19 among permanent residents of Dhaka City

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Abstract

A study was done on 385 people who survived from COVID 19 to assess the prevalence, symptom, and severity of COVID 19 of permanent residents of Dhaka city, Bangladesh during the second wave of corona manifestation. Data were collected purposively from a government and a private hospital, and general people taking treatment from home. A significant number of respondents took treatment from the Hospital during 2nd wave of COVID 19. Two-third of participants endured moderate (67.5%) type of suffering followed by mild (18.7%) and severe (13.8%) type of suffering. Most of the participants were married (88.8%) and female (51.2%). There was no significant difference between females and males suffering and the risk and severity of COVID 19 (p=694). Most of the participants (70%) had comorbidity. Time to recover from symptoms had significant relation with symptom patterns. One-third of the respondents (33%) required 4-7 days to recover from suffering. A little higher than a quarter (27.8%) recovered within 8 to 14 days and more than a quarter 105 (27.3%) recovered by 8-12 days respectively. Most of the respondents had a fever, cough, body ache and fatigue, sore throat, and breathing difficulty. Only (7.3%) had diarrhea (3.9%) and smell loss 13 (3.4%). People of permanent residence of Dhaka city suffered from COVID 19 irrespective of sex, education, professional status. They had comorbidity, required 8-14 days of hospitalization, and endured the moderate type of suffering of COVID-19.

Keywords: COVID 19 pandemic, situation of COVID 19, second wave, Dhaka city, Bangladesh

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Introduction

COVID 19 has affected 188 countries in the world. The cases of novel virus 2019-nCoV, latter known as COVID 19 was detected in Wuhan China, and first reported on December 31 when people are suffering from severe acute respiratory syndrome-like SARS-CoV outbreak [1]. Almost within a month, by 24th January the disease was spreading to a global level and the burden of risk and death was increasing in the United States, Europe, Thailand, Japan, South Korea, Singapore, Vietnam, Taiwan, and Nepal [2]. Dr. Tedros Adhanom Ghebreyesus, Director-General of the World Health Organization (WHO) declared COVID 19 pandemic on March 11, 2020 [3]. Bangladesh published its first case of COVID 19 on March 8, 2020, who returned from Italy [4]. Then Bangladesh experienced a disease burden of 1,580,750 infected patients; deaths toll 28,043 respectively reporting till 17 December at 9 pm [5].

Report from Bangladesh was found that male was predominate to COVID 19 infection [6,7]. The government of Bangladesh also reported that the prevalence of COVID 19 among males are higher than females [8]. However, elsewhere report found that there was no significant difference between males and females in risk and severity of COVID 19 [9].

The elderly, hypertension, and diabetes have shown a worse prognosis of COVID 19. The report showed that diabetes had a link to more hospitalization and intensive care unit (ICU) admissions [10]. A high number of hospitalizations, intensive care, and ventilation support was found among the patients with asthma and COPD as well in Turkey [11]. The most common comorbidities of COVID patients were hypertension (56.6%), obesity (41.7%), and diabetes (33.8%) respectively in the USA [12]. However, hypertension was more common comorbidity in COVID 19 followed by asthma, chronic kidney diseases, and diabetes from Bangladesh [7]. The prevalence rate of diabetes, hypertension, and cardiovascular disease (CVD) in COVID 19 patients varied in different country-specific data [13,14]. Moreover, no research has yet been done on time required for hospital stay during being infected by COVID 19.

Many of the studies were done on Bangladesh from specific hotspots or specific districts of Bangladesh. No report has yet been identified between the permanent residents of Dhaka city with risk and severity of COVID 19 those who reside with high hygiene, lighter population density, and a higher sense of physical and medical security at least theoretical term. This article tried to highlight the relation between gender, education, professional level, hospital stay, and the symptom and severity of COVID 19 in permanent residents of Dhaka city during the second wave of corona manifestation.

Materials and Methods

A retrospective cross-sectional study was done on 385 people, who survived from COVID 19 during the second wave of the corona, aged between 18 years and above to assess the prevalence, symptom, and severity of COVID 19 in permanent residents of Dhaka city, Bangladesh. Data were collected purposively according to the selection criteria, using a self-administered structured questionnaire from the Corona unit of a private (Shahabuddin Medical College Hospital), a government (Dhaka Medical College Hospital), and general people taking treatment at home. COVID 19 positive people confirmed by RT-PCR were recruited in this study. The risk and severity of COVID 19 were divided into three groups according to stay of hospital e.g. mild (4-7 days), moderate (8-14 days), and severe (16-21 days).

Informed consent was obtained from the participants after getting ethical clearance from the National Research Ethics Committee (NREC) of Bangladesh Medical Research Council (BMRC). To assure anonymity, no names or identifying information was included in the self-administered

questionnaire and the report. Participants had the right to refuse to respond to any question or withdraw from the study at any time.

Data were analyzed by using SPSS version 25.0 software IBM 2021, where marginal error-5%, CI-95%, and response distribution-50%. Demographic and other variables were analyzed by frequency and percentage distribution. The Chi-square test (x2 test) was done for the comparison mean. A $p < 0.05$ was considered statistically significant.

Results

Demography

The mean age ±SD of the respondents was 48.91 ±.15.57 range from 18 to 87 years of age. There were 197 (51.2%) females and 187 (48.6%) males among 385 respondents. There were 342 (88.8%) married, 30 (7.8%) unmarried and 13 (3.8%) widow respectively (Table 1). Most of them (70%) were educated where more than one third was graduate 152 (39.5%) from university and a little more than a quarter 119 (30.9%) had a postgraduate degree (Table 2). The profession of the participants was varied. Most of them were housewives 163 (42.3) followed by Business 52 (13.5%), private service 48 (12.5%) and Government service 44 (11.4%) and self-employed 44 (10.9%) respectively (Table 2). Most of the respondents had no income 190 (49.4%). More than a quarter 133 (34.7%) had income between 25-50 thousand, one-tenth 38 (9.9%) had income between 50 thousand to 1 lac and 11 (2%) had more than 1 lac respectively. Only 13 (3.8%) had income less than 25 thousand (Table 2).

Health condition before being infected by COVID 19

Before corona infection most of the respondents had comorbidity. Comorbidities had significant relationships with the risk and severity of COVID 19 (p=.000). More than a quarter had the pulmonary problem (Asthma-110 (28.6%), Diabetes 74 (19.2%), Hypertension 30 (7.8%) respectively. Diabetes was common in multiple comorbidities. Diabetes with hypertension 33 (8.6%), diabetes, hypertension with a history of surgery 10 (2.6%), and diabetes with hyperthyroidism 2 (0.5%) respectively. Some did not have any problem 88 (22.9%) at all (Figure 1). Only a quarter 100 (26%) were on the hypertensive drug.

Table 1. Socio-demographic characteristics of the respondents (n=385)

Variable	Range	Value (Percentage)	Remark
Age	Minimum	18	Mean ± SD 48.91 ±.15.57
	Maximum	87	
Sex	Female	197 (51.2%)	
	Male	187 (48.6%)	
Marital Status	Married	342 (88.8%)	
	Unmarried	30 (7.8 %)	
	Widow	13 (3.8%)	
Income	No income	190 (49.4%)	
	25-50 thousand	133 (34.7%)	
	50 thousand - 1 lac	38 (9.9%)	
	> 1 lac	11 (2%)	
	<25 thousand	13 (3.8%)	

Health condition during being infected COVID 19

More than half of the respondents 260 (67.5%) had moderate symptoms during COVID 19 infection. Of 62 (18.7%) had mild symptoms and 55 (13.8%) had severe symptoms during the corona pandemic (Table 2). In our study females suffered a little more moderate and severe form symptom than males. But there was no significant difference in risk and severity of COVID 19 between males and females (P=694) (Table 2). A significant number of respondents took treatment from Hospital during the 2nd wave of COVID 19 (p=.000). More than a half of respondents 247 (64.2%) were hospitalized and more than a quarter 138 (35.8) took medicine staying at home (Table 2). Time to recover from symptoms had significant relation with symptom pattern (p=.000). Most of the respondents 127 (33%) required 4-7 days to recover. More than quarter 107 (27.8%) recovered within 12 to 14 days and more than a quarter 105 (27.3%) recovered by 8-12 days respectively (Table 2). Table 3 showed the symptom during COVID 19. Most of the respondents had a fever, cough, body ache and fatigue, sore throat, and breathing difficulty. Only 28 (7.3%) had diarrhea 15 (3.9%) and smell loss 13 (3.4%) (Table 3).

Discussion

Demography: In our study, the maximum participants were females (51.2%) and housewives (42.3%). Research by Nazneen et al (2020) had also more female participants than males [6]. Females are easily approachable to ask a question and are more altruistic than males may be the cause of the more female respondents in our study [15]. In our study, there was no significant difference between males and females in risk and severity of COVID 19 which is consistent with the result of Jin et al. (2020) [9]. However, the Government of Bangladesh database shows that the prevalence of COVID 19 among males are higher than females [8]. WHO also said that males are infected more than females and males are higher than females in all death reporting [16]. Jin et al said that there was no difference between susceptibility of COVID 19 in males and females though men may have sought more care than females and males might have sought more care in the Government reporting system [9].

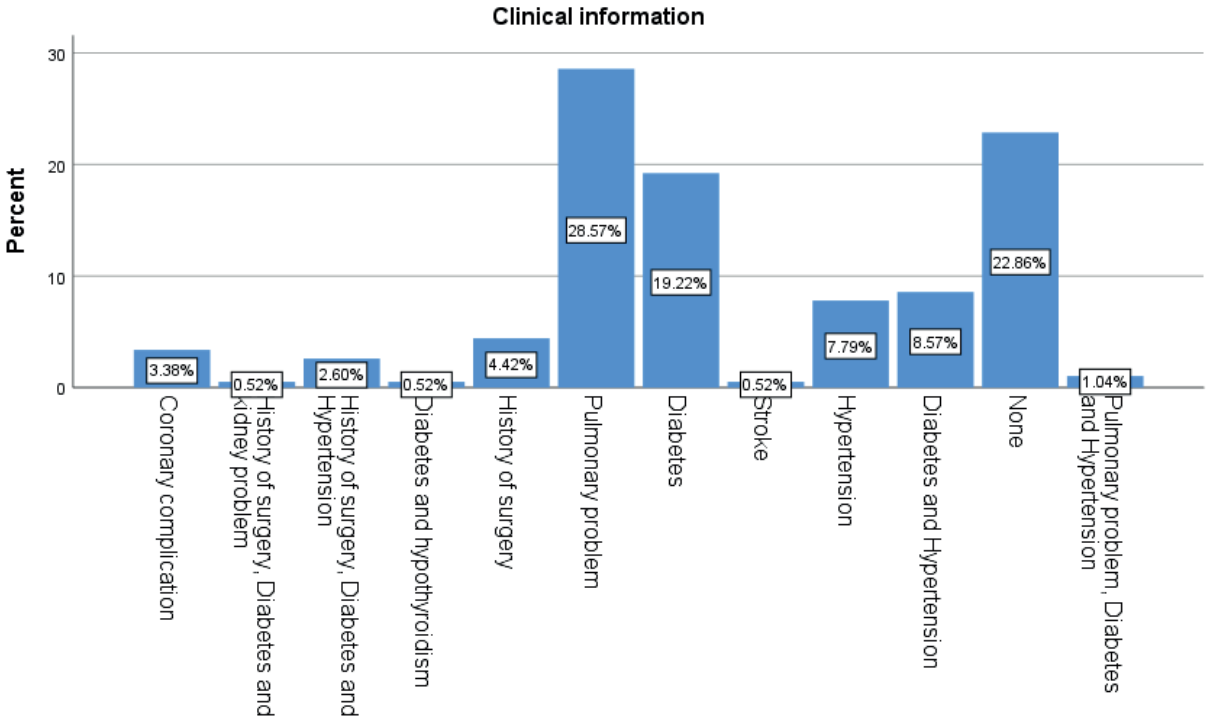

Figure 1. Clinical information of the respondents before infected by COVID 19 (n=385)

In our study, the majority of the participants were married (88.8%) and almost three-quarters were educated (70.4%). Most of them were graduates and above. Our research was done in a capital city-based setting may be the result of a higher educated population. In our research, almost half (49.4%) had no income. According to the social culture of Bangladesh, the housewife had no personal income as they usually lived on and were maintained by husbands. In addition, students, retired persons, and unemployed participants did not have a monthly salary.

