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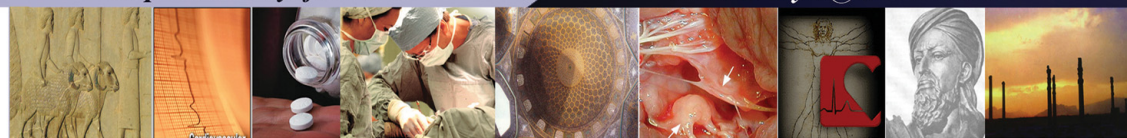

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Behavioral determinants of cardiovascular diseases risk factors: A qualitative directed content analysis

Leila Sabzmakan[(1)], Mohammad Ali Morowatisharifabad[(2)], Eesa Mohammadi[(3)], Seid Saied Mazloomy-Mahmoodabad[(4)], Katayoun Rabiei[(5)], Mohammad Hassan Naseri[(6)], Elham Shakibazadeh[(7)], Masoud Mirzaei[(8)]

Original Article

Abstract

BACKGROUND: The PRECEDE model is a useful tool for planers to assess health problems, the behavioral and environmental causes of the problems, and their determinants. This study aims to understand the experiences of patients and health care providers about the behavioral causes of cardiovascular diseases (CVDs) risk factors and their determinants.

METHODS: This qualitative study utilized content analysis approach based on the PRECEDE model. The study was conducted for over 6 months in 2012 at the diabetes units of health centers associated with Alborz University of Medical Sciences, which is located in Karaj, Iran. Data were collected using individual semi-structured interviews with 50 patients and 12 health care providers. Data analysis was performed simultaneously with data collection using the content analysis directed method.

RESULTS: Stress, unhealthy eating, and physical inactivity were the behaviors, which predict the risk factors for CVD. Most of the patients considered stress as the most important underlying cause of their illness. In this study, 110 of the primary codes were categorized into seven subcategories, including knowledge, attitude, perceived susceptibility, severity, perceived benefits, barriers, and self-efficacy, which were located in the predisposing category of the PRECEDE model. Among these determinants, perceived barriers and self-efficacy for the mentioned behaviors seemed to be of great importance.

CONCLUSION: Identifying behavioral determinants will help the planners design future programs and select the most appropriate methods and applications to address these determinants in order to reduce risky behaviors.

Keywords: Behavior, Cardiovascular Diseases, Risk Factors, Qualitative Research

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Introduction

Cardiovascular diseases (CVDs) are the number one cause of death globally, more people die annually from CVDs than from any other causes.[1] It is predicted that By 2030, almost 23.6 million people will die from CVDs, mainly from heart disease and stroke.[1] In Iran, CVDs are the leading cause of mortality and morbidity, with the high cost of health care.[2] The Inter Heart study showed that nine modifiable risk factors (abnormal lipids, smoking, hypertension, diabetes, abdominal obesity, psychosocial factors, consumption of fruit and vegetables, regular alcohol consumption, and regular physical activity) were associated with more than 90% of the risk of an acute myocardial infarction in this large global case-control study.[3]

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Evidence shows modifiable risk factors and behaviors related to unhealthy lifestyle are major determinants of CVD morbidity and mortality. If all forms of CVD were eliminated, the life expectancy will increase by approximately 7 years.[4]

To develop effective interventions, it is important to understand the behaviors of the target population. Qualitative methods are most ideal for gathering in-depth information to help develop this understanding.[5] On the other hand, qualitative methods can help the health educators to more fully understand the health problems, behavioral and environmental causes, and determinants from the perspective of the people involve.[6] Various studies have used qualitative methods to examine participants "perceptions, awareness, and attitude" toward CVD risk factors. The participants in focus group discussion demonstrated different levels of understanding and attitudes toward lifestyle risk factors of CVD.[7-9] Most participants were aware of modifiable CVD risk factors.[9] In this study, the barriers to improve the lifestyle in regards to physical activity and diet included lack of information such as how to cook and prepare healthy food, food preferences,[7] financial, love of food, stress and uncontrollable appetites,[8] concern about wasting food, lack of time.[9] These studies did not use theories related to individual health behavior in order to identify health problems, behavioral causes and their determinants. Health behavior theories are important in understanding the particular behavior. Furthermore, they are important in finding interventions to improve health behavior.[10]

The PRECEDE model that is often used in health education and health promotion is a logical model that describes the causes of health problem.[11] Based on the study by Green and Kreuter, the behavioral causes can be classified to factors as predisposing, enabling and reinforcing. These factors act as determinants for particular behavior, the most effective interventions for improving health can be expanded for each factor.[12] The predisposing factors are antecedents to behaviors that include knowledge, attitude, belief, values, perceptions, exiting skills, and self-efficacy. The enabling factors are antecedents to behavioral and environmental change include the availability, accessibility, laws, and policies. The reinforcing factors are those factors following a behavior that provide continuing reward or incentive, which include social support and significant others. The planners may see determinants as the processes of change that must be activated or set in motion if the necessary behavioral and environmental changes are to occur.[13] This study aims to understand the experiences of patients and health care providers about the behavioral causes of CVD risk factors and their determinants based on PRECEDE model.

Materials and Methods

A qualitative method with directed content analysis approach was selected. The goal of a directed content analysis approach is to validate or extend conceptually a theoretical framework or theory. Existing theory or research can help focus the research question and it can help researchers begin by identifying key concepts or variables as initial coding categories. This approach was employed by Hsieh and Shannon in 2005.[14]

Data collection

Data were collected through semi-structured in-depth interviews from September to March 2012. Totally, 62 face-to-face interviews with 50 patients and 12 healthcare providers were conducted. Each interview lasted between 30 and 60 min and all the interviews were conducted in a private room. The interview guide consisted of open-ended questions based on subcategories of predisposing category of PRECEDE model to allow respondents fully explain their own experiences. To begin, the participants explained their individual experiences on "their risk factors, such as diabetes, hyperlipidemia, and hypertension", "the factors influencing it/them, for example, if they point out to unhealthy diet/inactivity or stress, it was asked what means unhealthy diet/inactivity or stress? How does poor diet/inactivity/stress affect their illness?", "benefits of healthy diet/regular physical activity and control stress", "the factors inducing they maintain or stop healthy diet/regular physical activity and control stress" and "confidence in their ability to do healthy diet/regular physical activity and control stress" and "effective ways to prevent risk factors".

Setting and participants

The participants were 50 patients with a mean age of 46.5 ± 6.0. The main researcher look at documents of blood test results of patients performed by diabetes unit, if patients had at least one or more biochemical CVD risk factors such as pre-diabetes, type 2 diabetes (T2D), metabolic syndrome, hyperlipidemia, and hypertension for at least 1-month and previously had received advises of healthcare providers in order to change lifestyle, the main researcher contacted each of the potential participants to explain the objectives and the

research questions, and if the participant agreed to take part in the research, an interview was carried out. The patients were chosen using purposive method to consider the maximum variation sampling based on (sex, age, level of education, occupation, and the type of risk factor) from four health centers associated with Alborz University of Medical Sciences, which is located in Karaj, Iran. The four centers were chosen with the aim to obtain an understanding over an extensive range of socio-economical states. Patients with previous heart attack, stroke, open heart surgery or angioplasty patients, also newly diagnosed patients (< 1 month) and all type 1 diabetes were excluded from the study (Table 1). In addition, 12 health care providers from the diabetic units of four health centers, including three general practitioners, three nurses, and three dieticians were individually interviewed. The mean age of health care providers was 38.4 ± 9.8 and 10 of them were female.

Ethical considerations

Before data collection, ethics approvals were obtained from Ethics Committee of Shahid Sadoughi University of Medical Sciences. All participants were informed that participation in the study was voluntary, so they could refuse to participate or withdraw from the study at any time without being penalized or losing any benefits. Moreover, the participants were reassured about confidentiality and anonymity of their information.

Table 1. Patients' characteristics

Variables	Number	Percent
Sex		
Female	31	62
Male	19	38
Educational level		
Illiterate	5	10
Primary	14	28
High school	16	32
Diploma	7	14
College degree	8	16
Occupation		
Housewife	29	58
Retired	6	12
Employed	15	30
Disease		
Diabetes	28	56
Hyperlipidemia	45	90
Hypertension	12	24
Pre-diabetes	14	28
Metabolic syndrome	10	20

Data analysis

All interviews were conducted, recorded, transcribed verbatim, reviewed, coded, and immediately analyzed by the first researcher. According to the directed content analysis process, at first, each interview was read several times carefully to gain a deep understanding the data. Later, important statements were underlined to identify the initial codes or meaning units that exist in the interview text. In the next phase, these similar meaning units (codes) were placed initially in subcategories of the PRECEDE model and then into its three main categories (predisposing, enabling, and reinforcing). Any text that could not be categorized with the initial coding scheme would be given a new code. The data collection process was continued until data saturation–when adding further data showed no new information and the extra collected data were redundant. When the new code was not produced in the last three interviews, saturation was achieved and data collection was stopped. Due to the large volume of data obtained in this investigation, only predisposing categories reported as behavioral causes and the enabling categories will published as environmental causes as soon as. An example of coding and placement in subcategories and categories is shown in table 2. The participants were reassured about confidentiality and anonymity. The authors of this manuscript have certified that they comply with the principles of ethical publishing.

Consideration of rigor

Prolonged engagement in the field from September to March 2012 helped to establish some trust and rapport with participants, providing an opportunity to collect the data. To make sure that the analysis reveals the patients and health care providers' experiences, member checking was performed during the data collection, and where needed, some changes were done. To confirm dependability and conformability of the data, the interviews and results of the analyses, that is, the initial codes, subcategories and the categories of PRECEDE model, were audited by some experts, the external check method using two authors (LS and MAS) expertise in health education and familiarity with PRECEDE model. Professor Green, the designer of PRECEDE model, were contacted regarding this study and peer checked by two PhD students in health education who had previous experience with PRECEDE model. Maximum variation of sampling also confirmed the conformability and credibility of data. Sampling strategies allowed for maximum variation to occur and a vast range of views and perspectives to be considered.

Table 2. Example of the analysis process

Meaning unit	Codes	Subcategory	Category
"I see myself at risk of heart disease because my mother had history of high blood pressure, diabetes and stroke"	Belief about the chances of getting heart disease/stroke	Susceptibility perceived	Positive predisposing
"When I cook for the family, I eat it myself too. I cannot resist eating, it is hard making normal and dietary food"	Belief about the compatibility of patients food with family members	Perceived barriers	Negative predisposing
"The diet recommended to patients was not followed for a long time, they tend to follow it for some time and then give it up"	One's disability for performing healthy diet in a regular basis	Self-efficacy	Negative predisposing

Results

In this study, 110 codes, classified in seven subcategories of predisposing factors, were found. These include; knowledge, attitude, perceived susceptibility and severity, perceived benefits and barriers and self-efficacy.

Predisposing factors

Knowledge

Often patients by dieticians at the diabetes units found the beneficial and harmful foods for controlling their illness; they also felt to know how much of physical activity per week is needed for them to manage their disease; furthermore the most understood stress as an important factor in causing their disease, but did not know how to control their stress: "I didn't know how to control my lipid level using diet. Since I attended the diabetic unit, the dietician improved my awareness, also I know have to walk half an hour to managing diabetes and hypertension but I not doing it, I feel stress is an important factor in causing my disease, but I do not know how to control my stress". (Female–Aged 43, metabolic syndrome).

Most healthcare providers felt that the majority of patients say that they understand healthy foods; however when questioned about them in detail, their understanding was only partial and sometimes wrong: "Patients understanding of healthy foods is not enough, they don't understand what to eat, they don't understand how to reduce their intake, for example they say I understand what to eat but when you speak to them we realize they don't understand much (Nurse)".

Attitude

The healthy eating was considered to be important by the majority of patients, but few of them believed that healthy foods were enjoyable. Most of the patients liked sugar, cookie, and sweet foods and also they preferred oily and fried foods to boiled and steamed foods. Some of them preferred salty foods to low salt foods and the others did not like the taste of liquid oil and also some ladies were believed that because liquid cooking oil is more difficult to clean from the stove, they should be harmful for their body and felt that it sticks to heart vessels too. "Fried foods are much more delicious, steamed foods do not taste good, one does not like eating them, I really like sweets, also I don't like low salt foods; I am used to add salt to food. I always use solid oil as it is much easier clean from stove, in old days when people were using solid oil no one was sick, now that people use liquid oil everyone is sick". (Female–Aged 47, pre-diabetics and hyperlipidemic).

Some patients believed animal oil is the healthiest fat available, and even felt that after using animal fat their lipid level will be dropped "I mostly use animal fat, since I started using animal fat, I feel like both mine and my husband lipid leaves have been normalized" (Female–Aged 52, diabetic and hyperlipidemic).