Table 2. Health condition during COVID 19 (n=385)

Item	Specification	Mild	Moderate	Severe	Total/Percentage	*p*
Symptom pattern	-	72 (18.7%)	260 (67.5%)	53 (13.8%)	-	-
Gender* Symptom pattern Cross tabulation	Female	34	134	29	197 (51.2%)	0.694
	Male	38	126	24	187 (48.6%)	
Education* Symptom pattern Cross tabulation	Graduation	31	105	16	152 (39.5%)	0.144
	Post-graduation	25	81	13	119 (30.9%)	
	Secondary School Certificate (SSC)	16	72	24	2 (0.5%)	
	Below class ten	0	2	0	112 (29.1%)	
Profession* Symptom pattern Cross tabulation	House wife	26	111	26	163 (42.3%)	0.334
	Business	8	37	7	52 (13.5%)	
	Self-employed	11	27	4	42 (10.9%)	
	Private Service	14	30	4	48 (12.5 %)	
	Government Service	8	31	5	44 (11.4%)	
	Student	2	8	3	13 (3.4%)	
	Retired	2	10	4	16 (4.2%)	
	Rikshaw puller	0	6	0	6 (1.6%)	
	Unemployed	1	0	0	1 (0.3%)	
Place of taking treatment* Symptom pattern cross tabulation	Home	52	86		138 (35.8%)	0.000
	Hospital	20	174	53	247 (64.2%)	
Time to recover from symptoms* Symptom pattern cross tabulation	2 to 3 days	3	7	0	10 (2.6%)	0.000
	4 to 7 days	35	90	2	127 (33%)	
	8 to 12 days	21	73	11	105 (27.3%)	
	12 to 14 days	8	73	26	107 (27.8%)	
	15 to 21 days	5	17	14	36 (9.4%)	

Table 3. Symptom of the despondence during COVID 19 (n=385)

Symptom during COVID 19	Total / Percentage
Fever	16 (4.2%)
Fever, body ach and fatigue	13 (3.4%)
Fever, cough, body ach and fatigue	93 (24.2%)
Fever, cough and fatigue	44 (11.4%)
Cough and sore throat	5 (1.3%)
Fever and loss of smell	13 (3.4%)
Fever, cough and breathing difficulty	14 (3.6%)
Fever, cough, body ach and diarhoea	43 (11.2%)
Fever, cough, sore throat, body ach and fatigue	34 (8.8%)
Fever, cough, body ach and sore throat	40 (10.4%)
Fever and headache	1 (0.3%)
Cough	2 (0.5%)
Fever, cough and headache	3 (0.8%)
Fever and chest pain	2 (0.5%)
Fever and cough	30 (7.8%)
Fever and body ach	12 (3.1%)
Fever and fatigue	20 (5.2%)

In our study, we did not find any significant relationship between education, profession, and severity of COVID 19. No research has been found yet on the permanent residence of the capital city to compare our result.

Health condition before COVID infection: In our study, most of the respondents (77.1%) who were infected by COVID 19 had several comorbidities. Most of them had respiratory disease (28.6%), followed by diabetes (19.2%) and hypertension (7.8%) respectively. But rest had multiple comorbidities where diabetes was common (Figure 1). However, another study from Bangladesh showed that hypertension was more common comorbidity followed by asthma, chronic kidney diseases, and diabetes [7] and elsewhere in the world [13,14]. Most of our study population were urban, females and housewives may be the result of higher asthma followed by endocrine disease. Urban people use LPG gas for cooking causing asthma [17]. Literature also showed that asthma and Type 2 DM are two common chronic conditions of increasing prevalence and that often coexist in the same patient may be the result of higher asthma followed by endocrine in our study [18]. Some said that there was a relationship between asthma on diabetes but not significant, except for in patients with severe asthma [19].

Health condition during COVID infection: In our study, most of the respondents had several comorbidities before being infected with COVID 19. Therefore, a significant number of respondents need hospital treatment that increases the burden of government during 2nd wave of the corona. The report said that elderly, hypertension, and diabetes had a worse prognosis of COVID 19, and diabetes had been linked to more hospitalization and intensive care unit (ICU) admissions [10]. Our result was consistent with this result. Therefore, in our study, time to recover from COVID symptoms had significant relation with symptom patterns. As most of the respondents had comorbidity, they present moderate types of symptoms. The majority of the respondents 212 (54.1%) required 8-14 days to recover, where more than quarter 107 (27.8%) recovered within 12 to 14 days and more than a quarter 105 (27.3%) recovered by 8-12 days respectively. Most of the respondents had a fever, cough, body ache and fatigue, and sore throat. Hossain et al found that the most common symptom was fever followed by dry cough (60.5%), shortness of breath (52.3%), fatigue (43.7%) and sore throat (36.0%) diarrhea (49.2%), and alteration of consciousness (25%) [7]. We did not check the separate entity of symptom rather consider the combination of symptom

patterns the respondent had. However, our study was consistent with the study of Hossain et al [7].

Limitation: There were certain limitations in the present study. The research was questionnaire-based and hence the results relied upon the reply of participants received. All the questions have not been explored to the same extent. However, this study was done at Dhaka city only and data were collected from one private, one Government hospital, and permanent city dwellers. Furthermore, most of the participants were female, this may also have had subject to gender bias. Hence it needs to be validated by further study with a larger sample size in Bangladesh shortly.

Conclusion

People of permanent residence of Dhaka city suffered from COVID 19 irrespective of sex, education, professional status. Most of the participants had comorbidity, required 8-14 days of hospitalization, and endured the moderate type of suffering of COVID-19. Fever, cough, body ache and fatigue, and sore throat were the common symptoms during COVID 19. ***Recommendations:*** The general population needs public health education and awareness on non-communicable diseases to reduce being infected with COVID 19 and any other disease in the future that lessen the burden on health care.

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Conflict of interest

Authors declared no conflict of interest.

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Bionic construction of the human body in the light of the slippery slope argument

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Abstract

Composite tissue transplantation has gained a new dimension in line with advanced technological developments. In extremity losses, the traditionally implemented procedure is to enable the extremity to regain its functionality through replantation instead of transplantation. On the other hand, innovative studies are also carried out to support and strengthen the human body and improve the problematic body functions for increasing patients' quality of life. Studies on developing biomechatronic systems, which are related to biology, neurology, biophysics, mechanics, biomedical and tissue engineering, electronics, and computer sciences, are in progress, which indicates that a transformation has occurred in the approaches to composite tissue transplantation. This study aims to generate ideas about determining a conventional limit in the interventions towards the human body against the technological and scientific developments and to perform a value analysis on such interventions. This study was designed within the framework of the methodology of medical ethics and in the light of the slippery slope argument. The process of transformation from the medical procedures that aim to protect patients' bodily integrity to the innovative practices that provide an opportunity to bionically turn healthy human bodies into the half machine and half-human is investigated in the light of the slippery slope argument. This study indicated that the value-related problems regarding this issue are related to the principles of respect for autonomy, beneficence, non-maleficence, and justice. The limit to be determined for the practices that aim to protect the patients' bodily integrity and increase their quality of life and that are not life-saving depends on the distinction between an ill body and a healthy body. A meticulous clinical perspective and legislative regulations that prevent the instrumentalization of humans are required so as not to roll down to undesirable places on a slope. Advanced technological developments are implemented in medicine, protecting human dignity should be adopted as a fundamental value.

Keywords: Medical ethics, slippery slope argument, bionic construction

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Introduction

When people's bodily integrity is impaired and severe extremity losses occur causing a dysfunction, composite tissue transplantation is performed [1]. Such practices aim to reshape the body, enable the limbs to gain functionality, and increase patients' quality of life. Throughout history, people have always tried to eliminate bodily defects using the limited information they have had and to develop means to replace the lost extremities. A tool made of leather and wood was found on a mummy's big toe during the archaeological excavations, which shows that the first examples of prostheses date back to the Ancient Egypt [2]. Iron hand prostheses were used by high-rank soldiers who lost their extremities during a war [3]. Prostheses are also seen in the written works of Ambroise Pare (1510-1590). Pare designed mechanic extremities working through latches and springs to help soldiers whose bodily integrity was impaired [4]. In the following centuries, more competent tools were developed and commonly used along with technological developments.

Composite tissue transplantation has gained a new dimension in line with advanced technological developments. In extremity losses, the traditionally implemented procedure is to enable the extremity to regain its functionality through replantation instead of transplantation. Both transplantation and replantation have severe medical risks; however, trying to regain the patients' own extremities is accepted as the golden standard as there is no need for an immunosuppressive therapy [1]. When this condition cannot be met, replantation is applied. First transplantation was performed on September 23, 1998 in Lyon, France; one hand was transplanted from a 41-year-old brain-dead donor to a 48-year-old patient [5]. Although this transplantation was not supported by all hand surgeons, it was evaluated as a step towards a better medical treatment within the medical field and society [6]. The composite tissue transplantations, which started with hand transplantations in the world, was first performed in Turkey in Akdeniz University, Faculty of Medicine in 2010 with a double arm transplantation from a cadaver [7]. Lower and upper extremity and face transplants are successfully performed both in Western countries and Turkey considering legal norms and ethical principles [6,8].

Innovative studies are carried out to support and strengthen the human body and improve the problematic body functions using technological opportunities [9]. For example, a problem that occur in the case of a dysfunction in hand is related not only to the bodily integrity and also to the central nervous systems (CNS) [10]. Therefore, interdisciplinary studies must be conducted. Studies on developing biomechatronic systems, which is related to biology, neurology, biophysics, mechanics, biomedical and tissue engineering, electronics, and computer sciences, are in progress, which indicates that a transformation has occurred in the approaches to composite tissue transplantation.

The studies carried out on loss of extremities in innovative surgery and engineering today suggest that an unprecedented connection can be established between the human body and machines. Bodily integrity can be ensured through bionic extremities, robotic prostheses, osseointegrated implants, and basic mechanical connections. An extremity developed for this purpose functions as a designed means and offers an opportunity to increase the performance of a human body. For example, it is now possible that a mountaineer who has lost his/her lower extremities has crampon feet that he/she can use during a mountain climbing [11]. Here, the body is redesigned and the body is indicated to be a formable identity [12]. Such an intervention in human body is called as the bionic reconstruction of human body, i.e. *homo silicium* [12]. It is remarkable that a higher number of reports are being submitted on the practices regarding the bionic reconstruction of the human body today [13,14]. This study aims to generate ideas about determining a conventional limit in terms of ethics and laws for the interventions targeting the protection of the integrity of the human body using technological opportunities and to perform a value analysis on such procedures.

Materials and Methods

In this study, which was designed within the framework of the methodology of medical ethics, the bionic transformation of human body is discussed in the light of the slippery slope argument. The slippery slope argument is frequently used in the field of medical ethics for the critical evaluation of the decisions regarding the beginning and end of life [15-17], fair allocation of limited resources, the transplantation-related issues [18,19]. In composite tissue transplantation, some of the opportunities offered by advanced technological developments may include practices that can serve to reconstruct human body. The slippery slope argument was selected in this study because it allows the discussion of the ethical problems that may arise from the fact that the steps taken during the transition from transplantation and replantation to innovative practices, i.e. the construction of human body using technological means, in composite transplantation may lead to the transformation of humans into machines.

The slippery slope argument is also called by the metaphors such as *thin edge of the wedge*, *camel's nose*, and *open the floodgates* [20]. The fact that an action leads to other actions and that the results obtained by the new actions are unwanted or considered to be unacceptable means that innovative steps are not taken. A new practice should be restricted at a point to avoid obtaining a negative result or to prevent the occurrence of something bad, even if this new practice is not actually bad [21]. This point should be a conventional limit determined to avoid rolling down to undesirable places on a slope.

The slippery slope argument may be logical or causal according to the reasons of moving towards an undesirable process [21,22]. Since the acceptances regarding a phenomenon on the peak (P-0) of the slope in the current position under our control are not universally true, transition to a new position can be recommended. This new position, e.g. Position A, may frequently, if not necessarily, include the legislative regulations regarding a phenomenon. Emergence of the Position A is important; this position is not actually bad as it may include the moral values that were discussed in terms of ethics or agreed upon. The Position A can be a position which is considered to be generally good, accepted as good by the addressees of the relevant phenomenon, or accepted to be neither good nor bad. Even though a practice to be carried out on the Position A seems innocent now, it may lead to the logical acceptance of many other positions that will yield unpredictable and undesirable results. This is because the other positions to be adopted after the Position A are based on the previous position and a logical slippery slope emerges between the adopted new positions. Thus, the Position A requires the logical acceptance of the Position B, C, or even though it is undesirable, the Position N [23]. The presence of a causal connection rather than a logical connection between the positions looks differently on the slope: An action taken considering that it will yield positive results may lead to the emergence of other actions that cannot be refused and introduce a new position [22]. The emergence of new positions connected to each other with causal connections cannot be objected and each new position may lead to the emergence of other positions connected to each other with logical connections.

Results

The legislative regulations regarding composite tissue transplantation in Turkey

The Constitution of the Republic of Turkey includes the following statements: "the individual's right to life, the integrity of his/her corporeal and spiritual existence shall be inviolable" (Article 15); "Everyone has the right to life and the right to protect and improve his/her corporeal and spiritual existence. The corporeal integrity of the individual shall not be violated except under medical necessity and in cases prescribed by law; and shall not be subjected to scientific or medical experiments without his/her consent" (Article 17), and "Everyone has the right to live in a healthy and balanced environment. The State shall regulate central planning and functioning of the health services to ensure that everyone leads a healthy life physically and mentally, and provide cooperation by saving and increasing productivity in human and material resources." (Article 56) [24]. These articles in

the Constitution, which come to the forefront in respect of individuals' right to health and life, are evaluated within the scope of "individuals' self-realization right" by the Turkish Medical Association [1].

On the other hand, "the Law on the Harvesting, Storage, Grafting, and Transplantation of Organs and Tissues" published on May 29, 1979 in the Official Gazette involves regulations regarding the harvesting, storage, grafting, and transplantation of organs and tissues [25]. The Regulation on Organ and Tissue Transplantation Services published on 1 February, 2012 in the Official Gazette was created to determine the procedures and principles to be followed in the implementation of organ and tissue transplantation services by opening, running, and supervising organ and tissue transplantation centers, organ and tissue source centers, and tissue typing centers where the transplantations to enable the patients to maintain their lives when their treatment is possible through tissue or organ transplantation [26].