Most patients were interested in walking and preferred group sports to individual ones. "I mostly like to play sports in group with friends, which unfortunately is not possible due to the lack of resources, I don't like individual sports" (Male–Aged 49, metabolic syndrome).

Some patients believed that their daily activities at work and at home are a kind of sport "I have so much work at home too and to do that I don't have any free time to do any other sports, after all housework will burn fat too" (Female–Aged 41, pre-diabetics, hypertensive, and hyperlipidemic).

Most patients found the role of diet and physical activity in controlling their illness, however considered diet more important. A few believed that if they do enough exercise they can eat whatever they like. Furthermore, patients with low socio-economic status, who were on medication, believed that because they are on medication, they do not need to control their diet or do any physical activity, whereas patients with high socio-economic status

were more inclined to follow a healthy diet, involve in physical activity such as walking and control their stress and did not like to take medication for a long time: "I try not to take medication because medications make you addicted and prevent you from doing exercise and follow a healthy diet" (Male – Aged 50, diabetic and hyperlipidemic).

Belief

In PRECEDE model, belief consisted of four parts: perceived susceptibility, perceived severity, perceived benefits, and perceived barriers.

Perceived susceptibility: Some patients, particularly females, based on their level of risk factors considered themselves at risk of developing CVD. Most patients with pre-diabetes, diabetes and hyperlipidemia were more worried that they develop hypertension than CVD. Some patients with diabetes did not understand the relationship between diabetes and CVD. Compared to pre-diabetic patients, diabetes and hyperlipidemia, patients with hypertension and metabolic syndrome saw themselves at higher risk of developing stroke or CVD. Patients with hyperlipidemia considered themselves mainly at risk of developing stroke and though high lipids mean stroke, patient with pre-diabetes were mainly worried that they develop diabetes. It should be noted that if patients had a family history of these risk factors, they considered themselves at higher risk of the disease. "A lot of them don't understand the relation between diabetes and hyperlipidemia with CVD. They see the link between hypertension and CVD very strong, when their blood pressure goes up they think they are going to have heart attack or stroke" (dietician).

Perceived severity: Patients with diabetes and metabolic syndrome considered their illness as very dangerous and believed that diabetes is more dangerous than cancer, these patients were scared of consequences of diabetes such as losing the limbs, blindness and renal failure, in particular if they saw the consequences of diabetes in their relatives, as a result of fear from its consequences they were paying more attention to their illness and were following the health related behaviors. "I am mainly worried of my diabetes as my father also had diabetes. He suffered a lot and lost his legs and went blind, and died because of it" (Male–diabetic and hyperlipidemic).

Patients with pre-diabetes, hypertension and low lipids were not paying too much attention to their problem however patients who had very high lipids (triglyceride and cholesterol <350 mg/dl), were more worried and followed the given instructions more seriously. "Among patients presented to us, those with hyperlipidemia don't care at all. Unless it's very high or it is causing problem for them. Pre-diabetic and hypertensive patients also don't pay too much attention to these conditions. Those with diabetes pay more attention and follow the medical advices as they see the complications" (Physician).

Pre-diabetic and hyperlipidemic patients believed that if their problem was important, their doctors should have prescribed medications for them, and because no medication has been prescribed, they did not think their disease is important and hence they did not follow the prescribed diet or exercise regimen. "I still haven't really started to follow my diet as my glucose level and lipid level are not that high, my doctor has told me the levels are not high enough to get medication" (Female–Aged 48, pre-diabetic and hyperlipidemic).

Patients who were suffering from physical symptoms of their illness were more likely to follow the recommended behaviors, however if they did not feel any physical symptoms from their illness, they were less likely to be compliant with the diet, physical activity, control of stress and medication. "Some patients say we don't feel any problem from our disease or say we don't have any symptoms, they stop following their diet and stop taking their medications" (Nurse).

Perceived benefits: Most patients believed that control of stress, regular physical activity, and following healthy diet have an important role in controlling their hyperlipidemia, hyperglycemia, and decreasing their CVD risk. They believed that physical activity, more than anything else, help them to feel refreshed, improve their mood and reduce their stress. Most patients believed having a healthy diet and enough physical activities will result in CVD prevention, less need to take medication, weight reduction, and morbidity reduction associated with disease, increasing life and reducing health costs. "We recommend physical activity and a healthy diet to our patient, we tell them about the benefits, most of them know about these benefits, for example they know healthy diet and exercise can control sugar, lipids, blood pressure, reduce weight and reduce the health care costs. However, unfortunately they don't follow the instructions" (Dietician).

Perceived barriers: Most patients understood factors such as not having a partner, being busy at work, looking after children, having physical problems such as knee pain, arthritis, leg pain, back

pain, having more important things to do in life, psychological problems such as depression and anxiety, tiredness and laziness as barriers to do physical activity. Patients, who were unable to do physical activities due to physical problems, were recommended by healthcare providers to perform swimming. However, most of them perceived high cost of swimming pools as a barrier. Some patients, in particular obese female patients felt shy to attend swimming pools or gyms. "Most patients say they don't have time for doing physical activity, females who are housewife use tasks such as looking after home and children as an excuse not to exercise. A factor that most patients mention is knee pain, which is due to overweight, most patients here are obese. Most female patients who say they have bone pain have osteoporosis, arthritis or joint problems, we advise them to go to swimming pools and walk in the pool; however they say they can't go to the pool due to the high cost" (Nurse).

Patients and health care providers also understood factors such as lack of compatibility of patients food with family members, the high cost of healthy food, being tired of the taste of healthy foods, not feeling full and feeling weak after taking healthy diet (especially diabetic patients), psychological problems such as depression and anxiety, having problems more important than diet in their life, feeling hungry beyond control, particularly when angry, and laziness as barriers to being compliant with a healthy diet. One of the barriers to being compliant with a healthy diet was a contradiction in recommendations regarding to diet by healthcare workers and media, which confused the patients. The only barrier to control of stress, which most patients, particularly females, mentioned was the lack of stress control skills; most health care providers also confirmed these issues. "I one wants to follow the diet, one has to be rich. For example my dietician has told me eat white meat, but I can't regularly buy it, fish is also very expensive, olive oil is also very expensive. (Female–Aged 43, diabetic).

"Many of our patients are depressed, particularly among diabetics, many of them are depressed and are anxious, this led them to believe not being able to control their disease" (Physician).

Self-efficacy

In regard to self-efficacy in following healthy diet, most patients with TD2, metabolic syndrome and very high blood lipids (cholesterol and triglyceride above 350 mg/dl), felt their ability relatively good in this regard, however most of them in parties, trips, when eating with family or when very hungry or when they see a tempting food, they felt their ability to avoid the food or to adhere diet low. However, most patients with pre-diabetes, hypertension, and low hyperlipidemia (triglyceride and cholesterol less than 350 mg/dl), felt their ability to adhere to diet relatively weak in most instances. Some patients felt that they eat more when angry or stressed and do not have the ability to be compliant with their diet; some felt that when they do not have anything to do at home they eat more and cannot be compliant with their diet.

"Unfortunately when we have party I get forced to eat more, also anger and stress makes me eat more, the food that my wife cooks for herself is very tempting. When I have nothing to do at home, I can't stop myself to go and eat something to make my stomach full. The family just tell me be compliant with the diet, however they don't help me, if my wife cooks a low fat food the family complain, they say why should we spoil or diet for father, sometimes when I get really hungry I eat a lot" (Male–Aged 49, metabolic syndrome).

In regards to regular physical activity most patients thought that they have the ability to perform physical activities however most of them felt that when they have physical problem such as knee pain, back pain or leg pain, or when they are not supported by family and friends, or when they have psychological problems such as depression or stress, when the weather is not good, when they are busy with work, when they go to holiday or when they have guests or when they are very tired, they do not have the ability to do exercises such as walking at all, or had very limited ability. "I love walking, however because of my leg pain I cannot maintain it, on the other hand if someone comes with me to go walking, I will be more motivated to continue it. However, no one comes" (Female–Aged 53, diabetic and hyperlipidemic).

Most patients could commence a healthy diet or start physical activity; however, they have problem to continue it on a regular basis. "The diet instructions we give to patients does not last long, I always tell them that it should be permanent but they follow it for some times then give it up, same thing with physical activity" (Dietician).

Most patients found stress and daily stressors such as unemployment, addiction, divorce, death of a relative, arguments with their partner/children and stress at work as the main cause of their illness. Most patients, particularly females, felt it difficult to control their stress under these situations and most

were unsure of their ability to control stress. Most healthcare providers also believed that patients cannot cope with their stress, or if they can only for a limited time and to some extent.

"Patients felt life stressors which resulted in their blood sugar, lipid level and blood pressure to go high. For example they say their sons or husbands are unemployed and stays at home, or they are addicted, or their daughter has divorced. Some mention they have problem with their partner, he/she doesn't understand them, these are the problems most patients perceived as the cause of their illness" (Dietician).

Discussion

The experiences of patients and healthcare providers showed that, lack of behaviors such as stress control, healthy diet, and physical activity were the main underlying roots of CVD. Li et al.[15] reported, high proportion of their respondents had unhealthy diet and most did not have enough physical activity, also they considered work stress as a risk factor for CVD. According to previous studies[7,16-18] most patients perceived stress as the most important factor in causing their risk factors. A study reported that stress can directly affect coronary heart disease and indirectly impact on it by affecting behaviors such as low physical activity and poor diet.[19] It can be concluded that stress may have an effect on patient's diet, physical activity and compliance with medications, to the extent that most patients felt that at times of stress they eat more, could not follow their diet and could not be motivated enough to do physical activity. However, in some studies patients did not find stress as cause of their disease.[9,20,21] This can possibly be explained by different socio-economic situation in our country compared to developed countries. Patients in our study mainly pointed out psycho-social stressors such as unemployment, low income, and addiction, divorce and family problems as cause of their stress.

The behavioral determinants were included knowledge, attitude, perceived susceptibility, perceived severity, perceived benefits, perceived barriers, and self-efficacy. Some patients did not understand how diabetes influences CVD risk factors and few had not adequate understanding about hyperlipidemia and its association with CVD risk which has also been reported in other studies.[18,22] According to Andric and Vuletic patients with increased understanding and high level of health literacy, had better perception of importance of a healthy diet and physical activity in controlling their disease and were motivated to adopt such behaviors. The current study demonstrated that patients with good understanding and positive attitude towards healthy diet and physical activity were unable to change their behavior.[23] The present findings are consistent with other studies concluding that knowledge, understanding and attitude alone do not necessarily alter behavior.[8,9,24-26] While a minimum knowledge threshold is needed to achieve long-term healthy behavior patterns[27-29] addressing patients' own perceptions of barriers, as well as their values, motivations and goals, has been found to be more effective than knowledge alone in changing behavior.[30]

The concept of perceived susceptibility involves one's own opinion of the probability of developing a condition.[31] According to the literature, perceived susceptibility is instrumental in motivating behavior change.[32] The beliefs concerning the significance of contracting an illness or condition and the subsequent medical consequences (i.e., pain, disability, and death) and the social costs (the effect on an individual's work, family, and social relationships) were identified as perceived severity.[31] Some studies have found an inverse relationship between perceived seriousness and behavior change and reported a high perceived severity causing treat and avoiding of action.[33] This study showed despite the fact that participants had good understanding of perceived severity of their chronic illness complications, their perceived susceptibility of getting stroke and CVD was low. The patients with T2D, metabolic syndrome, very high blood lipids (cholesterol and triglyceride above 350 mg/dl), and systolic blood pressure (above 160 mmHg), were perceived their condition as a serious problem. Due to fear of their disease complications, they had perceived severity more than the patients with pre-diabetes, moderate hyperlipidemia (< 350 mg/dl) and systolic blood pressure (< 160 mmHg), but most of patients did not perceive their susceptibility of getting stroke or CVD. This finding is in accord with the findings of the study by Morowatisharifabad,[34] indicating, among diabetic patients deteriorating eyesight, aching legs and blurred vision were more than getting CVD, despite the fact that they had perceived severity of diabetes complications. An important difference between the findings of the current study and the study conducted by Folta et al.,[9] was lack of perceived severity among participants. Subjects believed, they could live with CVD or overcome it. The reason for low perceived severity among participants was that they have no present risk factors or symptoms. This

suggests that as patients get closer to developing cardiovascular risk factors, the perceived severity increases. The findings showed that-the patients, who had both perceived susceptibility and severity together, were more likely to follow the health-related behaviors advised to them. The combination of susceptibility and severity has been labeled as perceived threat.[31] It may be that perceived susceptibility is a stronger predictor of engagement, if severity of health-related behaviors is perceived higher than lower.[35] The previous studies showed high perceived susceptibility and severity in patients with diabetes results in increased healthy behaviors among them.[34,36-38] Moreover, findings of this study is similar to Avis et al.,[32] who showed females had higher perceived susceptibility and severity towards CVD compared to men.

Perceived benefits can be defined as one's belief that undertaking a recommended action could decrease the risk or severity of potential illness.[31] In their study Kelly et al.[39] found that perceived benefits are a strong predictor of health behavior change, more explicitly in the areas of stress management, diet and physical activity. Their findings showed that high benefits of health-related behaviors were perceived by subjects. The physical and psychological health was mainly perceived to be improving by getting involved in regular physical activity which is similar to other studies.[27,40-42]

The most significant perceived benefit was related to feeling happy and refreshed as well as helping with control of blood sugar, lipid level, and blood pressure. Perceived benefits have also been reported as an important factor to adhere a healthy diet. This study showed that the benefits of adhering to healthy diet such as living longer, controlling hyperlipidemia and hyperglycemias, losing or maintaining weight, preventing complications and feeling healthier were perceived more than other benefits statements that were consistent with those reported by others.[43,44]

The perceived barriers, or one's belief around the tangible and psychological costs of the advised action, are noted to be the strongest predictor to make change in health behavior.[31] However, despite the fact that patients understood the high benefits of controlling stress, following healthy diet and increasing physical activity, they perceived high barriers in performing and engaging in such behaviors. The barriers related to regular physical activity in this sample were consistent with those reported by previous studies,[8,9,40,45] that difficulties in finding time to exercise were due to work or home duties, laziness and not having a partner. An important barrier mentioned by our participants, which was not highlighted in the previous studies, was physical problems such as leg pain, knee pain, and back pain. A factor that can be attributed to physical pain among patients at the time of walking was the fact that most patients were overweight.

In addition, Barriers to adhering to healthy diet were similar to the findings reported by previous studies,[8,9,43,44,46] that the high cost of healthy food, unacceptability of patients' diet with other family members, being tired of the taste of healthy food and lack of will were among the most important barriers for following a healthy diet. Unlike study by Roberts,[26] lack of time as barrier of healthy eating did not perceived by patients in current study because majority of the women were housewives and men were retired. In a study by Folta et al.,[9] wasting food came up as a barrier to change; women reported eating more than they want because they do not want to throw food away. It should be noted that avoiding throwing the food away was not found in our study to be one of the barriers to a healthy diet, which may be due to cultural differences. The study by Ard[47] found, that despite the knowledge and beliefs as well as low value of perceived barriers to eat healthy foods and high value of perceived benefits, acculturations are important factors in consumption of fruits, vegetables and the amount of fat intake. Findings reported by Airhihenbuwa et al.,[48] also seem to support the influence of culture on food preferences. If the perceived barriers are minimal as compared with the perceived susceptibility to or perceived severity of the disease, there is greater likelihood that the recommended health related action will be taken.[49]

In the present study, most patients, to some extent believed to their ability to stress management, performing regular physical activity, especially walking, and following a healthy diet. This concepts refers to self-efficacy, that is, one's confidence in being capable of performing a difficult or novel behavior.[50] The role of self-efficacy in staring and retaining healthy behaviors has been reported before.[51,52] For a behavior change to be successful, an individual must have confidence in own ability to overcome perceived barriers and have a strong belief that a specific action will result in a positive outcome.[53] Aljasem et al.[54] had reported that self-efficacy was the most important predictor of diabetes self-care behaviors. A study remarked that self-efficacy had a strong effect on

older adults' participation rates in physical activity, especially sustain a lifelong exercise pursuits.[55] Williams[56] indicated, that women with high self-efficacy and absence of perceived barriers to healthy eating (time and cost) were more likely to consume components of a healthy diet and less likely to consume components of an unhealthy diet. Findings from present study showed, that the more the individuals believe in his or her ability in performing behavior, the more they follow that behavior. Despite the ability of most patients in starting to control their stress, performing physical activity and following healthy diet, the problem that most patients was not being able to do these behaviors on a regular and continuous basis, this concept refer to maintenance of self-efficacy. This means one's confidence in being capable of keeping up a difficult behavior and focus on coping with imminent barriers.[51] According to the findings of previous studies,[57,58] maintenance self-efficacy was the most important predictor of physical activity and healthy diet behaviors.

Limitations

Participants of the study belonged to different socio-economic backgrounds, were of various degrees of CVD risk factors, and were of both genders and the variety of ages, It increase applicability of findings. Furthermore, findings of current study could support the predisposing category of PREEDE model. Moreover, data were analyzed appropriately and results were corroborated by using multiple reviewers, especially correspondence with Professor Green, the designer of PRECEDE model, to ensure that participant's viewpoints were adequately interpreted.

Conclusion

Among determinants, the importance perceived barriers and self-efficacy seemed to be unique to our population. Identifying the determinants of these behaviors will help the program planners in designing of future programs to select the most appropriate methods and applications to address these determinants in order to decrease unhealthy behaviors. An intervention can be designed to change behavioral factors related to health, but the most immediate impact of an intervention is usually on a set of well-defined determinants of behavior.

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Conflict of Interests

Authors have no conflict of interests.

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The effect of calcitriol on lipid profile and oxidative stress in hyperlipidemic patients with type 2 diabetes mellitus

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Original Article

Abstract

BACKGROUND: Cardiovascular mortality is high among diabetic patients due to abnormalities in the plasma lipid and lipoprotein metabolism, and increased oxidative stress. This study aimed to investigate the effects of active vitamin D on serum lipids and oxidative stress markers in type 2 diabetic patients.

METHODS: A double-blind randomized placebo-controlled trial was carried out in 70 participants with type 2 diabetes, aged 30-75 years of age. The participants were randomly assigned to two groups. One group received two capsules of calcitriol (0.25 µg 1,25-dihydroxycholecalciferol per capsule) per day. The second group received placebo tablets. All participants received their oral hypoglycemic drugs as prescribed by the endocrinologist. At the beginning, after 6 weeks, and at the end of the 12-week supplementation trial, serum total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglyceride (TG), and serum malondialdehyde (MDA) levels were measured.

RESULTS: There was a significant reduction in total cholesterol, LDL-cholesterol, TG, and MDA levels in both treatment and placebo groups ($P < 0.05$). Serum HDL-cholesterol level decreased significantly in the placebo group ($P < 0.05$), while it remained unchanged in the treatment group. However, the P values related to the between group's comparisons were not significant for any variables.

CONCLUSION: Active vitamin D reduced lipid profile and oxidative stress markers in diabetic patients compared to the control group, but these alterations were not statistically significant

Keywords: Diabetes Mellitus, Lipoproteins, Oxidative Stress, Vitamin D

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Introduction

Cardiovascular disease (CVD) is the leading cause of mortality and morbidity in the world. In 2005, CVD accounted for approximately 30% of deaths worldwide.[1,2] In diabetic patients, coronary atherosclerosis risk is 3–5 times greater than non-diabetics, despite controlling other risk factors.[3] The high cardiovascular mortality rate in diabetics could be attributed to abnormalities in lipid and lipoprotein metabolism and up-regulated oxidative stress.[4,5]

The classic role of vitamin D is maintaining calcium homeostasis and bone health.[6,7] However, in recent years, new functions are proposed for this vitamin such as prevention of certain types of cancer, diabetes mellitus, auto-immune disorders, and CVD.[8]

Low serum level of 25-hydroxycholecalciferol (25(OH)D) is associated with CVD, diabetes, obesity, hypertension, and dyslipidemia.[9] In a meta-analysis of cross-sectional and observational studies, Parker et al. have reported a 43% reduction in cardiometabolic disorders in those with the highest serum concentration of 25(OH)D.[10,11] Several mechanisms could be involved in this association such as controlling blood pressure, glycemia, body fat percent, and serum lipids by vitamin D.[8,12-15]

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Glucose tolerance abnormalities negatively affect the lipid profile.[16] In addition to lipid abnormalities, increased oxidative stress is an obvious feature of diabetes mellitus, which is related to cardiovascular risk.[17] The results of experimental studies approved the role of active vitamin D in lipid metabolism.[18]

On the other hand, it is reported in some studies that diabetes mellitus can reduce serum concentration of 25(OH)D.[16]

There are limited data on antioxidant properties of vitamin D, but in some studies, its antioxidant potential was considered to be even stronger than vitamin E and melatonin.[19,20]

Regarding increased prevalence of CVD in diabetic patients, and with respect to the role of vitamin D in lipid and lipoprotein metabolism and oxidative stress reduction, this study aimed to investigate the effects of active vitamin D on serum lipids and oxidative stress marker in type 2 diabetic patients.

Materials and Methods

This study is a part of a larger study conducted in 2011.[21] Figure 1 shows the flow diagram of the trial.

Study participants

In this double-blind randomized placebo-controlled trial, 70 participants of which 35 males and 35 females with type 2 diabetes and hyperlipidemia, aged 30–75 years, on treatment with oral hypoglycemic and hypolipidemic drugs were recruited from the outpatient Motahari Clinic at Shiraz University of Medical Sciences, Shiraz, Iran. To find our cases, we evaluated 1000 dossiers in the diabetes clinic and called the patients. Ten of these patients had died before the researchers' call. A large number of them (n = 530) did not meet the inclusion and hence were excluded. Eligible patients were invited to participate in the trial, but 390 of them declined to participate. Finally, 70 patients participated in the trial.

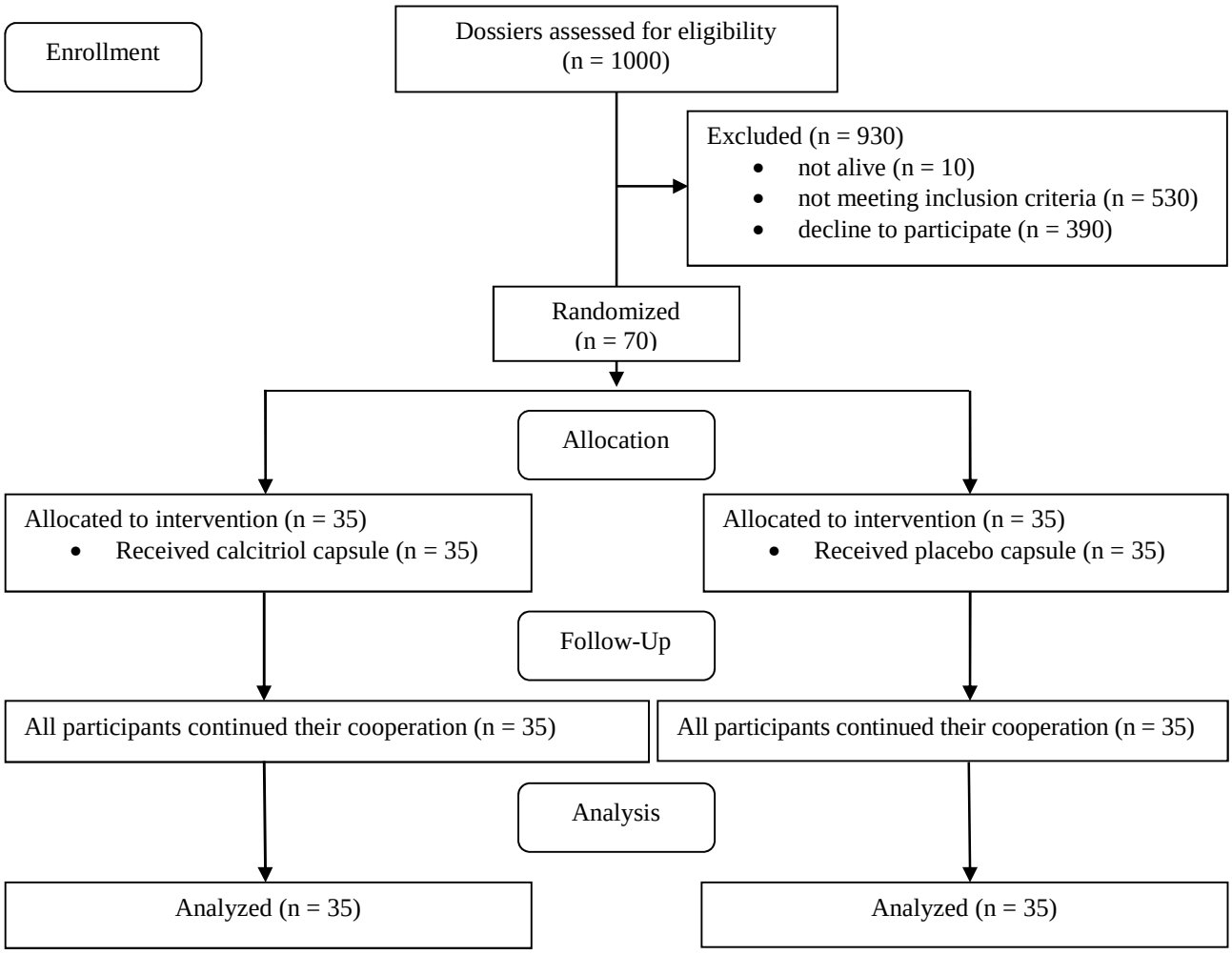

Figure 1. Flow diagram of the trial

No severe fluctuation was seen in their plasma glucose and hence there was no need to change their drugs dosage. Criteria for case inclusion were well-controlled fasting plasma glucose, serum calcium < 10.5 mg/dl, controlled low-density lipoprotein (LDL)-cholesterol, normal liver and kidney function and no history of kidney stone and hypercalcemia. The exclusion criteria included taking insulin for diabetes control, taking calcium and vitamin D supplements, history of diseases affecting vitamin D status, and intestinal malabsorptive disease.