The Composite Tissue Centers Directive published by the Ministry of Health includes information on how to make medical decisions on transplantation [8]. The Directive also explains the composite transplantation types and indications and presents a list of the indications regarding extremity transplantation [8]. Pursuant to the Directive, the Composite Tissue Transplant Scientific Advisory Commission is responsible for evaluating the transplantations in terms of indications and discussing on the exceptional cases where no decisions can be made according to the indications list. In addition, a Composite Tissue Transplantation Council including a medical ethics expert should be established in the hospitals with a Composite Tissue Center. It is indicated that transplantation can be performed for the patients approved by the Council and that the transplantation procedure, its results, and the Council decisions should be reported to the Ministry.

The Convention for the Protection of Human Rights and Human Dignity in Terms of the Implementation of Biology and Medicine: The Law on the Approval of Human Rights and Biomedicine Convention, which entered into effect by being published in the Official Gazette in Turkey, stipulates that the parties of the convention shall be responsible for the protection of all individuals' identity and dignity and guaranteeing that every individual, their integrity, and other fundamental rights and liberties are respected without any discrimination during the biological and medical practices [27]. The Convention also stipulates that the human body and its parts cannot be a subject of making commercial profits (Article 21) and that when any part of a human body is removed during an intervention, this part can be stored and used for a purpose other than the purpose of its removal only provided that the relevant information and obtaining consent procedures are followed (Article 22).

Ethical issues regarding composite tissue transplantation

It is accepted that whether composite tissue transplantation will be performed for a patient can be decided after all treatment options run out [1]. Therefore, patients' physical appearance itself is insufficient for performing such a practice; the practice should also aim to eliminate severe function losses in the extremity in question [1]. It should also be noted that composite tissue transplantation is not life-saving and the receivers will use immunosuppressive drugs and be subject to the complications and adverse effects due to these drugs throughout their life [8]. Moreover, before the transplantation, the candidate receivers of the composite tissue or their legal representatives must declare in writing that they are not satisfied although they used other existing alternatives such as mechanic and myoelectrical prosthesis or orthosis or despite the surgeries performed to fix the loss of tissue or organ [8]. The transplantation requests made by the patients who meet these criteria are evaluated within the scope of the right to health, and the accessibility and usability of this right are among the responsibilities of the state [1]. For the last 20 years, the ethical issues regarding composite tissue transplantation have been evaluated under the following titles considering human existence, dignity, and integrity [1,28,29].

***Respect for Autonomy*:** In medical ethics, respect for autonomy means that individuals make decisions about themselves based on their own values [30]. Whether this principle is complied with in a medical practice depends on the implementation of a valid informed consent process. In Turkey, the informed consent process in composite tissue transplantation continues for a long period of time and involves the investigation of any changes in the individuals' decisions. Unlike the informed consent obtained for other medical practices, consent is obtained before the transplantation to assess the patients' suitability for transplantation [8]. This consent includes the information that the patients will be in contact with the healthcare personnel and participate in the procedures assessing their suitability for transplantation with their free will, and that the success of the non-life-saving transplantation to be performed to increase the quality of life cannot be guaranteed. It also includes the information that rehabilitation may be needed after the transplantation and complications that can risk the patients' life can develop depending on the medication. In addition, it includes the preoperative interviews, explanations regarding the suitability evaluation procedures including psychiatric, hematological, microbiological, ethical, and legal evaluations, and the information that another consent will be obtained in the case that such evaluations require interventional routine procedures.

Other than the consent obtained from the patients subjected to preliminary evaluation, another consent is obtained before the practice aiming to increase the quality of life [8]. This consent includes the information that the patients will undergo a practice which is only on the onset around the world and that the following treatment can somewhat be evaluated as an experimental project. It is stated that the practice to be permitted by the patients is not life-saving. Interviews are carried out on the alternative practices, primarily including biomechanical prosthetics, which are previously known by the patients but is still reminded to them. The patients must report that they find biomechanical prostheses impractical and inappropriate for them although they already tried them repeatedly. The informed consent form was prepared with the following titles: social, economic, and business practices; surgical operation and direct complications; anesthesia; postoperative follow-up; privacy; confrontation; and ethics. The patients must express their request for the recovery and reduction of their defect with their strong will.

***Beneficence*:** In medical ethics, beneficence means doctors' duty to do their best to contribute to their patients' well-being [30]. Unlike the other principles of medical ethics, the principle of beneficence highlights the importance of the fact that when there is a benefit, patients should primarily take advantage of it [30]. Paying regard to the benefit-harm balance in composite transplantation is closely related to the effort to provide benefits to the patients. In this regard, it is accepted that effort should be made to minimize the risk that the patients will take, the risk should not exceed the benefits provided to the patients, and human health and well-being should be protected [31].

***Non-maleficence*:** In medical ethics, non-maleficence means that doctors should avoid causing damage to their patients [30]. While damage may occur when a doctor carries out a practice, it may also occur when a doctor does not carry out a practice considered to be useful to his/her patient [30]. As in the principle of beneficence, benefit-harm balance is also sought before, during and after composite tissue transplantation in the principle of non-maleficence. In the Turkish Bioethics Association's Statement on the Organ Transplantation and Ethics, it is accepted that practices related to composite tissue transplantation, which increases the quality of human life, should be avoided in the cases where the risk exposed by the patients is higher than the benefits they will take advantage of [31]. It is also stated that the success of the practice depends on the postoperative medical care, whether the body accepts the tissue, and as in the lower and upper extremity transplantation, the organs' gain of function. In this regard, the accepted approach is to avoid the practices with high risks [31].

***Justice*:** In medical ethics, the principle of justice means that no random discrimination will be made against anyone during the allocation of the fundamental rights and duties, social benefits, and burdens [30]. Particularly when the fair allocation of limited resources is in question as in composite tissue transplantation, the Central Organ Coordination system is accepted to be an appropriate solution [31]. In this context, the approach that can be ethically justified is to prioritize the patients in the most urgent and highest level of need according to the order of priority in patients list [31]. In addition, World Medical Association indicates that the surgical techniques developed today increase the success rates in transplantations and highlights the importance of several principles including equality and justice in terms of maintaining the ethical standards [32].

In connection with the above-mentioned fundamental principles of medical ethics, the relevant literature shows respecting the patients' privacy and private life, maintaining medical confidentiality, taking religious and cultural sensitivities into consideration, having realistic expectations from the practice, informing the public, planning the process transparently and in a way to allow investigation, and the size and length of the extremity as the other principles that should be considered [32].

Discussion

In the slippery slope argument, it is difficult to prevent the logically connected practices from being accepted one after each other. A conventional limit is needed between over restricting and unconditionally allowing the composite tissue transplantation and the adaptation of advanced technological practices to medicine. A discussion should be made on the practices to be allowed during the transition from traditional practices to the innovative practices offered by advanced technological developments so as not to roll down to undesirable places on the slope.

The first definitions of the concept of health throughout history include "health, physical well-being and competency" and "the fact that an organism functions well as a whole and uses the resources of the living body at the maximum level" [30]. Health was defined as the physical, mental, and social well-being of the World Health Organization; however, its meaning has expanded over time. As generally accepted, the purpose of medicine is to eliminate the patients' pain and heal and recover them. In line with the concept of health and the purpose of medicine, the composite tissue transplantation is defined as "the composite tissue transplantation which is performed for the restoration of form and function in patients with composite tissue loss that impairs their bodily integrity and causes loss of function and which aims to increase their quality of life" [8]. This definition clearly shows the aim and potential benefits of composite tissue transplantation from a clinical perspective. It should be noted that the concept of restoration in this definition emphasizes "repairing" the human body. Here, repairing the human body means ensuring the bodily integrity and regaining health. However, repairing a body (completing an incomplete body) also includes healing that body (in terms of medicine and competency). Thus, if this situation is not limited, construction of the human body will be possible because repairing a body can introduce practices that allow strengthening the functionality of the extremities of a healthy human body in the case of moving away from clinical purposes.

The presence of the above-mentioned possibility does not require the prevention of the innovative studies that require composite tissue transplantation to increase the quality of life and that aim to enable the extremities to gain functionality. On the contrary, it reminds us that clinical purposes should be adhered to. In medical practices, the opportunities offered by advanced technology should be utilized in line with clinical purposes.

In composite tissue transplantation, the peak of the slope is a position where ethical and legal consensus is reached. Moving away from this position is possible because the constant improvement of scientific information in addition to replantation, which is accepted as the golden standard today, inevitably leads to a

change in the practices. The indications list for composite tissue transplantation is reviewed by adding new transplantation types. Thus, staying away from the practices beneficial to the patients to avoid the negative situations that may arise prevents scientific developments. Such an attitude cannot be ethically accepted. Therefore, addition of the transplantation types that are not currently included in the indications list will pave the way for the transition to new positions. The transition from the current position to a more controversial position will probably be accepted with a sufficient and valid justification such as protecting bodily integrity. This new position will also change after a while in line with the new decisions to be made. In the last accepted position, removable body extremities with increased functions and different characteristics and in different appearances can contribute to the transformation of the human body into a demountable image. While rolling down on the slope, the human body can transform into a half-human and half-machine creature and new characteristics may lead to its use through instrumentalization.

The slippery slope arguments regarding composite tissue transplantation include the following:

Argument-0: Medical opportunities should be used to protect a patient's bodily integrity.

In the case that a patient with a lost extremity gives consent, protection of bodily integrity is the patient's right and the peak of the slope today. The Turkish Medical Association accepts that composite tissue transplantation is related to the right to life and health and interprets such practices within the scope of self-realization [1]. The aims of composite tissue transplantation include enabling the patients to get involved in life and maintain their lives without needing others' help. A legal limit was determined for lower and upper extremity transplantations based on the Composite Tissue Transplantation Indication List in Turkey. The guides on indications and contraindication are updated in line with scientific information. Therefore, addition of the transplantation types other than lower-upper extremity and face transplants, which are successfully implemented today, to the indications list will change the opinions on the Argument-0. In this regard, making new decisions to increase patients' quality of life may be required.

Argument-I: Innovative medical opportunities should be used to protect a patient's bodily integrity.

Medicine is liable to eliminate a defect, in other words, an undesirable situation, using the opportunities offered by technology [33]. However, it is generally accepted that doctors do not have to do everything that is technologically possible [34]. The possibility of a damage during the implementation of advanced technology in medicine should not prevent the use of the advantages of technology. Here, it should be noted that Argument-0 is not an absolute position and it can be criticized, changed, or improved. Difficult cases which are not currently included in the indications guide or where the risk-damage balance of the practice cannot be accurately evaluated even if they are included in the guide may lead to a change in the existing practices at the peak of the slope. On the other hand, it is expressed that transplantation should be the last method to be used and it is not appropriate to perform it to eliminate an aesthetic problem [1]. It is important to move away from the aim of eliminate a health problem or a severe loss of function in the body; otherwise, the way would be paved for some experimental practices. Innovative surgical practices are also supported by engineering. If robotic prostheses and/or osseointegrated implants contribute to increasing patients' quality of life compared to traditional prostheses, their use should be supported. In addition, considering the high number of patients waiting for a composite tissue transplantation and the low number of donors, using technological means may provide many advantages to the patients; primarily time. Today, the advantages and disadvantages of extremity transplantations and prostheses are being reported based on the patients' experiences [35, 36]. The Argument-I can contribute to a transformation in medical services even if it is not considered to be bad itself. Medicine can

transform into a service that supports recovering the body within the existing opportunities and/or aesthetically shaping the body in addition to eliminating a bodily defect.

Argument-II: Innovative medical opportunities should be used to increase a patient's body performance.

Acceptance of the Argument-I always means that the Argument-II will also be accepted. Protecting bodily integrity and increasing body performance are different phenomena. The Argument-I aims at obtaining positive results but it also generates a new phenomenon such as the Argument-II. In this case, a causal connection is established between the Argument-I and the Argument-II according to the slippery slope argument; presence of the Argument-I leads to the emergence of the Argument-II. The innovative studies carried out on loss of extremities today indicate that an unprecedented connection can be established between the human body and the machines. Bodily integrity is protected thanks to bionic extremities and basic mechanic connections. An extremity developed for this purpose functions as a designed means and the performance of a patient's body can be increased. In the Argument-II, patients' expectations will probably become a priority. Such practices become difficult to access for the majority of society when their costs are not met by social security or insurance systems. This may lead to a period when the inequalities in healthcare services deepen further.

The main purpose is to increase the quality of life for the patients who need composite tissue transplantation for any reason. When clinical perspective is not adhered to, this main purpose may turn towards a system where human body extremities are produced over time. In addition, patients who need an extremity that becomes a commercial instrument should be psychologically prepared for the transplantation process. When individually developed extremities have an economic value and making profit from the sales of extremities is determined as the main goal, whether the patients are ready to use such extremities can be ignored. Conflicts of interest can occur between healthcare professionals, patients, and the firms that provide the extremities; and the success of the practice can be evaluated based on customer satisfaction. Under such circumstances, maintaining an approach that accepts human health as a value can become difficult.