At the beginning of the study, participants were given an oral and written explanation of the study, including its benefits and procedure, and were asked to read and sign an informed consent document.

The study protocol was reviewed and approved by the Human Ethics Committee of Research council of the Vice Chancellor for research affairs of Shiraz University of Medical Sciences. The code and date of ethical approval was 2009/8/3 and 88-4617. Iranian clinical trial registration number of this study is IRCT138806282480N1.

Background characteristics assessment

Demographic data were collected by interviews and anthropometric indices were determined for each subject. Anthropometric assessments included measurement of weight and height. Body weight was measured to the nearest 0.1 kg using the Seca 713 scale, while subjects were minimally clothed. Height was determined using non stretchable measuring tape, without shoes and subsequently body mass index was calculated by dividing weight (kg) by squared height (m^2). All equipments were calibrated every morning.

Intervention design

This 12 weeks clinical trial was conducted between August and November month of 2009. Using balanced block randomization method, we allocated the patients randomly into one of the two study groups: treatment and placebo group. One group received two capsules of calcitriol (0.25 mcg 1,25-dihydroxycholecalciferol per each capsule) per day. The second group received identical-looking placebo tablets. All calcitriol tablets and their placebo had the same color and shape and were produced by Zahravi Pharmacy Company (Tehran, Iran). All the participants received their oral hypoglycemic drugs as well, as prescribed by the endocrinologist. The participants were asked not to take any vitamin or supplements during the trial. The researcher supervised the ingestion of supplements each week.

Biochemical assessment

At the beginning, after 6 weeks, and at the end of the 12 week supplementation trial, 10 ml fasting venous blood samples were drawn from the patients' arms after 12 h fasting. Blood was collected for measurement of serum total-cholesterol, LDL, high-density lipoprotein (HDL), triglyceride (TG), and malondialdehyde (MDA). Total cholesterol, HDL, and TG were measured by spectrophotometric methods. Serum LDL-cholesterol was calculated using Friedwald formula.[22] Serum concentrations of MDA were measured by the modified thiobarbituric acid method (spectrophotometric method).[23]

Statistical analysis

The normality of distributions was checked for all variables. Data processing and analysis were performed using SPSS for windows (version 15.5, SPSS Inc., Chicago, IL, USA). Normally distributed data were expressed as mean (± standard deviation). Baseline characteristics of treatment and placebo groups were compared using independent Samples t-test. General linear model repeated measures analysis was used for comparing triple measurements in each group. Significance level was set at $P < 0.05$.

Results

A total of 70 diabetic patients (35 males and 35 females) participated in our study. Background characteristics of the participants are displayed in table 1.

Table 1. Comparison of the baseline characteristics between treatment and placebo group

Variable	Treatment	Placebo	P*
Gender (%)			
Male	10 (28.5)	10 (28.5)	> 0.999
Female	25 (71.5)	25 (71.5)	
Age (year)	53.8 ± 8.9**	52.4 ± 7.8	0.462
Weight (kg)	72.9 ± 12.7	70.9 ± 12.5	0.514
Height (cm)	160.3 ± 8.9	161.1 ± 10.4	0.718
BMI (kg/m^2)	28.3 ± 4.4	27.0 ± 3.4	0.164
Education (year)	7.2 ± 4.5	7.2 ± 4.8	0.980
Diabetes duration (year)	6.3 ± 5.3	6.6 ± 4.8	0.819
Metformin (mg/day)	1450.0 ± 700.0	1200.0 ± 600.0	0.110
Glybenclamide (mg/day)	16.0 ± 6.5	14.5 ± 8.5	0.437
Atorvastatin (mg/day)	20.2 ± 9.2	18.4 ± 6.8	0.605

* Independent samples t-test; ** Mean ± SD; SD: Standard deviation; BMI: Body mass index

Table 2. Between group and within group comparison of lipid profile and oxidative stress marker in diabetic patients*

Variable	Placebo				Treatment				Placebo versus treatment	Time-treatment interaction
	Baseline (1)	6 weeks (2)	12 weeks (3)	P§	Pair wise comparisons**	Baseline (1)	6 weeks (2)	12 weeks (3)	P§	Pair wise comparisons**	P¥	P€
FBS (mg/dl)	141.8 ± 48.5	153.7 ± 57.2	157.7 ± 60.8	0.038	1, 3 (P = 0.03)	145.6 ± 52.1	148.1 ± 52.0	143.8 ± 51.8	0.712		0.66	0.12
Total cholesterol (mg/dl)	199.7 ± 46.2	182.7 ± 44.7	158.2 ± 40.8	< 0.001	1, 2; 1,3; 2,3 (P < 0.001)	195.7 ± 36.0	170.8 ± 34.1	150.2 ± 37.9	< 0.001	1, 2; 1, 3 (P < 0.001) 2, 3 (P = 0.002)	0.36	0.55
LDL-C (mg/dl)	123.7 ± 41.9	109.1 ± 33.8	97.0 ± 33.8	< 0.001	1, 2 (P = 0.010) 1, 3 (P < 0.001)	120.8 ± 34.6	98.5 ± 27.7	89.7 ± 28.6	< 0.001	1, 2 (P = 0.001) 1, 3 (P < 0.001)	0.31	0.57
HDL-C (mg/dl)	35.6 ± 9.6	37.0 ± 11.2	33.0 ± 8.3	0.040	2, 3 (P = 0.04)	39.2 ± 12.5	38.0 ± 13.9	35.4 ± 10.7	0.100		0.30	0.58
TG (mg/dl)	201.6 ± 116.2	190.4 ± 124.7	140.7 ± 102.9	< 0.001	1, 3 (P < 0.001) 2, 3 (P = 0.002)	178.0 ± 83.1	147.8 ± 67.3	124.8 ± 73.3	< 0.001	1, 2 (P = 0.02) 1, 3 (P < 0.001)	0.19	0.29
MDA (µmol/l)	4.2 ± 0.8	3.70 ± 0.8	3.5 ± 0.7	0.001	1, 2 (P = 0.01) 1, 3 (P < 0.001)	4.17 ± 0.7	3.68 ± 0.7	3.52 ± 0.7	< 0.001	1, 2 (P < 0.001) 1, 3 (P < 0.001)	0.93	0.89

* General linear model repeated measures analysis; § Within groups; ** Adjustment for multiple comparisons: Bonferroni; ¥ Between groups; € Time-treatment interaction
FBS: Fasting blood sugar; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; TG: Triglyceride; MDA: Malondialdehyde

The mean dose of metformin prescribed to control their blood glucose was 1450 ± 700 and 1200 ± 600 mg/day in treatment and placebo groups, respectively. These values were 16 ± 6.5 and 14.5 ± 8.5 mg/dl, respectively for glybenclamide.

At the beginning of the study, there was no significant difference in the variables between placebo and control group. As shown in table 2, there was a significant reduction in total cholesterol, LDL-cholesterol and TG level in both treatment and placebo groups ($P < 0.05$). Serum HDL-cholesterol level decreased significantly in the placebo group ($P < 0.05$); while it remained unchanged in the treatment group. We also measured MDA as oxidative stress marker. It decreased in both groups significantly ($P < 0.05$). However, the P values related to the between group's comparisons were not significant for any variables. Furthermore, time-treatment interactions were not statistically significant for any variables.

Table 3 shows the mean difference of variables between the beginning and end of the study. Although the reduction in total cholesterol and LDL was more pronounced in the treatment group, it was not statistically significant.

Discussion

The present study showed that active vitamin D reduced lipid profile and oxidative stress markers in diabetic patients compared to the control group, but these alterations were not statistically significant.

Several studies demonstrated that 25(OH)D levels were inversely correlated with total cholesterol, LDL, TG, and low HLD level.[8,16] Multiple interventional studies have investigated the effect of vitamin D supplementation on lipids and have produced conflicting results. An early small study evaluating the effect of short-term calcium (1000 mg daily) and vitamin D (800 IU daily) supplementation in healthy postmenopausal women showed no change in the levels of lipid parameters.[18] Motiwala and Wang[18] and Zittermann et al.[24] randomized overweight participants to vitamin D supplementation versus placebo over 12 months and found a significant decrease in TGs, but not LDL level. Jorde and Figenschau[25] found in their study that high dose vitamin D supplementation in diabetic patients did not have any effect on the lipid profile. Major et al.[26] showed that in overweight or obese women with low calcium intakes, supplementation with calcium and vitamin D improved blood lipid and lipoprotein during a weight-loss intervention. In a study by Bonakdaran et al.,[27] supplementation with 0.5 µg

Table 3. Comparison of the mean difference of variables at the beginning and end of the study (end-beginning) between the two groups

Variable	Placebo	Treatment	P*
Total cholesterol (mg/dl)	−41.5 ± 5.90**	−45.5 ± 5.60	0.635
LDL-C (mg/dl)	−26.7 ± 5.50	−31.0 ± 4.40	0.544
HDL-C (mg/dl)	−2.6 ± 1.40	−3.8 ± 1.80	0.610
TG (mg/dl)	−60.9 ± 12.40	−53.2 ± 1107.00	0.657
MDA (µmol/l)	−0.7 ± 0.10	−0.6 ± 0.09	0.784

* Independent *t*-test; ** Mean ± standard error; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; TG: Triglyceride; MDA: Malondialdehyde

calcitriol versus placebo for 8 weeks in chronic renal failure patients on hemodialysis lowered the serum TG and total-cholesterol. Ultraviolet (UV) radiation for 12 months did not have any effect on the serum lipids, but in a subgroup of subjects with vitamin D insufficiency (25(OH)D < 30 ng/ml), UV radiation increased apo-AI and decreased apo-AII level.[28]

Several mechanisms are recommended for the impact of vitamin D on the serum lipids. In theory, vitamin D could affect the serum lipid levels directly, but also indirectly through its effect on serum parathyroid hormone (PTH) and/or on the calcium balance.[10]

Two mechanisms might be involved in vitamin D mediated reduction in serum TGs: (1) vitamin D increases intestinal calcium absorption. This calcium could then reduce the serum TGs by reducing hepatic TG formation and secretion; (2) via a suppressive effect of vitamin D on serum PTH concentrations. A reduction in serum PTH may reduce the serum TGs via increased peripheral removal.

Free radical production is up-regulated in hyperglycemia.[29,30] Increased free radicals in oxidative stress cause DNA, lipid, carbohydrate and protein oxidation and hence tissue damage.[31] There are limited data on antioxidant properties of vitamin D. It is shown in some studies that vitamin D acts as a membrane antioxidant.[19] Antioxidant properties of vitamin D was proved in two animal studies,[32,33] and it has been estimated to be even stronger than vitamin E and melatonin.[20] Vitamin D supplementation in vitamin D deficient subjects decreased the level of the serum thiobarbituric acid reactive substances (TBARS) significantly.[20] In our study, active vitamin D did not reduce serum TBATS significantly.

We saw a significant decrease in total cholesterol, LDL, and TG level in the placebo group. These changes could have two reasons. First, it can be related to the "regression to the mean" phenomenon. In statistics, regression toward the mean (also known as regression to the mean) is the phenomenon in which if a variable is extreme on its first measurement, it will tend to be closer to the average on a second measurement, and a fact that may superficially seem paradoxical—if it is extreme on a second measurement, it will tend to be closer to the average on the first measurement.[34,35] To avoid making wrong inferences, the possibility of regression toward the mean must be considered when designing experiments and interpreting experimental, survey, and other empirical data in the physical, life, behavioral, and social sciences.[34,35] Second, it can be attributed to the placebo effect and behavior modification in the placebo group during this follow-up.

Future studies on vitamin D deficient subjects, and within the subgroups of vitamin D receptor polymorphisms are worth to be done. The strength of our study included its randomized, placebo controlled design and a drawback to our study is that we assessed only one marker to evaluate oxidative stress.