Argument-III: Innovative medical opportunities should be used to increase an individual's body performance.

For the patients who do not have a lost extremity but suffers from loss of function in their extremities, increasing body performance can be evaluated within the scope of a healthcare service. However; the subjects of the new practices on the slope can shift from the patients who have problems with their extremities to healthy people. Thus, a logical connection is established between the Argument-II and the Argument-III, and even if they are undesirable, objection to new arguments is prevented. In this regard, the limit of the autonomous decisions of individuals without any health problems on their own bodies can be a subject for discussion because in such a scenario, individuals' autonomous choices about their extremities will be no longer related to health, and reconstruction of body can come into question. This reconstruction can even lead to legitimization of any interventions (such as adding or removing an extremity) in bodily integrity, which would probably be difficult to reasonably evaluate.

In medical ethics, the consistency between supporting the treatment of a health problem for many years and objecting to the health promoting practices (which seek perfection in a sense) is discussed. Harris (1993) claims that there is no moral difference between the interventions to treat a defect by reasoning based on gene therapy and the practices that aim at achieving perfection [37]. All steps to be taken to increase the quality of life of a mountaineer or a dancer who has lost his/her lower extremities and to eliminate the existing defect should be supported. Practices that aim to ensure bodily integrity and heal a defective body are positive developments for humanity.

The problem, or the point to take into

consideration, is that the first steps of an ontic transformation that will lead to dehumanization are taken. This can be individuals' autonomous decision; however, when rolling down from the slope continues, a healthy individual's hands, arms, and legs can be strengthened and/ or shaped in line with the purpose without obtaining their autonomous decision. This can enable the use of humans for increasing the efficiency of the production system or similar systems. When human body is introduced as a formable identity, humans can be used for certain purposes; and it is ethically impossible to accept this last position.

Conclusion

To avoid rolling down to undesirable places on the slope and instrumentalizing the humans, composite tissue transplantation indications should be meticulously evaluated in clinical terms. The aim of protecting bodily integrity and increasing the quality of life should be adhered to. Non-life-saving innovative opportunities should be offered to be used for ill bodies, not for healthy bodies, and should be legally regulated. Protection of human dignity while using advanced technological developments in medicine should be adopted as a main value.

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ORIGINAL ARTICLE

Reciprocal regulation of glycogen synthase kinase-3 and β-catenin affects cell proliferation of fructose treated rat hepatocytes

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Abstract

High consumption of fructose might lead to obesity, diabetes, and metabolic syndrome in the long term. Recent studies demonstrated the induction of insulin resistance in the liver tissues by down-regulation of insulin signaling pathway elements. Glycogen synthase kinase-3 (GSK-3), one of the insulin signaling elements, suppresses the β-catenin function that is required for cell proliferation and integrity. This study is designed to demonstrate the effects of fructose on the proliferation of rat hepatocytes and its effects on GSK-3 and β-catenin expression. Accordingly, rat hepatocytes were treated with different concentrations of fructose, and cell proliferation was followed with an xCELLigence real-time cell analysis system. Besides, gene and protein expression levels of GSK-3β and β-catenin were evaluated in fructose-treated cells with qRT-PCR and Western blot, respectively. The results demonstrated proliferative effects of fructose at low doses (0-25-50 mM), but cytotoxic properties are pronounced at higher doses (100-150 mM). The IC_{50} value was calculated as 140±7 mM fructose for Clone-9 cells. Molecular effects of fructose over GSK-3β and β-catenin appeared at gene and protein levels at 100- and 150-mM concentrations at which GSK-3β were suppressed. Conversely, high-dose fructose leads to β-catenin induction as a compensatory mechanism to counteract the antiproliferative effects of fructose at these doses. In conclusion, high-dose fructose-induced cytotoxicity activates a compensatory molecular mechanism involving β-catenin induction which might protect the cells in the long-term fructose exposure.

Keywords: Fructose, cytotoxicity, GSK-3β, β-catenin, gene expression

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Introduction

There has been a significant increase in high fructose consumption due to changes in dietary habits around the world. Several studies demonstrated strong evidence for the induction of metabolic disorders such as obesity, diabetes, and metabolic syndrome with a high-fructose-containing diet [1-3]. However, the direct link between excessive fructose intake and the onset of these pathologies is not well-known yet. Most of the metabolic effects of fructose stem from its rapid utilization in the liver tissues since its metabolism bypasses the main regulatory steps of glycolysis. The sudden increase in hepatic intermediates of glycolysis leads to a shift towards the oxidation reactions [4] which are associated with a state of imbalance between reactive oxygen species production and antioxidant capacity. Oxidative stress contributes to the pathophysiological processes of metabolic diseases mainly affecting the liver tissues and also activates proteins involved in proliferation control [5]. It has been shown that low levels of free radicals might increase the antioxidant enzyme activities and promote cell proliferation but at high levels, they activate several redox-sensitive signal transduction pathways to induce apoptosis and necrosis [6]. Fructose has also been shown to mediate cell proliferation in a dose-dependent manner by regulating many signal transduction elements such as insulin signaling and wnt/β-catenin pathways [7,8].

Recently, we have shown the downregulation of the main insulin signaling elements in various tissues with a high-fructose-containing diet [9,10]. Especially, IRS1/PI3K/AKT downstream signaling was repressed with high-fructose. One of the targets of AKT includes glycogen synthase kinase-3 [GSK-3β] which regulates insulin-dependent glycogen synthesis. GSK-3β was also reported to provide a regulatory function over β-catenin protein [11] since it phosphorylates β-catenin for its ubiquitination and degradation through proteasomes [12,13]. β-catenin is the key effector to trigger transcription of specific genes functioning in the promotion of cell proliferation, migration, and invasion [14].

Herein, we hypothesized that fructose could modulate rat hepatocyte cell [Clone-9] proliferation through a mechanism including GSK-3β and β-catenin function. It is, therefore, of interest to investigate whether fructose regulates cell proliferation via insulin signaling intermediate GSK-3β and β-catenin function which might provide new strategies in regulating hepatoma cell growth. To examine the connection between these signaling elements and proliferation reaction, we evaluated the cell growth inhibitory potential of fructose in a dose-dependent manner by a real-time cell analysis system and determined the gene and protein expression levels of GSK-3β and β-catenin.

Materials and Methods

Cell culture

Clone 9 cells, healthy rat liver cells showing normal physiological features were obtained from the American Type Culture Collection (ATCC, Manassas, VA, USA) and cultured as recommended using F12K medium (Kaighn's Modification of Ham's F-12 Medium, ATCC® 30-2004™, ATTC, Wesel, Germany) supplemented with 10% FBS, L-glutamine (2 mM), penicillin (100 U/ml), and streptomycin (100 mg/ml). The growth of the cells was continued in a 37ºC incubator (Sanyo MCO 17AIC, USA), providing 95% humidity and 5% CO_2 until they reached 90% confluency. Then, the cells that were removed with trypsin/EDTA solution were subcultured to the new growth media.

Determination of cell proliferation with real-time cell analysis

The effects of fructose on Clone-9 cell viability and the rate of proliferation were analyzed using the real-time cell analysis system (xCELLigence RTCA S16, ACEA Biosciences, USA). Accordingly, Clone-9 cells ($1x10^{+4}$ cells/100 µl F-12K medium) were seeded into the wells of gold-plated 16-well E-plates of the xCELLigence system and treated with different amounts (25-250 mM) of fructose, prepared in the growth medium, at the cell growth was in log phase. The real-time growth dynamics of the cells were measured instantaneously for 72-hours.

Determination of protein expressions of GSK-3β and β-Catenin by Western blot

After determining the IC_{50} value of fructose, Clone-9 cells were treated with different amounts of fructose (0-25-50-100 and 150 mM) for 48-hours in the T25 cell culture plate. After that, cells were scraped from the surface with a cell scraper (Sarstedt, USA) and collected in 100 µL of homogenization medium containing 50 mM Tris, 150 mM sodium chloride, 1 mM EDTA, 1% (w/w) NP-40, 0.25% (w/v) sodium deoxycholate, 1 mM sodium fluoride, 1 mM sodium orthovanadate and 1 mM phenylmethylsulfonyl fluoride, pH:7.4. Cell suspensions were homogenized with Tissue Ruptor™ homogenizer (Qiagen, USA) on ice for one minute and then ultrasonicated (Sonopuls, Bandelin, Germany) for 30 seconds to ensure complete cell disruption. Homogenates were then centrifuged at 1,200g for 10 min at +4ºC and the supernatants were removed for protein determination with the Lowry method [15]. Fifty µg of total proteins were separated with 12% polyacrylamide gel by electrophoresis and transferred onto the polyvinylidene fluoride membranes using a semi-dry electroblotting apparatus (TransBlot Turbo, BioRad, Munich, Germany) after which the membranes were blocked with 5% bovine serum albumin for 1 h. Then, the blots were incubated with primary antibodies of GSK-3α/β (anti-GSK3 α/β rabbit IgG 1:1000, Cell Signaling Technology, Danvers, MA, USA), β-Catenin (anti-β-Catenin rabbit IgG, 1:1000, Abcam, Paris, France) overnight at +4ºC. As an internal control, GAPDH proteins were also labeled with GAPDH (anti-GAPDH Rabbit IgG, 1:5000, Abcam, Paris, France) antibody for the data normalization. After the washing step, horseradish peroxidase (HRP) conjugated secondary antibodies (Goat Anti-rabbit IgG–HRP conjugate; 1:5000, Santa Cruz, Dallas, TX, USA) was applied for 1 h, and then the blots were treated with Clarity™ Western ECL (Bio-Rad Laboratories, Hercules, CA, USA) substrate solution for 5 min. Images of the blots were gained using the ChemiDoc™ MP Chemiluminescence detection system (Bio-Rad Laboratories, Hercules, CA, USA) equipped with a CCD camera. The relative expression of proteins with respect to GAPDH was calculated using the Image J software [16].

Determination of gene expressions with quantitative real-time polymerase chain reaction (qRT-PCR)

Total RNAs were isolated from fructose treated Clone-9 cells using miRVANA miRNA isolation kit (Thermo Scientific, Waltham, MA, USA) as described according to the manufacturer's total RNA isolation protocol. After isolation, the amount and the quality of the total RNAs were determined by spectrophotometry at 260/280nm and Qubit 4.0 System (Invitrogen, Carlsbad, CA, USA). Then, 1 µg of total RNA was reverse transcribed to cDNA using a commercial first-strand cDNA synthesis kit (Thermo Scientific, Waltham, MA, USA). Expression levels of *gsk-3β* and *β-catenin* were determined with a real-time quantitative polymerase chain reaction (qRT-PCR, LightCycler480 II, Roche, Basel, Switzerland). Accordingly, 1 µl cDNA, 5 µl 2X SYBR Green Master Mix (Roche, Basel, Switzerland) and 2 µl primer pairs of each (Table 1) at 0.5 µM concentrations in a final volume of 10 µl were mixed. qRT-PCR was performed as follows: initial denaturation at 95ºC for 10 min, denaturation at 95ºC for 10 s, annealing at 58ºC for 15 s, and extension at 72ºC for 15 s with 40 repeated thermal cycles measuring the green fluorescence at the end of each extension step. All reactions were performed in triplicates, and the specificity of PCR products was confirmed using melt analysis. The relative expression of genes with respect to internal control glyceraldehyde 3-phosphate dehydrogenase (*gapdh*) was calculated with the efficiency corrected advance relative quantification tool provided by the LightCycler-II 480 SW 1.5.1 software (Roche, Basel, Switzerland).

Statistical analysis

Gene and protein expressions of *gsk3β* and *β-catenin* in Clone-9 cells were normalized to corresponding housekeeping gene and protein expression of GAPDH. Data are expressed as the fold-change value over the untreated cells and represented as mean ± standard error of the mean (SEM). Statistical comparisons were performed using one-way ANOVA followed by an

appropriate posthoc test (Tukey). Comparisons giving *P*-values less than 0.05 were accepted as statistically significant. All analyses were done using SPSS 21.0 software (IBM Corporation, Armonk, NY, USA).

Results

Time and dose-dependent effects of fructose on Clone-9 cell proliferation

In this study, real-time cell monitoring was performed for Clone-9 cells which were treated with various amounts of fructose to demonstrate time and dose-dependent effects. The xCELLigence® RTCA instrument (Roche, USA) was utilized for this purpose which uses non-invasive electrical impedance monitoring to determine cell proliferation in a real-time and label-free manner. Gold-coated plate wells of the instrument measures the adherent cell amount which is then converted to a cell viability index with its software. Real-time monitoring of cell index provides a dynamic view of cell health which is very valuable especially as the time of incubation is very important. Hence, Clone-9 cells were seeded into the wells of gold-plated 16-well E-plates of the xCELLigence system and treated with different amounts of fructose (25-250 mM) at the log phase and real-time growth dynamics were measured instantaneously over 72-hours.

According to the results, low-dose fructose (25 and 50 mM) administration did not have a significant effect on the growth of Clone-9 cells (Figure 1). Although there was a slight decrease with 50 mM application in the number of cells in a very short time after the application, the cells approached the growth dynamics of the control cells within two hours.

In addition, the cytotoxic effect reaches a much more pronounced level in moderate fructose applications (100 and 125 mM) (Figure 2). It was determined that cell viability was halved within two hours of fructose application, but the number of viable cells approached the control samples 24-hours after the fructose application.

The effects of high-dose fructose (150, 200 and 250 mM) on Clone-9 cell proliferation were much more pronounced and dramatic (Figure 3). Accordingly, 150 mM fructose decreased cell

Table 1. Primer sequences of *gsk3β*, *β-catenin* and internal standard *gapdh* used for the mRNA expression determination with qRT-PCR

Gene	**Forward Primer Sequence (5'→3')**	**Reverse Primer Sequence (5'→3')**
β-catenin	TGTGGTTAAACTCCTGCACC	AAGCAGCTGAACTAGTCGTG
gsk3β	TATGGTCTGCAGGCTGTGTG	CCGAAAGACCTTCGTCCAA
gapdh	TGATGACATCAAGAAGGTGGTGAAG	TCCTTGGAGGCCATGTGGGCCAT

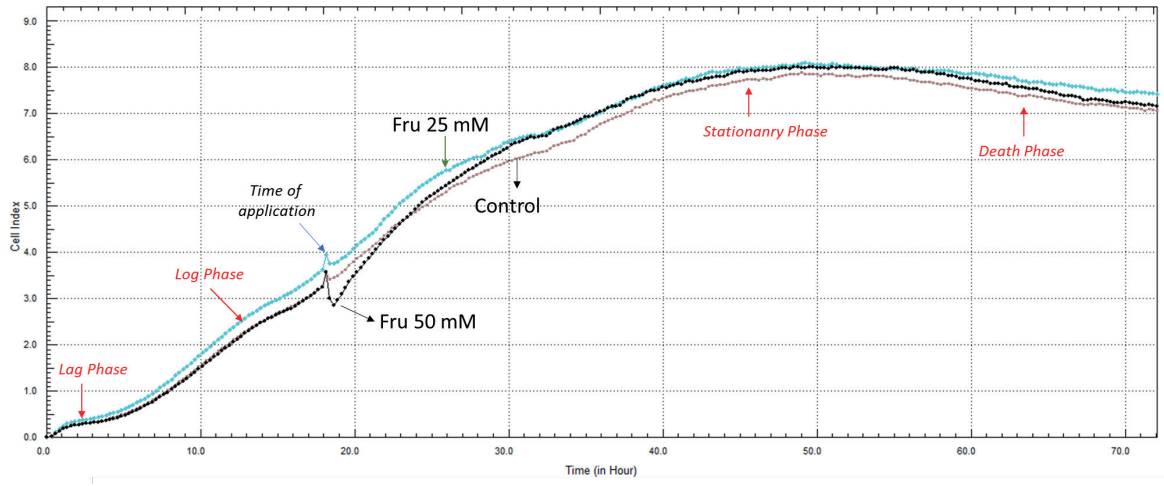

Figure 1. Growth plots of Clone-9 cells treated with low dose (25- and 50- mM) fructose. Lines are shown as the mean of two biological replicates

viability by 80% within two hours. However, unlike the medium-dose applications, cell viability could not reach the behavior of control cells in the later stages. Application of 200- and 250-mM fructose literally ended cell viability, since no living cells were left at these doses, cell recovery did not occur in the later stages.

As can be seen from the real-time cell analysis, the cytotoxic effects of fructose on Clone-9 cells were most evident within two hours after fructose administration. In this context, the IC50 value for the first two hours was calculated as 140±7 mM fructose.

Regulation of GSK-3β and β-Catenin expression with different doses of fructose

In this study, Clone-9 cells were treated with different doses of fructose (0, 25, 50, 100 and 150 mM), and qPCR and Western blot analysis were conducted to reveal GSK-3β and β-catenin expressions. Figure 4 demonstrates the changes in GSK-3β levels and Figure 5 demonstrates the alterations of β-catenin at both gene and protein expression levels, respectively.

According to the results, low levels of fructose (25 mM) did not change the gene and protein expression levels of GSK-3β which is also in parallel with the insignificant proliferative effects at this dose. Fructose exerted slight

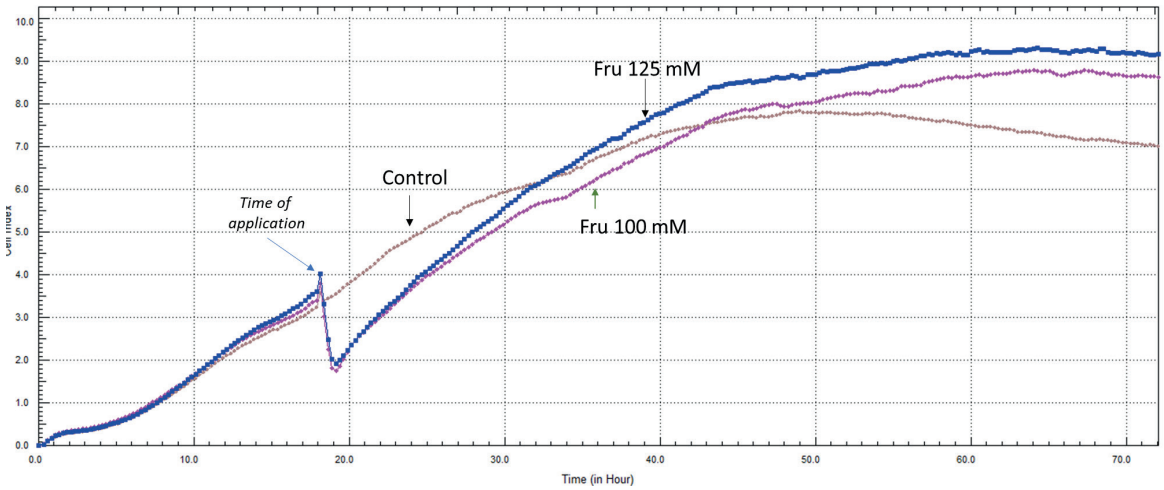

Figure 2. Growth plots of Clone-9 cells treated with medium dose (100- and 125- mM) fructose. Lines are shown as the mean of two biological replicates

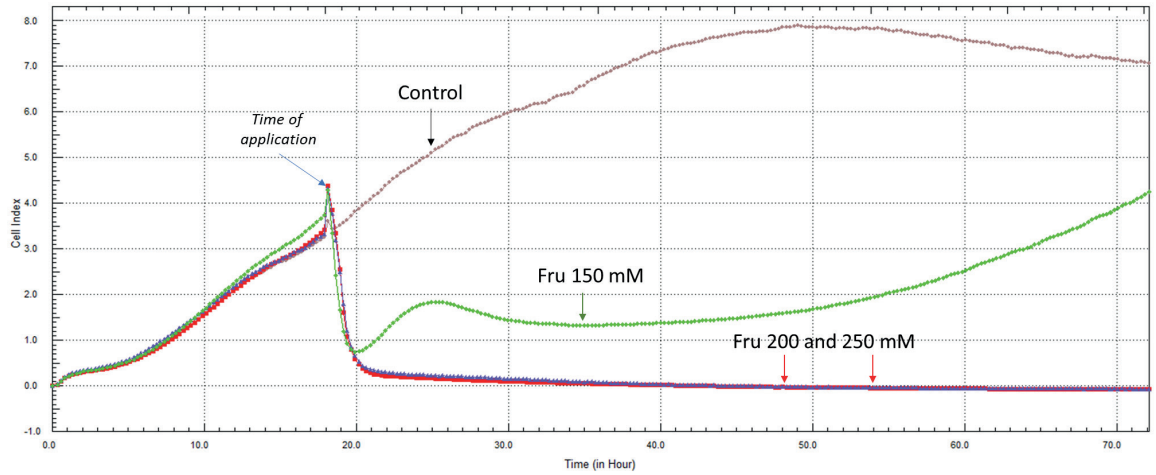

Figure 3. Growth plots of Clone-9 cells treated with high dose (150- , 200- and 250- mM) fructose. Lines are shown as the mean of two biological replicates

cytotoxic effects which also suppressed GSK-3β at both gene and protein levels by 20% at 50 mM concentration. In line with increased cytotoxicity, 100- and 150-mM concentrations further reduced GSK-3β expressions of Clone-9 cells (Figure 4B and 4C).

Considering β-catenin levels, completely inverse associations were observed as compared with GSK-3β in such a way that an increase in fructose concentration augmented the β-catenin levels at both gene and protein levels. Even though low levels of fructose did not modify β-catenin expression significantly, high-fructose (100- and 150- mM) induced β-catenin levels in a dose-dependent manner (Figure 5B and 5C).

Discussion

Fructose is an important ingredient of soft drinks and fast foods, and its increased consumption might contribute to the high prevalence of metabolic disorders worldwide. The metabolic effects of fructose have been mainly well-characterized by insulin resistance, hypertriglyceridemia, and fatty liver [17]. However, it is not well known if there are dose-dependent cytotoxic effects of fructose over hepatic cells and the differential expression of β-catenin and GSK-3β proteins could have a role in proliferation control. Therefore, this study assessed the potential effects of fructose on the rate of hepatocyte proliferation in conjunction with the expression of the antiproliferative β-catenin protein that is thought to be regulated by GSK-3β.

Glycogen synthase kinase 3 is a constitutively active protein kinase [serine/threonine] mainly controlled by IRS1/PI3K/AKT signaling, and phosphorylation by AKT inhibits its activity [18]. In addition to initially reported substrate glycogen synthase, it also phosphorylates several

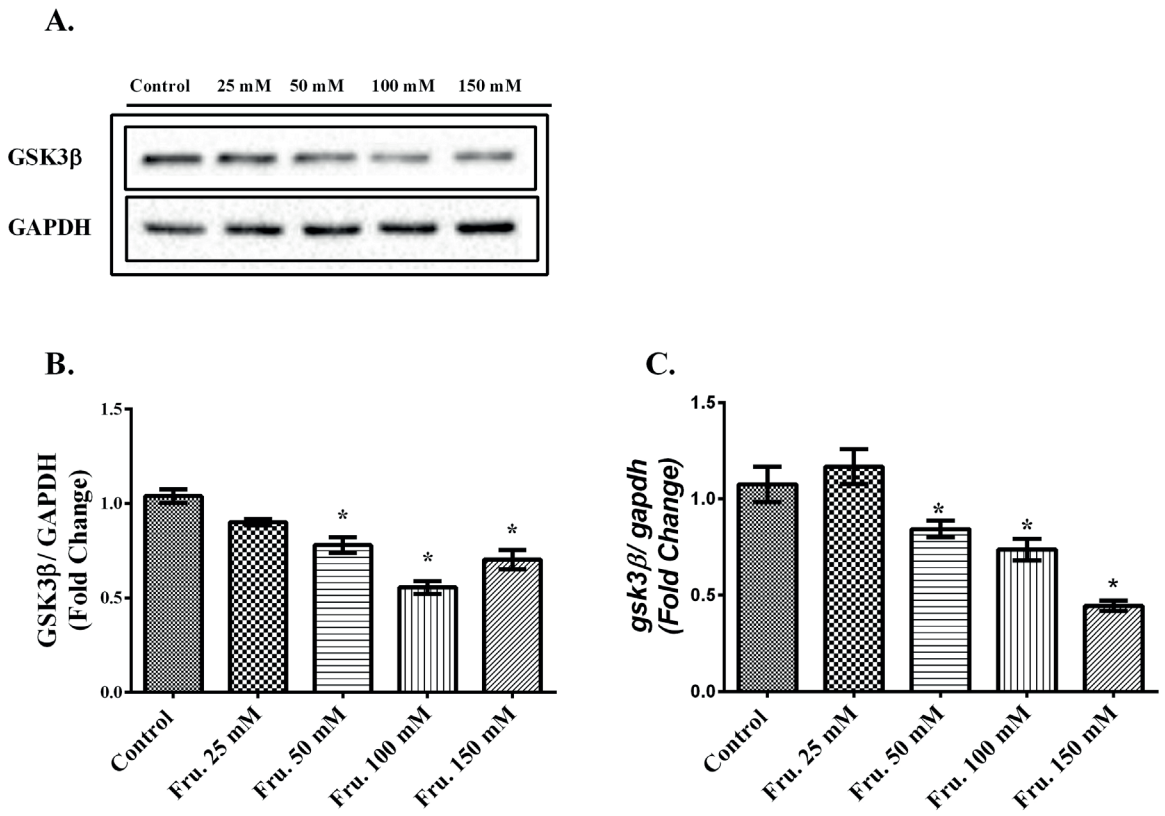

Figure 4. Representative Western blot bands of GSK-3β proteins in fructose-treated Clone-9 cells (A) and its relative protein (B) and mRNA expression levels (C). Data were normalized with corresponding GAPDH and *gapdh* expression and given as fold-change over non-treated Clone-9 cells. Values are given as mean ± SEM and the number of biological replicates was greater or equal to three (n ≥ 3). *$P < 0.05$, significant from the control group. Fru: Fructose

upstream and downstream components of the IRS1/PI3K/AKT signaling network to provide feedback control over its function [19]. Besides, more than a hundred other GSK-3 substrates have also been identified, the phosphorylation of which may result in the suppression of their activity. In mammals, GSK-3 has two closely related isoforms GSK-3α and GSK-3β which are encoded by two distinct genes but catalyze similar substrates. Their activity is found to be modulated by numerous extrinsic factors such as food components, food metabolic products, lipids, and drugs [20], and also it has prominent roles in the NF-κB and the WNT/β-catenin pathways which are often aberrantly regulated in cancer, tumor progression and uncontrolled cell proliferation [21]. Thus, the modulation of GSK-3 activity via natural compounds is still a promising target to various therapeutic approaches for proliferation control.