Conclusion

Active vitamin D reduced lipid profile and oxidative stress markers in diabetic patients compared to the control group, but these alterations were not statistically significant.

Acknowledgments

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Conflict of Interests

Authors have no conflict of interests.

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Acute effects of smoking on QT dispersion in healthy males

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Original Article

Abstract

BACKGROUND: Cigarette smoking increases the risk of ventricular fibrillation and sudden cardiac death (SCD). QT dispersion (QTD) is an important predictor of cardiac arrhythmia. The aim of this study was to assess the acute effect of smoking a single standard cigarette containing 1.7 mg nicotine on QT interval and QTD in healthy smokers and nonsmokers.

METHODS: The study sample population consisted of 40 healthy male hospital staff, including 20 smokers and 20 nonsmokers. They were asked to refrain from smoking at least 6 h before attending the study. A 12-lead surface electrocardiogram (ECG), recorded at paper speed of 50 mm/s, was obtained from all participants before and 10 min after smoking of a single complete cigarette. QT interval, corrected QT interval, QTD, and corrected QT dispersion (QTcD) were measured before and after smoking.

RESULTS: Smokers and nonsmokers did not have any significant differences in heart rate (HR) (before smoking = 67.35 ± 5.14 vs. 67.70 ± 5.07, after smoking = 76.70 ± 6.50 vs. 76.85 ± 6.50, respectively), QTD (before smoking = 37.75 ± 7.16 vs. 39.15 ± 6.55, after smoking = 44.75 ± 11.97 vs. 45.50 ± 9.58, respectively), and QTcD (before smoking = 39.85 ± 7.40 vs. 41.55 ± 6.57, after smoking = 50.70 ± 14.31 vs. 51.50 ± 11.71, respectively). However, after smoking a single cigarette, HR, mean QTD, and QTcD significantly increased (all had P value <0.001) in comparison to the measures before smoking.

CONCLUSION: Smoking of a single complete cigarette in both smokers and nonsmokers results in significant QTD increase, which can cause arrhythmia and SCD.

Keywords: Cardiac, Death, Electrocardiography, Smoking, Sudden

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Introduction

Effects of smoking on various organ-systems such as the cardiovascular system are evaluated in a vast range of researches. Chronic cigarette smoking, as a risk factor of atherosclerosis and endothelial dysfunction, can cause acute coronary syndrome and sudden death.[1,2] Acute effects of smoking on cardiovascular function are complex. It can transiently raise systemic blood pressure, peripheral vascular resistance, heart rate (HR), it also can change parameters of HR variability and also cause echocardiographic evidences of diastolic dysfunction.[3-5] It is already known that smoking not only increases mortality due to coronary artery disease but also increases mortality secondary to sudden cardiac death (SCD).[6] On the other hand, long QT interval is reported as a predictor of arrhythmia risk. Prolonged QT interval dispersion (QTD) can predict ventricular arrhythmia due to excessive loss of synchronization of ventricular

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repolarization.[7,8] Our study was conducted to determine the acute effect of smoking on QTD in the smoker and nonsmoker healthy males.

Materials and Methods

A prospective cohort study with before and after the design was performed in Taleghani Hospital, Tehran, Iran in April and May 2012. The sample size was calculated as 20 subjects in each group considering $\alpha = 5\%$, $d = 1$, statistical power of 0.925.

Hence, 40 persons included 20 professional smokers (with smoking habit of at least 5 pack/year before the study onset), and 20 nonsmokers (with smoking habit of 0.5 pack/year or less prior to the study onset), selected from 63 young male hospital staff (age < 40 years) volunteers after considering exclusion criteria randomly. All selected cases did not have a history of hypertension, cardiac, or pulmonary disease with normal resting electrocardiogram (ECG) and normal echocardiography. Cases with diabetes mellitus, renal failure, and those with signs or symptoms of coronary artery disease were excluded. None of the subjects was on chronic medication. Two cardiologists confirmed health of all participants according to routine cardiovascular examination.

To control the effect of other confounding factors such as recent smoking, tea, caffeinated beverage, and body position, all participants were asked to refrain from smoking at least 6 h before attending the study and were also asked not to consume tea and caffeinated beverages for 3 h before the study. Test was done in the morning, all subjects rested in the supine position to stabilize HR. After 10 min, a baseline standard 12-lead surface ECG was obtained during normal respiration. Later, participants were asked to smoke a single complete cigarette containing 1.7 mg nicotine in a sitting position and again lay down in the supine position. Ten minutes after smoking, second ECG records were obtained.

This research was accomplished with the budget of Shaheed Beheshti University of Medical Sciences, and all stages were in accordance with ethical issues of the university Ethics Committee (Ethical Approval Code: 308/290-2011). The participants were informed about the study protocol and then requested to sign the consent form.

ECG tracing

ECGs were traced with the speed of 50 mm/s and amplitude of 20 mA. QT interval was measured manually in each lead from the onset of QRS to the end of T-wave. Termination of T-wave was defined as its return to the TP isoelectric baseline. At the presence of U-wave, nadir of the curve between T- and U-waves was defined as the end of T-wave. In biphasic T-wave, the final return to the baseline was selected. Leads, in which due to low amplitude T-wave, QT interval could not be measured reliably, were omitted from the analysis. QTD was defined as a difference between maximum and minimum interval of measured QT intervals in the 12 lead ECGs. Corrected QT (QTc) and Corrected QT interval dispersion (QTcD) were calculated according to Bazett's formula by dividing QT by the square root of the RR interval.[9] $QTc = QT/\sqrt{RR}$.

ECG parameters were measured by two blind cardiologists who were oriented to the QT measurement method. If there was a difference in their measurement, the mean value accepted.

Statistics

All data are expressed as mean ± SD. Data analysis was performed by using SPSS statistical software (version 17.0, SPSS Inc., Chicago, IL, USA). Normal distribution was checked by Kolmogorov-Smirnov test. Data before and after smoking were compared by paired Student's t-test. As QT dispersion and QTc dispersion had not a Gaussian distribution, Wilcoxon signed-rank test was used. The magnitude of change in QTD and QTcD with smoking was compared by Mann-Whitney U test. Pearson correlation coefficients were calculated to determine the strength of linear relationships between changes of QTD, QTcD, and HR changes before and after smoking. Results were considered as significant at an error probability level of $P < 0.05$.

Results

All 40 participants completed the study, and there were not any missing value. The mean age of professionals was 31.6 ± 4.8 years and of nonsmokers was 31.0 ± 5.6 years. Mean baseline and post-interventional measures (HR, QTD, QTcD) in both groups are summarized in table 1. There was no statistically significant difference in the baseline measures and measures obtained after smoking in both groups.

As there was no significant difference between the indices of the two groups, we pooled data from both professional and nonprofessional smokers to evaluate the effect of smoking on our variables.

Among 40 subjects, the mean HR, mean QTD, and mean QTcD were 67.53 ± 5.04, 38.45 ± 6.81, and 40.70 ± 6.92 respectively. After smoking a single cigarette, the same parameters increased significantly ($P < 0.001$) to 76.78 ± 6.41, 45.13 ± 10.71, and 51.10 ± 12.91, respectively (Table 2).

The difference between HR before and after smoking had positive linear correlation with QTD difference (r = 0.741) and changes in QTcD (r = 0.812) (Figures 1 and 2).

Table 1. Electrocardiogram (ECG) findings obtained before and after smoking in professional smokers and nonsmokers separately

	Before smoking		P	After smoking		P
	Nonsmokers	Professional smokers		Nonsmokers	Professional smokers	
HR (bpm)	67.70 ± 5.07	67.35 ± 5.14	0.82	76.85 ± 6.50	76.70 ± 6.50	0.97
QTD (ms)	39.15 ± 6.55	37.75 ± 7.16	0.69	45.50 ± 9.58	44.75 ± 11.97	0.84
QTcD (ms)	41.55 ± 6.57	39.85 ± 7.40	0.55	51.50 ± 11.71	50.70 ± 14.31	0.81

HR: Heart rate; QTD: QT interval dispersion; QTcD: Corrected QT interval dispersion; Values are mean ± SD

Table 2. Electrocardiogram (ECG) findings obtained before and after smoking

	Before smoking	After smoking	Difference	P
Mean HR (bpm)	67.53 ± 5.04	76.78 ± 6.41	9.25 ± 4.27	0.001
QTD (ms)	38.45 ± 6.81	45.13 ± 10.71	6.67 ± 7.99	0.001
QTcD (ms)	40.70 ± 6.92	51.10 ± 12.91	10.40 ± 10.32	0.001

HR: Heart rate; QTD: QT interval dispersion; QTcD: Corrected QT interval dispersion; Values are mean ± SD

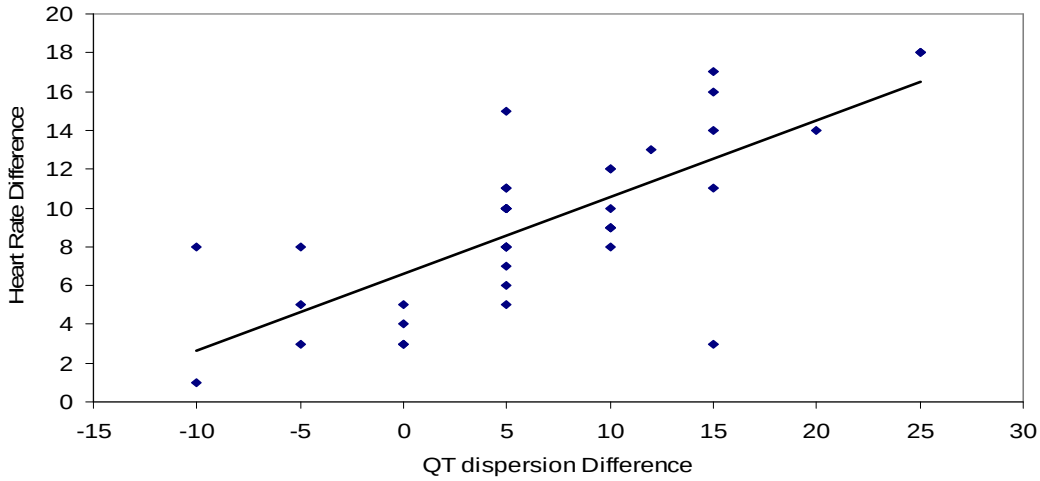

Figure 1. Scatter plots of correlation between difference of heart rates before and after smoking and QT dispersion difference

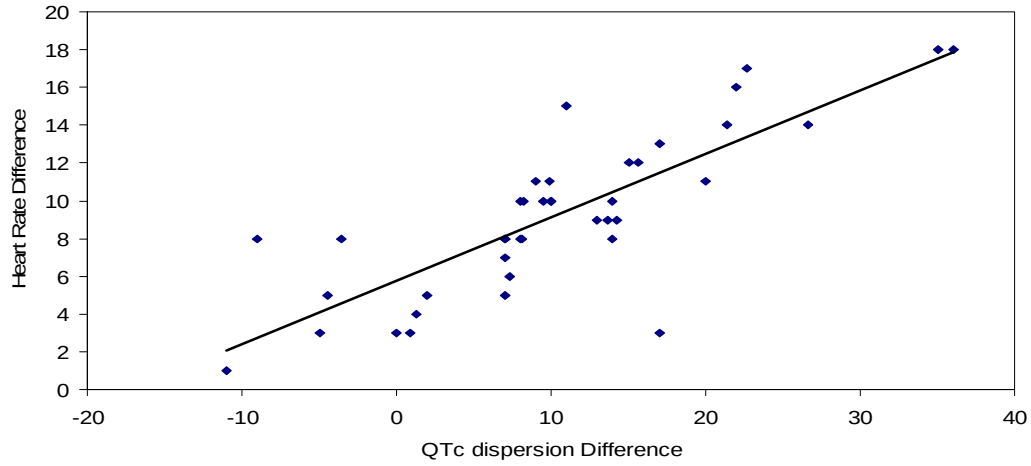

Figure 2. Scatter plots of correlation between difference of heart rates before and after smoking and QTc dispersion difference
QTc: Corrected QT

Discussion

As smoking can increase coronary artery disease, it may cause some harmful changes in electrical function of myocardial cells. It may predispose to ventricular fibrillation and SCD by altering ventricular recovery time dispersion indices. QTD is an important parameter that reflects heterogeneity of ventricular repolarization and predicts ventricular arrhythmia and sudden death.[10] Apart from the cumulative effect of smoking on the cardiovascular system, it should be considered that even a single cigarette induces the potential of SCD and arrhythmia by prolongation of QTD. Products of nicotine, tar, and nitric oxide derived free radicals interfere with normal chemical interactions of the body after smoking.[11,12] For example, it is known that nicotine is a nonspecific blocker of potassium channels and has several pathophysiologic effects, including tachycardia, increased blood pressure, and catecholamine release, particularly within the short period after smoking. It can also prolong the action potential duration and depolarize membrane, so may cause QTD too.[1,13] It has been reported that QT dispersion > 80 ms increases risk of cardiac death.[8]

In our research in accordance with previous researches, acute smoking significantly increased QTD and QTcD,[14,15] but in contrast to Singh findings, in our study this increase was significant in both smokers and nonsmokers.[14] And in addition to QTD and QTcD values, which were measured in Khosropanah and Barkat study, we have also assessed the relationship between QT interval increase and acute smoking, which was significant.[15] Our results differ from Karakaya et al. findings of no significant difference between QT interval and QTD measures before and after smoking.[16]

Our study results showed that, the difference between HR before and after smoking had a strong correlation with QTD and QTcD. Consequently with more increase in HR after smoking, there would be more increase in QTD and QTcD and vice versa.