One of the well-defined targets for GSK-3β is the β-catenin protein having roles in cell proliferation and transition from epithelial to mesenchymal form that is critical for cancer development and metastasis. Activated GSK-3β phosphorylates β-catenin leading to its ubiquitination and degradation which suppresses the transcription of crucial genes in cells [22]. The β-catenin regulates cell adhesion, proliferation, signal transduction, metabolism, and other biological processes and its dysregulation could be associated with some metabolic diseases such as obesity, diabetes, nonalcoholic fatty liver disease, and metabolic syndrome [23]. Together with GSK-3β, β-catenin could play pivotal roles in transmitting various extracellular and intracellular regulatory signals which are critical to cell growth, survival, regeneration, or cell death.

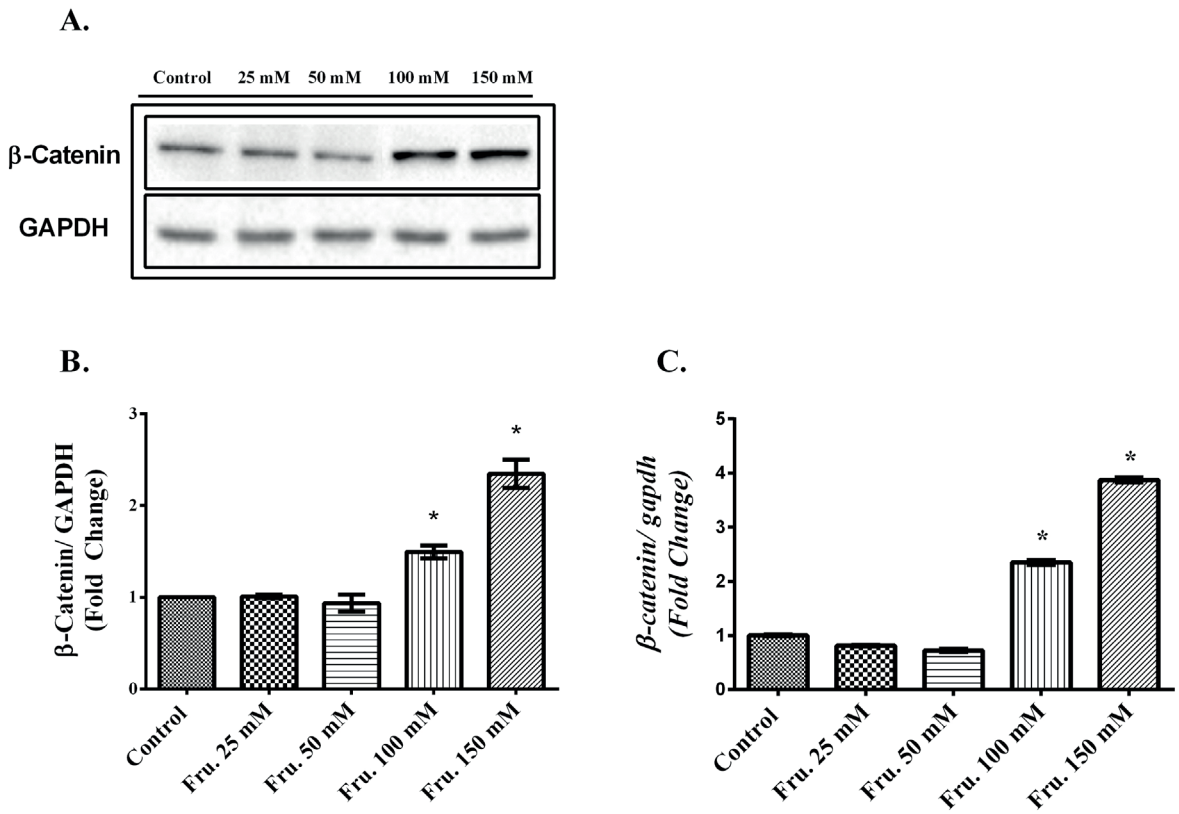

Figure 5. Representative Western blot bands of β-catenin proteins in fructose-treated Clone-9 cells (A) and its relative protein (B) and mRNA expression levels (C). Data were normalized with corresponding GAPDH and *gapdh* expression and given as fold-change over non-treated Clone-9 cells. Values are given as mean ± SEM and the number of biological replicates was greater or equal to three (n ≥ 3). *P < 0.05, significant from the control group. Fru: Fructose

Previously, downregulation in hepatic gene and protein expressions of insulin receptor downstream molecules has been demonstrated in the liver of high-fructose-fed rats [24]. In rat models of fructose-induced metabolic syndrome, we recently showed that hepatic insulin signaling appears to be suppressed due to reduced expression of IRS-1/2 and AKT [25] that would eventually modulate GSK-3 in the long run. Herein, this study demonstrated the proliferative role of low-dose fructose [25 mM] on hepatic cells, but high-doses over 100 mM concentration remarkably induced the cytotoxicity probably due to impaired insulin signaling in association with reduced GSK-3β levels which would eventually induce a compensatory proliferative response by activated β-catenin levels. Thus, this compensatory response of β-catenin might maintain hepatocellular integrity by triggering regeneration rather than promoting apoptosis at high-fructose levels.

Conclusion

In conclusion, the results presented in this study show that hepatic Clone-9 cells respond differently to fructose applications. While low doses and low treatment time augments the cell proliferation, high concentrations above 100 mM significantly reduced cell viability within two hours of incubation. Thus, effective, and non-toxic concentrations of fructose and the duration of treatment need to be carefully titrated for at least in vitro studies. Various molecular and genetic approaches should also be employed to dissect out the molecular mechanisms responsible for fructose-induced cytotoxicity. Especially the functional relationships between GSK-3β and β-catenin should be revealed to better understand the pharmacological activation of the canonical β-catenin pathway which provides proliferation control. Our data offer strong evidence of an interaction between GSK-3β and β-catenin, and we propose that the GSK-3β/β-catenin axis is essential to maintain cell survival in hepatocytes under high-fructose treatments.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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ORIGINAL ARTICLE

Assessment of plasma lipid parameters, exhaled nitric oxide fraction, and systemic immune-inflammation index on stable asthma patients

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Abstract

Asthma is a chronic disease characterized by the presence of inflammatory agents in the airways, and diagnosis and treatment are based on clinical questioning, physical examination, laboratory results, and spirometric analysis. This study investigated the effect of asthma alone on routine laboratory parameters in adults and whether an idea about the course of the disease can be obtained using these parameters. Two hundred and fourteen patients with known asthma history, diagnosed, and treated according to guidelines, were included in our study. Among all patients and between gender-specific groups, total cholesterol (CHOL), HDL, LDL, VLDL, triglyceride (TG), albumin, total protein (TP), lactate dehydrogenase (LDH), glucose, urea, creatinine, C reactive protein (CRP), FeNO, SII, INR, and complete blood count value parameters of the patients were analyzed. When we consider all asthma patients, we found that the mean glucose, LDH, CRP, TG, FeNO, and INR values outpaced the upper limit of the reference range. In contrast, the mean HDL value was below the reference range for all patients. In addition, our study found a significant correlation between triglyceride levels within the biochemical parameters with FeNO and SII). Finally, when we compared the mean values of gender-specific groups, we found a statistically significant difference between VLDL, HDL, TG, CRP, FeNO, creatinine, lymphocyte, eosinophile, basophile, and hemoglobin. CRP, LDH, TG, FeNO, SII, and INR levels may help clinicians in adult patients with stable asthma. In addition, differences depending on gender could be observed in the biochemical parameters of asthma patients.

Keywords: Asthma, biochemistry, adult, laboratory

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Introduction

Asthma is a chronic disease that interests more than 300 million people globally [1]. In the world's urban population, 100 million more people will develop asthma, according to estimated figures by 2025 [2]. However, the definition of asthma has not changed for many years. Pathophysiologically, asthma is a chronic inflammatory disease of the respiratory tract and causes bronchial remodeling in addition to the restriction of airflow [3]. Asthma is characterized by the presence of inflammatory agents in the airways, and diagnosis and treatment are based on clinical questioning, physical examination, laboratory results, and spirometric analysis [4]. The general clinical signs and symptoms are dyspnea, cough, chest tightening, and wheezing that may reflect airway hypersensitivity to a range of stimuli, such as exercise and inhaled irritants, with limitation in expiratory airflow, varying with time and intensity. Various genetic and environmental factors determine the disease's occurrence and the severity of the clinical course. Although most cases occur in childhood, the condition can also begin adulthood under allergens' influence [5].

In the classification of atopic asthma directed by interleukin (IL)-4, IL-5, and IL-13 cytokines, blood eosinophil counts with total, and allergen-specific IgE tests are used [6]. Studies have suggested that sputum eosinophils predict poor prognosis, especially in children with atopic asthma [7]. As a result of microarray studies, the TH2-high blood biomarker periostin has been identified as an IL-13 inducible protein produced by the respiratory epithelium [8]. High fractional NO [FENO] excretion by expiration has generally been reported as an inflammation indicator [9]. Blood biochemistry and hematological analyses are essential in supporting the diagnosis of asthma. The required blood volumes for cell count and most biomarker measurements are low and carry a low risk, especially for children [10]. Systemic immune-inflammation index (SII) has been assessed in several malignancies and vasculitis as an essential indicator of systemic inflammation and prognosis [11]. Although literature searches address routine laboratory parameters in asthma patients, studies have generally been carried out to discover possible specific biomarkers, and these parameters are not easy to reach. Hoping that routine laboratory analyzes can give an insight into the clinical course of asthma patients, we set out for research. Also, since the differences between male and female physiological mechanisms are known even in the healthy population, we aimed to find differences according to gender in asthma patients. Based on this, the effect of asthma alone on routine laboratory parameters and whether an idea about the disease can be obtained using these parameters was examined in our study. Standard laboratory parameters are easily reproducible globally and can easily compare with different workgroups. This logic is used in the preparation of the study.

Materials and Methods

Afyonkarahisar Health Sciences University Ethics Committee approval was obtained for the study with 08.01.2021 date and 2021/1 number. Two hundred and fourteen patients with known asthma history, diagnosed and treated according to guidelines at Afyonkarahisar Health Sciences University, Faculty of Medicine, Department of Pulmonology, Afyonkarahisar, Turkey, were included in our study. Patients with chronic diseases other than asthma, using long-term medication other than asthma treatment, having organ failure or transplantation, diagnosed with obesity or metabolic syndrome, and not attending regular follow-up examinations were excluded from the study. Total cholesterol (CHOL), high-density lipoprotein (HDL), low-density lipoprotein (LDL), very-low-density lipoprotein (VLDL), triglyceride (TG), albumin, total protein (TP), lactate dehydrogenase (LDH), glucose, urea, creatinine, c reactive protein (CRP), FeNO, SII (neutrophil*platelet/lymphocyte), INR, and complete blood count value parameters of the patients were analyzed. Univariable and multivariable analyses were assessed to investigate the association between biochemical parameters, FeNO, SII, CBC, and INR. All blood tests were performed after an 8-hour overnight fast. Biochemistry parameters were studied from serum using spectrophotometric and enzymatic

methods in an autoanalyzer. CBC parameters were obtained from whole blood by electrical impedance and flow cytometry. We evaluated lung inflammation in three groups in terms of FeNO values; <25 ppb mild inflammation, 25-50 ppb moderate inflammation,> 50 ppb severe inflammation according to the American Thoracic Society 2011 guideline. INR data were determined from blood plasma by an optical method in a coagulometer. All patients and gender difference values were evaluated whether the results were within the test reference range and how far beyond the reference range limits. Besides, whether the data conformed to the normal distribution was found with the Excel (Microsoft Inc, Redmont, Washington, USA) application. Paired sample t-test was used to compare group means of normally distributed variables, and the Wilcoxon test was used to compare group means of variables that did not show normal distribution. We summarized variables as mean ± standard error (SE) mean ± standard deviation (SD). Pearson's correlation analysis test was used for correlation analysis of parametric variables. Spearman correlation analysis test was used for correlation analysis of non-parametric variables. P-values below 0.05 were considered significant. Statistical analyses were performed using JASP 0.14 statistical software (JASP team, Amsterdam, Netherlands). Descriptive statistics are given in Table 1. Graphical data analysis is demonstrated in Figure 1.

Results

We found that the mean glucose, LDH, CRP, TG, and INR values outpaced the reference range's upper limit when we considered all asthma patients. In contrast, the mean HDL value was below the reference range for the whole group. Mean values for other parameters remained within the reference range. When we evaluated gender differences in females, mean CRP, LDH, glucose, and INR levels were measured above the reference range, while the average HDL values were below. In males, mean CRP, TG, LDH, glucose, and INR were measured above the reference range, while the average HDL values were also found below the reference range. When we considered FeNO values, we found that our patients had moderate inflammation (mean: 28.167). In addition, we found a significant correlation between triglyceride levels within the biochemical parameters with FeNO and SII, ($R2 = 0.912$ and $p = 0.031$, $R2 = 0.894$ and $p = 0.042$, respectively). Other parameters were within the reference range in both genders. When we compared the mean values of both groups statistically, we found a statistically significant difference between VLDL, HDL, TG, CRP, creatinine, lymphocyte, eosinophile, basophile, and hemoglobin ($p=0.002$, $p<0.001$, $p=0.002$, $p=0.028$, $p=0.01$, $p=0.027$, $p=0.009$, $p=0.002$, and $p<0.001$ respectively). Statistical analysis results are shown in Table 2. Correlation analyses are demonstrated in Figure 2 and 3.

Discussion

Serum and sputum LDH levels have been reported to be high in asthma patients in studies [12,13]. The increased LDH subtype is thought to be the LDH-3 isoenzyme. It has been reported that the lungs contain 28% of the LDH-3 isoenzyme compared to the whole body [14]. At this point, it has been emphasized that increased LDH levels can be used directly or indirectly as a marker of airway inflammation. The results we obtained in our study are consistent with this information. It can be thought that LDH is released into the circulation from cells that die or break down due to respiratory tract damage in patients. Besides, the blood-air barrier may become more absorbent for LDH by losing its selective permeability over time in the lung damaged by chronic discomfort. Acting on the same logic, it can be thought that the high CRP levels in patients again reflect chronic airway inflammation. Even if there is no worsening due to the disease for many years, some increase in CRP is understandable, considering that asthma is not only a local but also a systemic disease. The investigators stated that serum CRP levels increased in steroid-independent asthma patients compared to healthy controls and demonstrated a negative correlation with lung function indexes and a positive correlation with sputum eosinophil counts [15]. However, this relationship could not be shown in steroid-dependent allergic asthma. The fact that our

patients are adults in our study may indicate that asthma subtypes are most likely non-atopic, which may explain why we found high CRP levels in our results.

Although different studies and evaluations about lipid metabolism changes in asthma patients have been proposed in the literature, the mechanism has not been fully elucidated. A study indicated that serum triglyceride levels decreased in patients with an asthma attack, while no change was found in stable patients similar to our study group [16]. It has also been determined that the use of LDL and VLDL increased, and their levels decreased due to the increase in surfactant production so that asthma patients could breathe more easily. It has been reported that HDL, which contributes little to surfactant production, remains in the tissues longer and increases proportionally [17,18]. Although we could not detect a difference in LDL and VLDL levels due to our data, we found decreased HDL levels for all patients and both sexes. These findings may have developed due to the morphological change and fibrous tissue formation in the lungs as a result of years of inflammation and the decrease in the surface to produce surfactant and the cells that will produce surfactant. A different explanation for these results may be advanced age. A severe reduction in estradiol levels, especially in women with aging and entering menopause, may explain our results.

Recent studies have found increasing evidence of coagulation activation in asthmatic patients' airways as a result of allergen stimulation [19]. It is widely known that the coagulation system is activated in diseases that develop systemic inflammation. The systemic coagulation pathway is activated during an asthma exacerbation by increasing airway and systemic inflammation. Therefore, even chronic asthma patients are often exposed to exacerbation attacks until they are brought under control. Also, subacute inflammation continues outside of the attack. In the light of all this knowledge, it is understood why INR levels increase in our patients.

Current National Institute of Health and Clinical Excellence (NICE) guidelines in the UK recommend using non-invasive FeNO as the first test for people with suspected asthma [20]. The FeNO measurement enables clinicians to have detailed knowledge of airway inflammation, which significantly changes treatment plans compared to clinical evaluation alone [21]. The increase is valuable in diagnosing asthma, steroid-responsive chronic obstructive pulmonary diseases, while the decrease is meaningful in primer ciliar dyskinesia, cystic fibrosis, interstitial lung disease, and systemic sclerosis [22]. Besides, it might help diagnose and monitor complications in lung transplant patients. For these reasons, it is crucial to keep other lung pathologies in mind while evaluating FeNO and focusing on differential diagnosis. Bringing a new perspective to the assessment of inflammation, the systemic immune inflammation index (SII) can comprehensively reflect the balance of host immune and inflammatory status [23]. We found a significant correlation between these two inflammatory indicators and triglyceride levels. This conclusion suggests that there may be a link between the course of inflammation and response to treatment in asthma and triglyceride levels. Perhaps the progression of inflammation may contribute to the increase in triglyceride levels by turning fatty acids and glycerol toward glucose utilization.

Our study's absence of a control group made it impossible to compare the biochemical parameters we evaluated in asthma patients with a healthy population since it was a retrospective analysis, and this was the missing part of our study. Studies involving healthy volunteers can provide more information by comparing values within the reference range. In addition, separating patients according to clinical severity and treatment groups and analyzing them as we could not do in our study may be beneficial for more efficient results.

Table 1. Descriptive statistics of biochemical, CBC, and INR parameters. SE: Standard Error, SD: Standard Deviation. High-level values are shown in red, low-level values are shown in blue, and values between reference ranges are shown in green. For FeNO results, the blue color indicates low inflammation, the yellow indicates moderate inflammation, and the red indicates severe inflammation

	Mean	SE	SD	Minimum	Maximum
CRP	1.154	0.134	1.732	0.100	11.300
CHOL	178.291	3.207	46.913	43.700	332.400
VLDL	30.509	1.172	17.072	5.940	117.580
LDL	121.496	2.829	41.286	25.700	251.300
HDL	46.543	0.977	14.192	7.900	98.500
TG	151.851	5.893	85.810	10.700	587.900
ALBUMIN	4.335	0.041	0.554	1.360	5.520
T. PROTEIN	66.319	1.178	15.133	6.490	80.700
LDH	235.640	6.444	87.889	41.000	674.000
GLUCOSE	118.148	4.185	56.917	10.600	525.000
INR	1.407	0.149	0.879	0.870	4.530
UREA	38.333	1.817	26.578	10.600	197.600
CREATININE	0.915	0.052	0.760	0.390	8.090
WBC	8.299	0.189	2.752	2.870	24.960
NEU	5.140	0.161	2.343	1.550	19.120
LEN	2.619	0.259	3.785	0.590	51.200
EOS	0.232	0.015	0.221	0.000	1.390
BAS	0.054	0.002	0.032	0.010	0.210
HGB	13.317	0.128	1.864	7.700	17.800
PLT	268.615	5.262	76.800	61.000	617.000
AGE	59.860	1.019	14.900	20.000	87.000
FeNO	28.167	0.918	7.611	2.000	59.000
SII	700.817	71.812	156.594	258.125	3459.67

Table 2. Statistical analysis results of asthma patients' parameters between genders. SE: Standard Error, SD: Standard Deviation. High-level values are shown in red, low-level values are shown in blue, and values between reference ranges are shown in green. For FeNO results, the blue color indicates low inflammation, the yellow indicates moderate inflammation, and the red indicates severe inflammation

		Mean	SE	SD	p-value
CRP	**F**	1.277	0.163	1.868	**0,028**
	M	0.717	0.169	1.027	
CHOL	**F**	179.190	3.641	47.053	0,598
	M	175.098	6.823	46.774	
VLDL	**F**	28.638	0.989	12.740	**0,002**
	M	37.263	3.934	26.681	
LDL	**F**	121.751	3.291	42.398	0,866
	M	120.594	5.471	37.506	
HDL	**F**	48.891	1.085	13.900	**<0,001**
	M	38.351	1.767	12.111	
TG	**F**	142.302	4.994	64.339	**0,002**
	M	186.311	19.670	133.408	
ALBUMIN	**F**	4.303	0.045	0.547	0,123
	M	4.458	0.092	0.569	
T. PROTEIN	**F**	65.769	1.360	15.624	0,352
	M	68.521	2.257	12.966	
LDH	**F**	241.221	7.257	87.388	0,104
	M	215.902	13.723	87.872	
GLUCOSE	**F**	120.331	5.142	61.272	0,948
	M	110.937	5.944	38.980	
INR	**F**	1.403	0.164	0.866	0,951
	M	1.426	0.379	1.002	
UREA	**F**	37.432	1.782	23.031	0,351
	M	41.534	5.346	36.651	
CREATININE	**F**	0.844	0.045	0.583	**0,01**
	M	1.166	0.171	1.169	
WBC	**F**	8.287	0.199	2.562	0,905
	M	8.341	0.492	3.370	
NEU	**F**	5.152	0.173	2.228	0,884
	M	5.096	0.399	2.738	
LEN	**F**	2.315	0.098	1.262	**0,027**
	M	3.693	1.119	7.669	
EOS	**F**	0.211	0.016	0.212	**0,009**
	M	0.306	0.034	0.236	
BAS	**F**	0.050	0.002	0.027	**0,002**
	M	0.067	0.006	0.042	
HGB	**F**	12.911	0.123	1.582	**<0,001**
	M	14.751	0.304	2.084	
PLT	**F**	273.777	6.065	78.140	0,065
	M	250.383	10.155	69.616	
AGE	**F**	60.479	1.114	14.399	0,253
	M	57.660	2.412	16.536	
FeNO	**F**	37.263	3.248	8.642	**<0,001**
	M	24.712	1.547	3.189	
SII	**F**	764.123	37.916	94.152	0,358
	M	694.763	35.614	84.254	

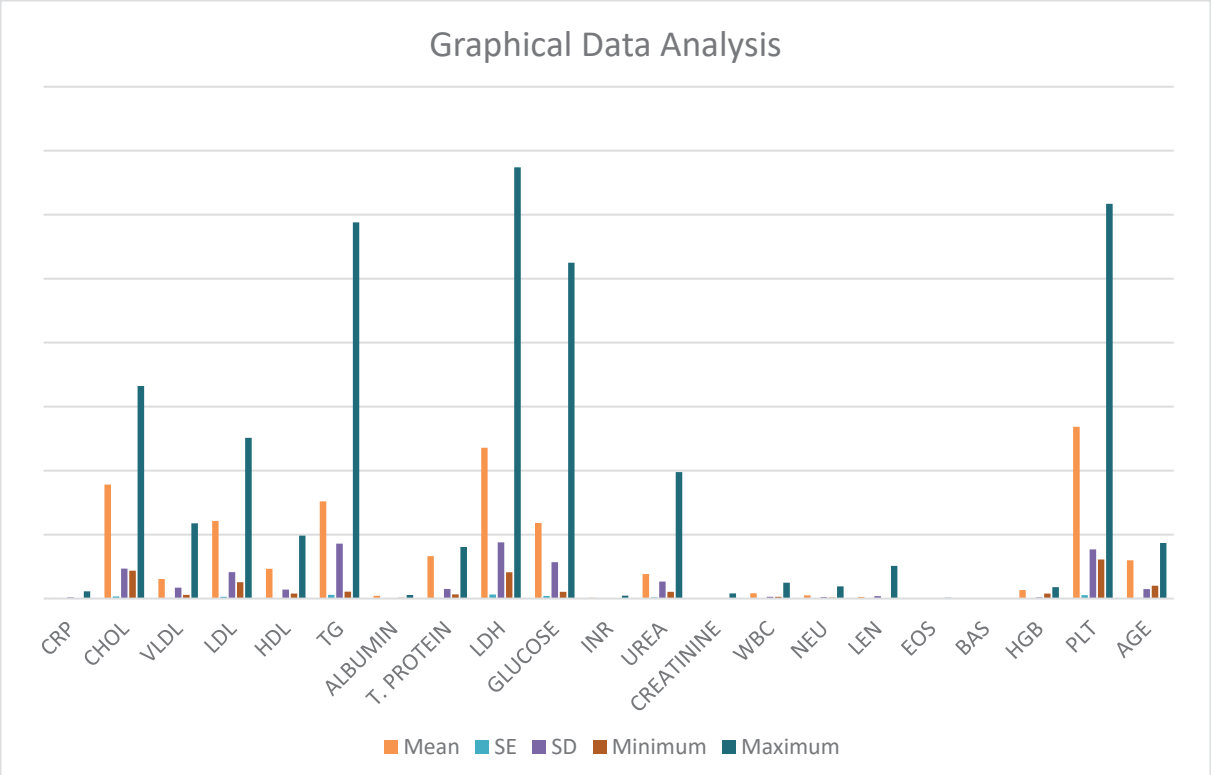

Figure 1. Graphical data analysis. SE: Standard Error, SD: Standard Deviation

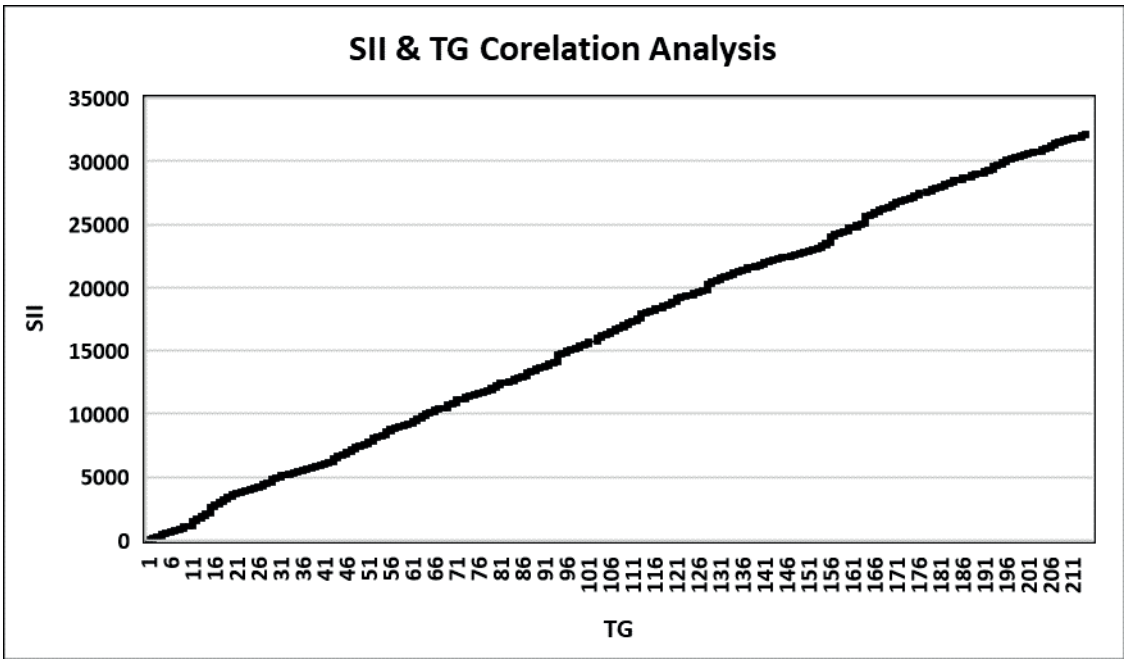

Figure 2. Correlation analysis of SII and TG values. SII: Systemic immune-inflammation index. TG: Triglyceride