According to our results, QTD increase occurs in both groups of smokers and nonsmokers. Hence, it seems that there is no cardiac adaptation or tolerance to effects of smoking even in professional smokers, and smoking of even a single cigarette, regardless of past history of smoking increases QT dispersion, which is a predictor of cardiac arrhythmia and SCD.

Limitation of Study

Our study has some limitations. First, we included a small number of participants. So, we pooled two groups of professional and nonprofessional smokers for analysis. However, despite this small size, we were able to detect a significant change of QT dispersion associated with smoking. Second, we studied on young healthy participants. Therefore, our results should be interpreted with caution in other groups. Third, this study simply observed the acute change of QT with smoking, there is always chance that this change was due to some unobserved confounding variable or systematic bias.

Acknowledgments

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Conflict of Interests

Authors have no conflict of interests.

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Subarachnoid block with low dose of bupivacaine and sufentanil in patients with coronary artery disease

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Original Article

Abstract

BACKGROUND: Subarachnoid block with local anesthetics and opioids enable efficacious spinal anesthesia because of their synergistic effect and permit the use of low-dose local anesthetics, which results in a stable hemodynamic state. The purpose of this study was to describe the cardiovascular effects of spinal anesthesia with low-dose bupivacaine and sufentanil on patients with coronary artery disease.

METHODS: This study was a double-blind randomized clinical trial. A total of 18 patients who had known coronary artery disease were enrolled. Our subjects underwent spinal block for lower limb surgery with 7.5 mg hyperbaric bupivacaine 0.5% and 5 µg sufentanil. Complications related to anesthesia such as hypotension, bradycardia, vasopressor need, and blood or volume use were recorded.

RESULTS: The average mean arterial pressure decreased 15% in the first 15 min of spinal block in our cases. No patients presented with hypotension and the subjects were without complaints during the spinal anesthesia. All patients remained alert, and no ST segment changes were observed intraoperatively and until 6 h after the operation. Baseline ejection fraction (EF) 40% or less was observed in 10 patients and these subjects were compared with other patients. Systolic and diastolic blood pressures, mean arterial pressure, and heart rate decreased during the first 15 min in response to spinal anesthesia in both groups of patients, but decreased more significantly in patients with EF > 40%.

CONCLUSION: We recommend spinal block with low-dose bupivacaine and sufentanil in patients with coronary artery disease and especially in patients with low EF.

Keywords: Bupivacaine, Coronary Artery Disease, Subarachnoid Block

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Introduction

Spinal anesthesia is used as a safe method in patients because of hemodynamic benefits compared with general anesthesia such as minimum decrease in myocardial contractility and only modest decreases in blood pressure and cardiac output.[1] These characteristics are attractive for elderly patients, especially with known coronary artery disease because of reduced cardiovascular reserve and predispose to hemodynamic instability. Sympathetic nervous system activity increases in patients with heart disease,[2,3] therefore, these patients after spinal anesthesia could be at risk of greater decreases in systemic vascular resistance (SVR) and blood pressure. In previous studies was shown that using small dose of local anesthetic could be minimized hypotension of spinal anesthesia.[1,4] Low-dose of local anesthetic may not provide acceptable anesthesia, then opioids and local anesthetic administered together because of potent synergistic analgesic effect. Sufentanil has a higher affinity for the opioid receptor than fentanyl and it superior to fentanyl for hemodynamic stability and postoperative pain relief in patients.[5] The problem of general anesthesia in patients with low cardiovascular

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reserve is hemodynamic instability and sometimes operation of these subjects is canceled. It seems that spinal anesthesia with a small dose of local anesthetics and opioid in these patients can safely be done. The purpose of this study was to describe the cardiovascular effects of spinal anesthesia with low dose of bupivacaine and sufentanil on patients with coronary artery disease.

Materials and Methods

Study design and samples

Eighty patients with American Society of Anesthesiologists (ASA) physical status I–III who underwent spinal anesthesia for lower limb surgery were identified in this randomized, double-blind clinical trail from June 2011 to February 2012. After approval of this study in local ethical committee, 18 patients with ASA physical status III, who had known coronary artery disease provided written informed consent and included in our study. Patients with recent deterioration in their medical status, such as unstable angina, severe congestive heart failure, and malignant arrhythmia were excluded. Standard monitoring including continuous electrocardiogram, heart rate, non-invasive arterial blood pressure, and continuous pulse oximetry and ST segment analyzer (Novin S1800, Iran) was used during surgery. The sensory and motor block was evaluated by pinprick test and modified Bromage scale (0 = no motor block; 1 = hip blocked; 2 = hip and knee blocked; 3 = hip, knee, and ankle blocked), respectively.[6]

Procedures

All patients preloading with 5 ml/kg ringer lactate and then underwent dural puncture with the midline approach at the L3-L4 interspace using a 25-Gauge Whitacre spinal needle. After free cerebrospinal fluid flow had been observed, 7.5 mg hyperbaric bupivacaine 0.5% (Marcaine Spinal Heavy, Astra, Sweden) and 5 μg sufentanil (Janssen-Cilag, Belgium) was injected through the needle. Specific gravity of the solutions at 37°C was 1.020. Then, patients were immediately turned to supine. The complication related anesthesia such as hypotension, bradycardia, vasopressor need, and blood or volume use were recorded. Hypotension was defined as a systolic blood pressure < 90 mmHg or a decrease of more than 25% from the baseline mean arterial pressure at the first 30 min after spinal anesthesia. The hypotension episodes were treated with a loading dose of intravenous fluids and intravenous bolus of ephedrine 5–10 mg.

Statistical analysis

The statistical significance of the effect of spinal anesthesia was assessed by using SPSS for Windows (version 16, SPSS Inc., Chicago, IL, USA). Associations among variables were assessed by the Student's t-test and the ANOVA test. Associations among variables were assessed with the Pearson correlation coefficient. Values are reported as mean ± SD. Significance was defined as $P < 0.05$.

Results

The average mean arterial pressure decreased 15% (11.2 mmHg to 9.52 mmHg) in first 15 min of spinal block in our cases. The level of sensory block following anesthesia was observed in T6 (n = 2), T7 (n = 2), T8 (n = 10) and T10 (n = 4). The grade of motor block after spinal anesthesia was 0 (none), 1 (none), 2 (n = 4), and 3 (n = 14). No patients presented with hypotension and the subjects were without complaints during the spinal anesthesia. All patients remained alert, and no ST segment changes were observed intra-operative and till 6 h after operation. No patients presented with bradycardia or HR above 95 bpm during spinal anesthesia. In our study none of subjects complained of pain intraoperatively, although some of the surgical operation lasted as long as 120 min. Ten patients had baseline ejection fraction (EF) 40% or less and these subjects compared with other patients with EF more than 40%. Systolic, diastolic, mean arterial pressure, and heart rate were decreased during first 15 min in the response to spinal anesthesia in both groups of patients, but significantly more decreased in patients with EF > 40% (Table 1, Figures 1A–D).

Discussion

This study evaluated the effects of spinal anesthesia with low dose of bupivacaine and sufentanil in 18 patients with ASA class 3 who had coronary artery disease. The 15% average decrease in mean arterial pressure was not dramatic compared with other report with 21–32% decrease in mean arterial pressure in patients with regular dose of bupivacaine.[4,6,7] Patients with cardiac disease may have played a different role in the response to spinal anesthesia compared with healthy patients. Resting sympathetic nervous system activity and norepinephrine release from nerve terminals have increased in patients with cardiac disease,[8,9] therefore sympathetic activity block following spinal anesthesia would be expected to exaggerate the decrease in SVR and more episodes of hypotension. In our study, no patients presented with hypotension and did not need to vasopressor. The main mechanism for hypotension after spinal block

is a decreased in SVR and loading of crystalloid alone may not be able to compensate decrease in SVR. Decreases in cardiac output during spinal anesthesia due to shift in blood from the heart to peripheral arteries, but not due to decrease in cardiac contractility, therefore, use of vasopressor injection is associate with an increase in cardiac output.[10] Although the most commonly used vasopressor for hypotension associated with spinal anesthesia (HAS) is ephedrine, but may not be the drug of choice in this situation. It is not a potent vasopressor; therefore, ephedrine may not reliably reverse decrease in SVR.[11,12] Moreover, ephedrine treatment of hypotension increases heart rate and would be expected to be particularly deleterious in the patient with ischemic cardiac disease.[13,14] Epinephrine infusion during spinal anesthesia has been shown to restore systolic arterial pressure and increase cardiac output, but with no increase in diastolic or mean arterial pressure.[15] Our study showed that use of low dose of bupivacaine plus sufentanil for lower limb surgery in patients with coronary artery disease provides successful anesthesia and with minimum episodes of hypotension and minimum need for vasopressor support. Cardiac output remains constant when the decrease in systolic arterial pressure is < 25% following spinal anesthesia.[4] Furthermore, it was shown that the small dose of bupivacaine plus sufentanil caused dramatically less hypotension and nearly eliminated the need for vasopressor support of blood pressure.[6] It was noted that the EF increased in patients with baseline EF 25% or less and unchanged in patients with baseline EF 50% or more.[6] We think that the reason for increase in EF in patients with low EF was afterload reduction and lack of change in the pressure-volume ratio contractility index. Previous studies showed that left ventricular function in patients with coronary artery disease has been preserved during lumbar epidural anesthesia with reporting no regions of diminished wall motion,[5] but one study reported new wall motion abnormalities in 4 of 10 subjects.[16-19] It was shown that heart rate varies by 10% during subarachnoid block, usually decreasing with traditional dose of local anesthetic. However, several studies have suggested that there are opposing factors affecting heart rate.[4,7] Heart rate in our subjects was unchanged with low dose of local anesthetic. In our study, none of the subjects complained of pain intraoperatively, although some of the surgical operation lasted as long as 120 min.

Table 1. The comparison of decreased of systolic, diastolic, mean arterial pressure, and heart rate during first 60 min in response to spinal anesthesia in patients with ejection fraction (EF) ≤ 40% and EF > 40%

Variables	EF ≤ 40% (%)	EF > 40% (%)	P
Systolic blood pressure			
5 min	2.8	10.8	
10 min	7.0	16.5	
15 min	11.9	19.4	< 0.001
30 min	11.9	20.0	
60 min	11.2	18.8	
Diastolic blood pressure			
5 min	2.2	8.7	
10 min	3.3	14.5	
15 min	15.5	19.4	< 0.001
30 min	16.6	18.4	
60 min	14.4	19.4	
Mean arterial pressure			
5 min	1.9	10.0	
10 min	4.7	15.7	
15 min	14.0	19.6	< 0.001
30 min	13.0	19.6	
60 min	12.1	18.8	
Heart rate			
5 min	3.1	6.2	
10 min	6.2	7.4	
15 min	9.4	12.3	< 0.001
30 min	9.3	13.5	
60 min	8.3	11.1	

EF: Ejection fraction

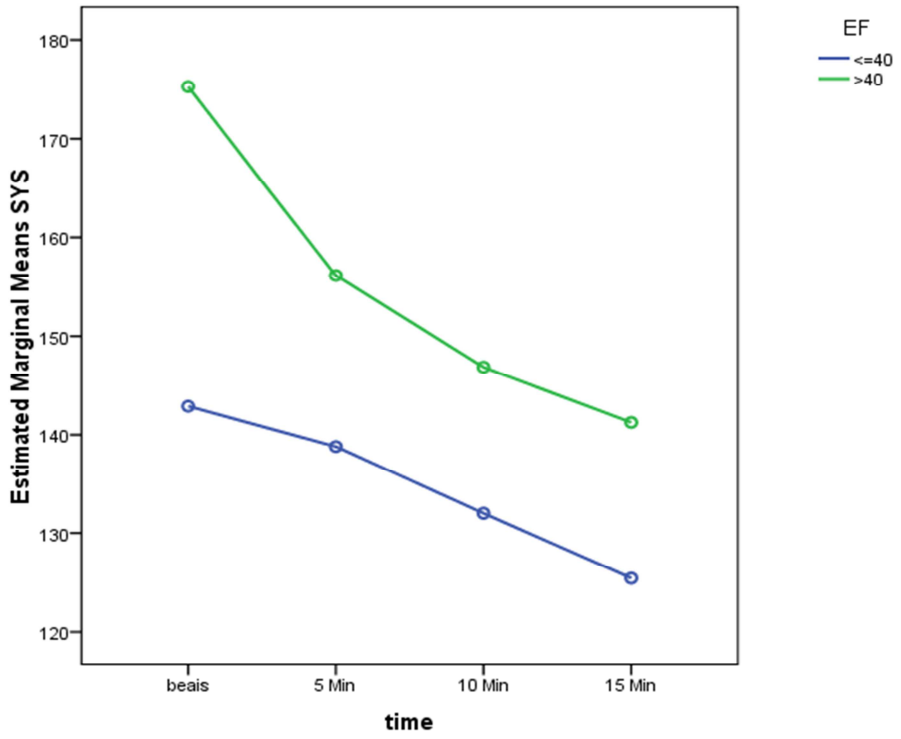

Figure 1A. The comparison of decreased of systolic blood pressure in the response to spinal anesthesia in patients with ejection fraction (EF) ≤ 40% and EF > 40%
Sys: Systolic blood pressure

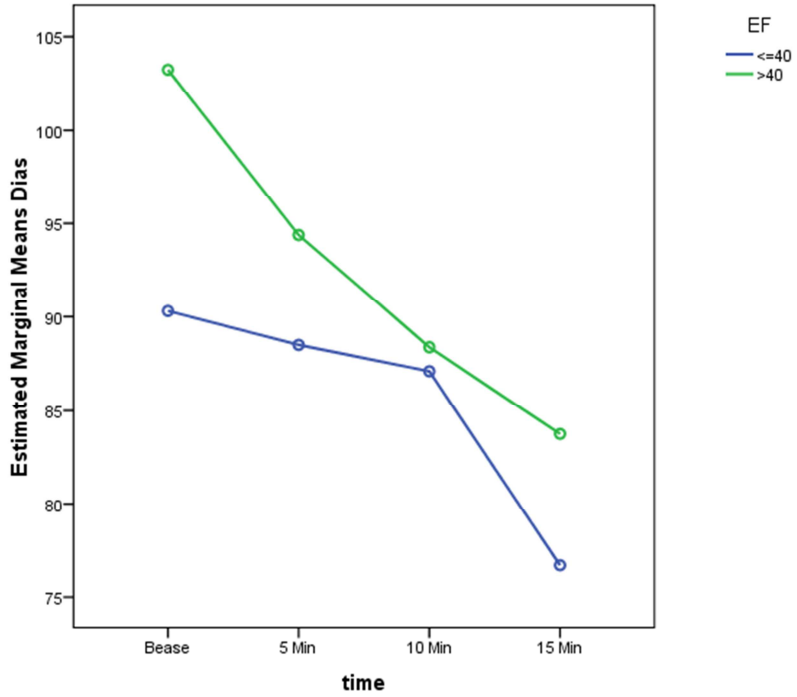

Figure 1B. The comparison of decreased of diastolic blood pressure in the response to spinal anesthesia in patients with ejection fraction (EF) ≤ 40% and EF > 40%
Dias: Diastolic blood pressure

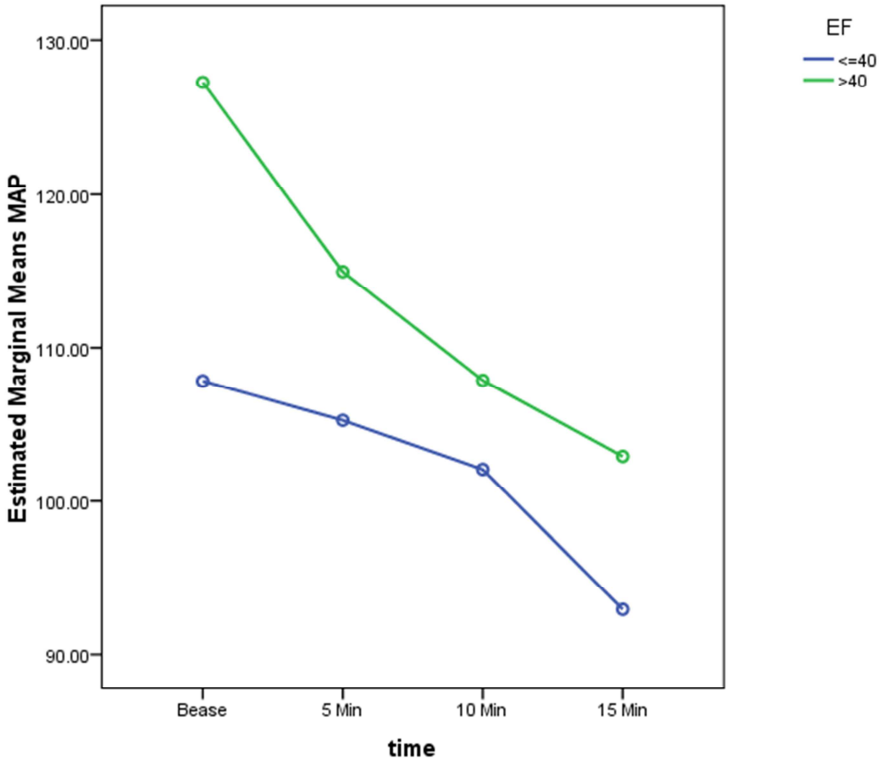

Figure 1C. The comparison of decreased of mean arterial pressure in the response to spinal anesthesia in patients with ejection fraction (EF) ≤ 40% and EF > 40%
MAP: Mean arterial pressure

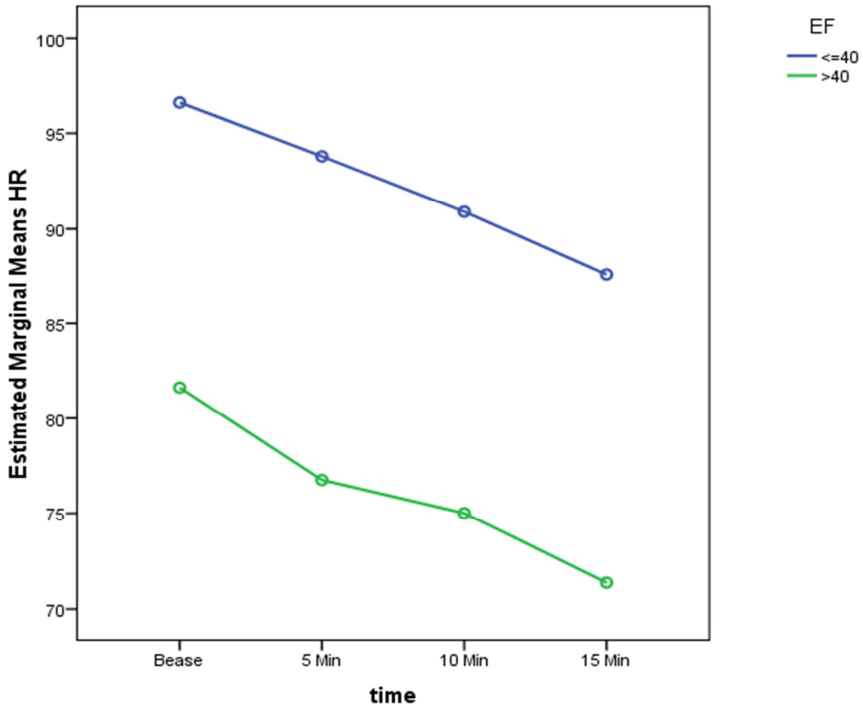

Figure 1D. The comparison of decreased of heart rate in the response to spinal anesthesia in patients with ejection fraction (EF) ≤ 40% and EF > 40%
HR: Heart rate

Conclusion

Our study showed that use of low dose of bupivacaine plus sufentanil for lower limb surgery in patients with coronary artery disease provides successful anesthesia and with minimum episodes of hypotension and nearly eliminate the need for vasopressor support of blood pressure and without tachycardia and ST segment changes. Therefore, we recommend that spinal block with low-dose local anesthetic and sufentanil for lower limb surgery in patients with coronary artery disease and especially for patients with low EF.

Conflict of Interests

Authors have no conflict of interests.

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Prediction of short-term clinical outcome of percutaneous coronary intervention in patients with acute coronary syndrome through myeloperoxidase levels

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Original Article

Abstract

BACKGROUND: The present study assessed the significance of troponin and myeloperoxidase levels in the prediction of major adverse cardiac events (MACE) during the 1st month after percutaneous coronary intervention (PCI).

METHODS: This prospective, longitudinal study included 100 patients with acute coronary syndrome who underwent PCI. The participants' characteristics were recorded in a questionnaire. Blood samples were obtained before and 24 h after PCI, and troponin, and myeloperoxidase levels were measured. During the 1st month after PCI, death, myocardial reinfarction, and revascularization during admission were investigated through weekly phone calls. The value of troponin and myeloperoxidase levels before and after PCI in predicting MACE was evaluated using Cox regression.

RESULTS: Considering the obtained methods and the short duration of the study, 99% of the patients completed the study. Moreover, one death and four cases of myocardial infarction and revascularization were reported. Cox regression did not show significant relations between the incidence of MACE and myeloperoxidase levels before (hazard ratio = 1.12; 95% confidence interval 0.9, 1.39) and after PCI (hazard ratio = 0.86; 95% confidence interval = 0.43, 1.71), or troponin levels before (hazard ratio = 0.97; 95% confidence interval = 0.81, 1.17) and after PCI (hazard ratio = 1.03; 95% confidence interval = 0.96, 1.11).

CONCLUSION: It seems that the few cases of MACE, due to the small sample size and short duration of follow-up, had been insufficient for determining the predictive value of troponin and myeloperoxidase levels before and after PCI. Therefore, further studies with larger sample size and longer follow-up duration are recommended.

Keywords: Percutaneous Coronary Intervention, Acute Coronary Syndrome, Major Adverse Cardiac Events, Myeloperoxidase

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Introduction

Percutaneous coronary intervention (PCI) is currently recommended to patients with acute coronary syndrome (ACS).[1] Each year more than a million Americans with ACS or even non-acute coronary disease are treated with PCI. Previous meta-analyses have indicated PCI to improve outcome of patients with ACS.[2]

Various studies have also reported the major adverse cardiac events (MACE) of PCI (mainly due to restenosis of coronary arteries). A 2-year cohort study on 1010 patients who underwent PCI found recurrent events in 361 subjects and the need for revascularization in 201.[3] The Randomized Intervention Treatment of Angina showed that PCI was associated with slight increments in the incidence of myocardial infarction and death.[4]

Scientists have been seeking ways to predict and

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prevent the side-effects of PCI. Many studies have focused on measurement of different biomarkers. For instance, myocardial infarction-related biomarkers have been suggested to increase by 1–30% following PCI.[5,6] Meta-analysis revealed that increased troponin levels during the hospital stay after PCI augments the risk for the incidence of MACE.[6] Another meta-analysis reported a relationship between increased troponin levels and elevated risk of side-effects.[5] Meanwhile, troponin is only an indicator of myocardial injury and cannot be an appropriate predictor in early disease course or in cases without myocardial injury.[7] In addition, only Troponin elevation more than 3 times is associated with MACE.[8] Finding an alternative mediator with early increments is essential to the prediction of side-effects.

During the incidence of ACS, degranulation of polymorphonuclear neutrophils (PMN) is one of the earliest events in the coronary circulation. The reaction between myeloperoxidase (a major enzymes secreted by PMN)[9] and hydrogen peroxide causes the formation of atherosclerotic plaques, endothelial dysfunction, plaque instability, and finally ventricular remodeling after ischemic injury.[10-12]

The c7E3 Anti-Platelet Therapy in Unstable Refractory angina (CAPTURE) study on patients with ACS who had undergone PCI showed death and myocardial infarction rates during a 6-month follow-up period to be related with serum myeloperoxidase concentrations. Such a relation was also evident in patients without troponin increase.[13] In contrast, Moldoveanu et al. failed to find a significant relation between myeloperoxidase levels and restenosis in patients with ACS who had undergone primary PCI.[14]

The frequency of PCI in Iran has been reported as 1260/month;[15] moreover, the rate of MACE during the 24-month period after PCI is 10.3% in the country.[16] Considering this high frequency of their impact on post-PCI outcome, identifying the risk factors of MACE in patients undergoing PCI will result in substantially decreased incidence of side-effects. This study assessed the relation between myeloperoxidase levels and short-term incidence of MACE in patients receiving PCI for ACS.