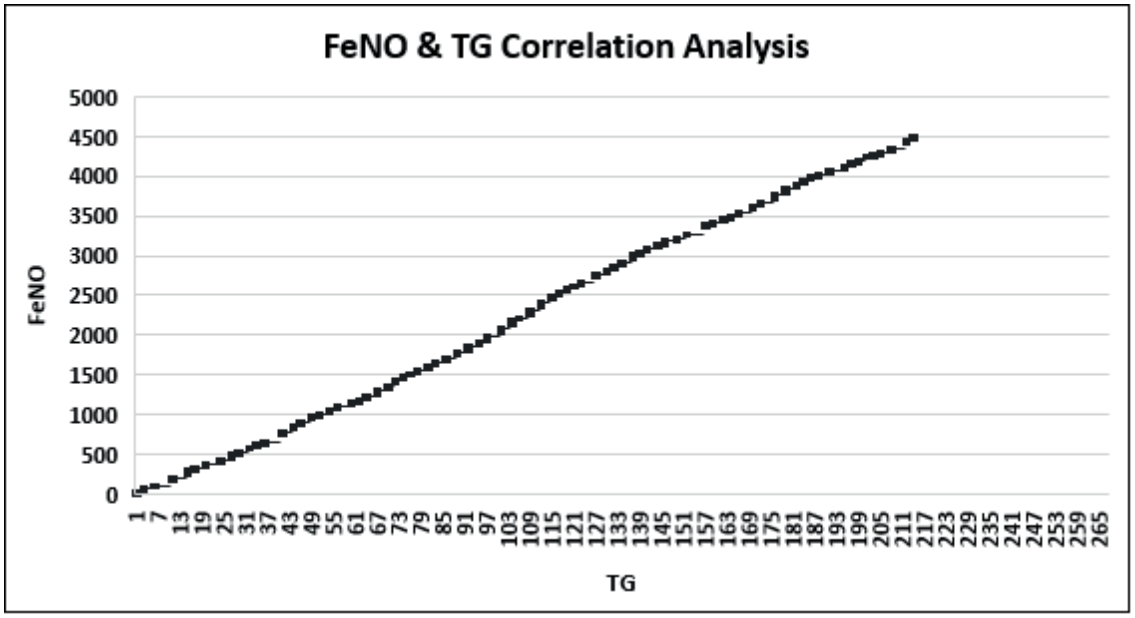

Figure 3. Correlation analysis of FeNO and TG values. SII: Systemic immune-inflammation index. TG: Triglyceride

Conclusion

In conclusion, as a result of comparing parameters between genders, we found increased levels that would make a statistically significant difference in men compared to women in terms of CRP, VLDL, HDL, TG, creatinine, lymphocyte, eosinophil, basophil, FeNO, and hemoglobin. However, we could not interpret our findings as a variable depending on gender associated with asthma. Studies involving control, clinical course, and treatment groups can guide more informative data.

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Conflict of interest

There is no conflict of interest.

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CASE REPORT

Vocal cord hemangioma

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Abstract

Hemangiomas of the larynx can be divided in two main forms: infantile and adult. The infantile form is more common in the subglottis and the adult form is usually found at or above the level of the vocal cords. Laryngeal hemangioma of the vocal cord is a very rare condition. We present a case of a 39-year-old female with a large hemangioma of the left vocal cord causing hoarseness and respiratory distress. The lesion was surgically removed successfully at our center.

Keywords: Hemangioma, vocal cord, hoarseness, larynx

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Introduction

Hemangiomas are the most common benign vascular tumors. Two-thirds are found in the head and neck and have a female / male ratio of 3-5:1 [1].

The occurrence in the larynx is very rare and can be divided in two main forms: infantile and adult. The infantile form is more frequent than adult ones, is commonly found in the subglottis and can cause stridor and respiratory distress. They can also coexist with cutaneous hemangiomas. The adult form is infrequent, usually found in the glottis or supraglottis, and the symptoms can vary from being absent or mild forms of hoarseness to severe dyspnea and dysphagia, depending on the size and location of the hemangioma [2,3].

Case report

A 39-year-old female was referred to our emergency room complaining of progressive hoarseness for two years and respiratory distress for the past month. She was an active cigarette smoker but had no history of alcohol use, any preceding infection, past intubation, trauma, voice abuse, reflux symptoms or any other systematic diseases. She had previously done a neck computed tomography (CT) scan revealing a "large polypoid mass, with approximately 10 mm diameter, occupying 50% of the glotic space, originating from the anterior half of the left vocal cord".

The flexible nasopharyngolaryngoscopy showed a movable bulky mass on the left vocal cord extending to the subglottic space (Image 1). The vocal cords were symmetrically mobile. The vocal folds and ary-epiglottic folds were normal as well as other otolaryngologic findings. A provisional diagnosis of a vocal cord polyp was made. The patient was submitted to microlaryngeal surgery under general anesthesia and the examination revealed a pink large pedunculated mass attached to the free edge of the left vocal cord, with its body extending to the subglottis. There was no extension to the anterior commissure or the arytenoids. The stalk of the lesion was isolated and excised completely with a microscissor. The minimal bleed was controlled with application of cotton balls and local pressure. The postoperative period was uneventful and the patient experienced no further symptoms, with prompt relief from respiratory distress. Voice rest was advised for a fortnight followed by speech therapy.

Histopathological examination of the specimen revealed capillary hemangioma of the vocal cord with vascular structures covered by a layer of non-atypical endothelial cells, with a lumen filled with erythrocytes (Image 2).

At two months after the operation, there was considerable improvement in the voice of the patient and laryngeal examination findings were normal.

Discussion

The occurrence of laryngeal hemangiomas in adults is very rare and generally seen in males. The etiologic factors are thought to be cigarette smoking, vocal abuse, and laryngeal trauma (i.e. intubation). [2,5] The main symptom is hoarseness. Respiratory distress, hemoptysis and dysphagia are usually seen in advanced cases.

The site of origin is variable with most of these lesions appearing at or above the level of the vocal cords. To the best of our knowledge there are only few than 10 cases reported in the literature of hemangiomas originating from the free edge of the vocal cords [2,5-7].

Laryngoscopy is almost always sufficient for the diagnosis of a hemangioma. Other exams, such as CT, magnetic resonance imaging with contrast and angiography are reserved for larger lesions and for patients with respiratory symptoms. Biopsies are usually unnecessary and dangerous, due to the risk of severe bleeding [3,4,9].

Although the patient in this case is a female, she was an active cigarette smoker. She presented with hoarseness and respiratory distress, and the lesion originated from the free edge of the left vocal cord. Since our patient had previously done a neck CT scan, considering the size of the lesion, the exam was important to define its limits and dimensions.

Histopathologically, laryngeal hemangiomas are generally of the cavernous type. According to our search, there are only three cases of capillary hemangiomas described in the literature, similar to the one in our case. These lesions also need to be distinguished pathologically from polypoidal vascular granulation tissue that may arise after laryngeal biopsy, intubation or trauma. [6-10] There is no uniformly accepted treatment of head and neck hemangiomas. The various modalities of therapy are dependent on the age of the patient, the site and size of the lesion, and the hemodynamic pattern of the hemangioma. In adults, smaller hemangiomas can be managed conservatively but larger lesions may require a tracheostomy. Systemic steroids, intralesional steroid injection, laser ablation, interferon, microdebrider, radiation therapy, cryosurgery and surgical excision have all been used [2,6,7].

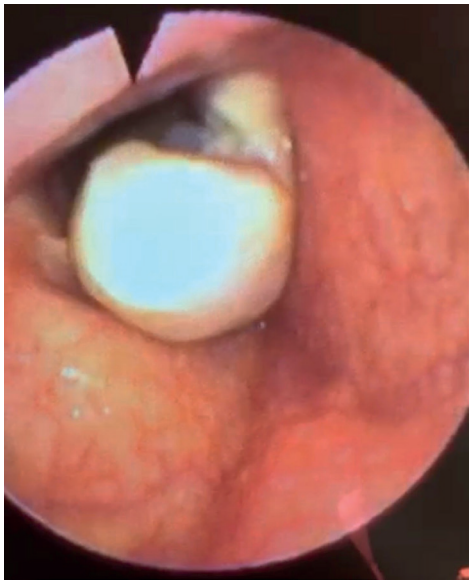

Image 1. Bulky mass on the left vocal cord

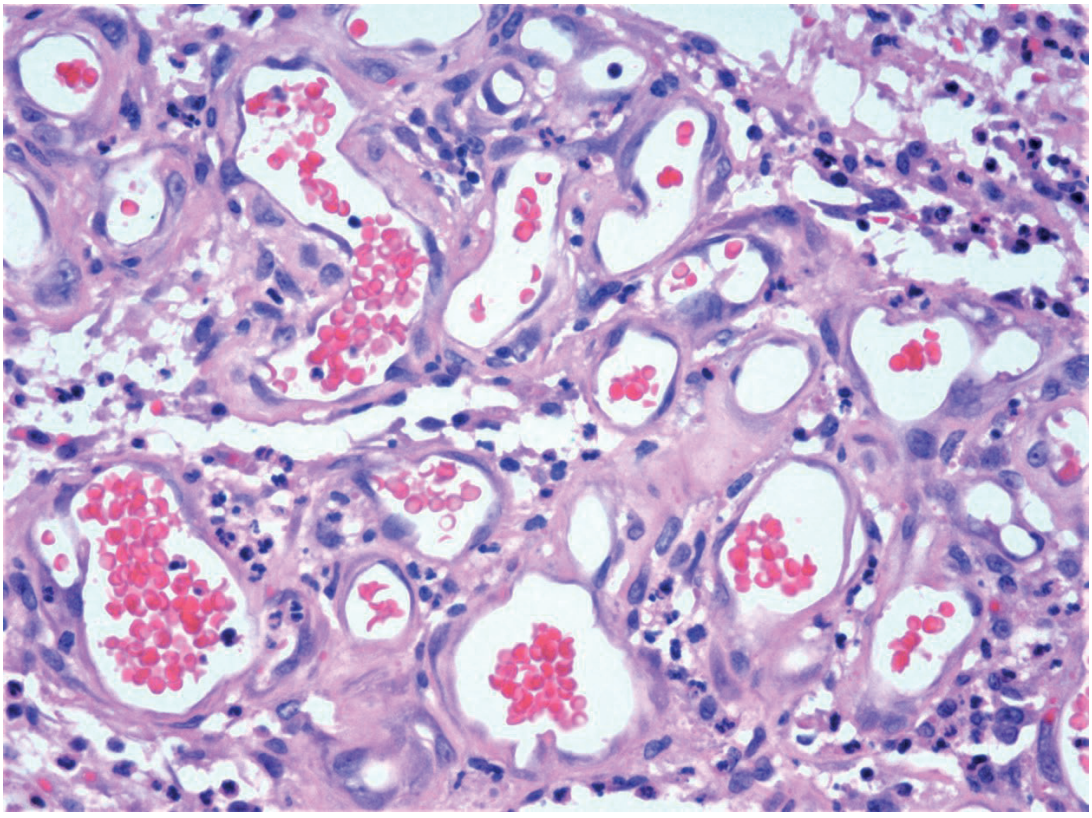

Image 2. Vascular structures covered by a layer of non-atypical endothelial cells, with a lumen filled with erythrocytes

Conclusion

Given the infrequency of vocal cord hemangiomas in adults, these lesions can easily be misdiagnosed as polyps. Also, it is not possible to standardize the diagnostic and therapeutic approach of such rare lesions.

Endoscopy should be meticulous and carefully done considering the possible extension of the lesion to adjacent structures and association with other lesions such as tumors.

Excision of the hemangioma with microlaryngoscopic techniques gives satisfactory results in terms of eradication of the lesion and improvement of voice quality.

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Conflict to interest
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Data availability statement
The authors confirm that the data supporting the findings of this study are available within the article and its supplementary material.

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