Materials and Methods

This prospective longitudinal study evaluated the frequency of MACE after PCI in patients with ACS who were eligible for PCI. The subjects had undergone PCI in winter 2011 in Isfahan, Iran. The eligible subjects were the patients with ACS who needs intervention based on the recommendation of interventional cardiologist. The inclusion criteria were aging over 18 years, consenting to participate, and not having a history of PCI or coronary artery bypass graft (CABG) surgery. Individuals with malignancies, acute febrile diseases, chronic inflammatory diseases, or a surgery during the two months prior to the study were not included since these conditions elevate myeloperoxidase levels.[17]

Convenience sampling was performed to reach a sample size of 100 based on the formula:

$$N_{\text{Discordant}} = \frac{(z_{1-\alpha/2}(\psi+1)+2z_{1-\beta}\sqrt{\psi})^2}{(\psi-1)^2} \quad N_{\text{Pairs}} = \frac{N_{\text{Discordant}}}{\pi_{\text{Discordant}}}$$

In this formula, α was < 5% with a power = 80% and effect size = 1.5.

The eligible patients were first explained about the objectives of the study. After receiving consent and before performing PCI, a questionnaire containing demographic characteristics (age, gender, education, and occupation), history of diseases (diabetes mellitus, stroke, hypertension, coronary artery disease, and hyperlipidemia), physical activity and smoking status, medications (aspirin, heparin, plavix, integrilin, inotrope, beta-blockers, angiotensin-converting-enzyme inhibitors, and streptokinase), type of myocardial infarction, if present (anterior, posterior, inferior, lateral or septal), and symptom onset was completed for all subjects.

Systolic and diastolic blood pressure and anthropometric indices, including height, weight, and waist circumference were measured according to standard methods. PCI-related data, that is, the time each patient entered the angiography department, exact time of PCI, number of involved vessels, level of stenosis in angiography (as 100%, 90–99%, and 75–90%), type, size, and number of stents, number and size of balloons, and the need for thrombectomy, was extracted from the participants' angioplasty reports and recorded in the questionnaire. Blood samples were obtained before and 24 h after PCI and myeloperoxidase and troponin levels were measured by using enzyme-linked immunosorbent assay.

All subjects were followed for 1-month, and the incidence of MACE was recorded. The studied events were death, acute myocardial infarction, unstable angina, cerebrovascular accident, target vessel revascularization (a second PCI or CABG), and number of readmissions.

A cardiology resident phoned patients weekly and filled out the questionnaires. In case of any incident except death, the patient was asked to

provide the resident with his/her records to confirm the type of event. Otherwise, death certificates were reviewed to find the cause of death. Patients who were not willing to continue the study and those who were out of access were excluded.

All collected data were entered into SPSS for Windows (version 19.0, SPSS Inc., Chicago, IL, USA). The frequency of events was analyzed using descriptive statistics. Patients with and without MACE were compared using the Student's t-test for quantitative variables and by Chi-square and Mann-Whitney tests for qualitative variables or quantitative variables without normal distribution. Cox regression was employed to assess the relations between myeloperoxidase and troponin levels and the incidence of events. Therefore, hazard ratios were calculated in crude and three adjusted models by age, sex, and troponin or myeloperoxidase before and after PCI.

Results

This study assessed 100 patients of which 26 women and 74 men during 73 days. The mean age of the participants was 58.62 ± 10.80 years and all subjects were married. The majority of patients (n = 43) were illiterate, and only seven individuals held a university degree. Almost half of the study population (n = 48) had unstable angina and 52 had a myocardial infarction.

During 1-month period, one patient died, and revascularization was performed for four subjects (three cases of a second PCI and one case of CABG), but no cases of myocardial reinfarction were detected. Five participants experienced MACE among whom two (40.0%) were female, and three (60.0%) were male. The frequency of men and women who did not suffer from MACE during 1-month of follow-up was 66 (89.2%) and 23 (88.5%), respectively (P = 0.919). The mean age of patients with and without MACE was 59.55 ± 14.02 and 58.51 ± 10.44 years, respectively (P = 0.603). The two groups were not significantly different in terms of the incidence of myocardial infarction or unstable angina before PCI (P = 0.933).

The participants' demographic characteristics, diagnosis of coronary disease at the time of admission, history of diseases, lifestyle, blood pressure, anthropometric indices, PCI target vessel, and the method of PCI in the two groups with and without MACE are presented in table 1. The myeloperoxidase and troponin levels before and after PCI did not have a normal distribution and Mann-Whitney test was used to compare them. Table 2 shows non-significant differences between the mean of myeloperoxidase and troponin levels before and after PCI.

Cox regression was used to find relations between myeloperoxidase and troponin levels and the incidence of MACE. Such possible relations were first evaluated in a crude model and then in models adjusted for one of the enzymes. Finally, myeloperoxidase and troponin levels before and after PCI were not found to have significant relationships with the incidence of MACE (Table 3).

Discussion

A total of 100 patients who had undergone PCI for ACS were followed for 1-month in the current study. The frequency of MACE was 11.0%, and only one subject died during this 1-month period. In a study on complications of PCI during the 1st month after the procedure, Khosravi et al. have reported the frequency of death as 2.2% and the overall frequency of target vessel revascularization, myocardial infarction, and stroke as 3.2%.[18] Wu et al. performed a retrospective study to evaluate 12-h and 28-day mortality rate in 2299 patients who had undergone PCI after ACS during a 14-year period. They found 50 individuals (2.2%) to have died in the first 28 days after PCI.[19] Thirty-day mortality rate was calculated as 0.38% in a research on 51,695 subjects who had undergone PCI after ACS in New York.[20] Although the mortality rates of patients with PCI after ACS in the studies of Khosravi et al.[18] and Wu et al.[19] were higher than that in the present research, Hannan et al. found lower rates.[20] This difference might have been caused by the large sample size in the latter study. The higher incidence of stroke, myocardial infarction, and target vessel revascularization in the present study (4.45%) compared to the study of Khosravi et al.[18] can be justified by the difference is the sample size since both samples were selected from the same hospital.

In the present study, two groups with and without MACE during the 30 days following the PCI did not have significant differences in any of the measured indices. Moreover, myeloperoxidase and troponin levels before and after PCI were not significantly different between the two groups and hence had no significance in prediction of MACE. Considering the few incidences of MACE due to the small sample size and short duration of follow-up, we could not adjust models for other variables. However, eliminating the effects of troponin for myeloperoxidase and vice versa did not result in significant relationships.

Table 1. The comparison of basic characteristics and the type of percutaneous coronary intervention (PCI) between patients with and without major adverse cardiac events (MACE)

Variables	Total	Without MACE (n = 89)	With MACE (n = 11)	P
Demographics				
Sex*				
Men	74 (74)	66 (89.2)	8 (10.8)	0.919
Women	26 (26)	23 (88.5)	3 (11.5)	
Married*	100 (100)			
Educational level*				
Illiterate	43 (43)	37 (41.6)	6 (54.5)	
Elementary	36 (36)	33 (34)	3 (27.3)	0.898
High school	14 (14)	12 (13.5)	2 (18.2)	
Academic	7 (7)	7 (7.9)	0 (0)	
Diagnosis before PCI*				
Myocardial infarction				
≥2	12 (12)	10 (11.2)	2 (18.2)	
Anterior	10 (10)	9 (10.1)	1 (9.1)	
Inferior	19 (19)	16 (18.0)	3 (27.3)	
Septal	3 (3)	3 (3.4)	0 (0)	0.933
Extensive anterolateral	2 (2)	2 (2.2)	0 (0)	
Non-STEMI	6 (6)	6 (6.7)	0 (0)	
Unstable angina	48 (48)	43 (48.3)	5 (45.5)	
History*				
Hyperlipidemia	38 (38)	33 (37.1)	5 (45.5)	0.589
Hypertension	41 (41)	35 (39.3)	6 (54.5)	0.333
Diabetes	23 (23)	21 (23.6)	2 (18.2)	0.687
Coronary heart disease	30 (30)	26 (29.5)	4 (36.4)	0.643
Cerebrovascular disease	0 (0)			
Medications*				
Aspirin	100 (100)	89 (100)	11 (100)	1.000
Heparin	3 (3)	3 (3.4)	0 (0)	1.000
Plavix	81 (81)	72 (80.9)	9 (81.8)	0.942
Streptokinase	1 (1)	1 (1.1)	0 (0)	1.000
Integrilin	5 (5)	4 (4.5)	1 (9.1)	0.449
Beta blocker	97 (97)	(86) 96.6)	11 (100.0)	1.000
ACE I	55 (55)	49 (55.1)	7 (63.6)	0.589
Statins	99 (99)	88 (98.9)	11 (100.0)	1.000
TNG*	99 (99)	88 (98.9)	11 (100.0)	1.000
Lifestyle*				
Sedentary lifestyle	83 (83)	72 (80.9)	11 (100.0)	0.112
Smoker	36 (36)	30 (33.7)	6 (54.5)	0.196
PCI*				
Vessel				
Saphenous vein graft	6 (6)	5 (5.6)	1 (9.1)	
Left circumflex	11 (11)	11 (12.4)	0 (0)	
Right coronary	24 (24)	21 (23.6)	3 (27.3)	0.677
Left coronary	47 (47)	42 (47.2)	5 (45.5)	
≥2 arteries	11 (11)	9 (10.1)	2 (18.2)	
Balloon	10 (10)	8 (9)	2 (18.2)	
Stent	18 (18)	16 (18)	2 (18.2)	0.673
Balloon and stent	70 (70)	63 (70.8)	7 (63.6)	
Type of the stent				
Bare	42 (42)	36 (40.4)	6 (54.5)	
Drug eluted	40 (40)	38 (42.7)	2 (18.2)	0.328
Both	6 (6)	5 (5.6)	1 (9.1)	
Physical examination**				
BMI	26.11 ± 3.29	26.29 ± 3.33	24.71 ± 2.64	0.165
Waist	81.31 ± 8.29	81.57 ± 7.98	79.18 ± 10.67	0.662
Systolic blood pressure	118.04 ± 16.36	118.09 ± 15.82	117.64 ± 21.18	0.478
Diastolic blood pressure	75.46 ± 8.99	75.80 ± 8.85	72.73 ± 10.09	0.323
Age**	58.62 ± 10.80	58.51 ± 10.44	59.55 ± 14.02	0.996

* Number (%); ** Mean ± SD; MACE: Major adverse cardiac events; PCI: Percutaneous coronary intervention; STEMI: ST segment elevation myocardial infarction; ACE I: Angiotensin-converting enzyme inhibitors; TNG: Trinitroglycerin; BMI: Body mass index; SD: Standard deviation

Table 2. Comparison of myeloperoxidase and troponin between patients with and without major adverse cardiac events (MACE) before and after percutaneous coronary intervention (PCI)

Laboratories	Total mean ± SD	Without MACE (n = 89) mean ± SD	With MACE (n = 11) mean ± SD	P
Myeloperoxidase				
Before PCI	3.29 ± 2.21	3.21 ± 2.21	3.95 ± 2.17	0.207
After PCI	5.45 ± 3.44	5.49 ± 3.35	5.15 ± 4.29	0.570
Troponin				
Before PCI	1.13 ± 1.02	1.14 ± 0.99	1.02 ± 1.21	0.331
After PCI	3.50 ± 6.24	3.32± 6.09	4.09 ± 7.47	0.643

P values were reported based on Mann-Whitney test; MACE: Major adverse cardiac events; PCI: Percutaneous coronary intervention

Table 3. The hazard ratio of myeloperoxidase and troponin before and after percutaneous coronary intervention (PCI) for occurring events

	Hazard ratio (95% CI)	P
Myeloperoxidase		
Before PCI		
Crude	1.12 (0.9, 1.39)	0.31
Adjusted*	1.13 (0.9, 1.43)	0.28
Adjusted**	1.11 (0.89, 1.39)	0.34
Adjusted***	1.13 (0.89, 1.42)	0.31
After PCI		
Crude	0.86 (0.43, 1.71)	0.67
Adjusted*	0.97 (0.81, 1.17)	0.76
Adjusted$	0.93 (0.77, 1.13)	0.49
Adjusted£	0.93 (0.77, 1.13)	0.49
Troponin		
Before PCI		
Crude	0.97 (0.81, 1.17)	0.76
Adjusted*	0.86 (0.43, 1.71)	0.67
Adjusted§	0.89 (0.45, 1.76)	0.74
Adjusted∫	0.89 (0.45, 1.78)	0.75
After PCI		
Crude	1.03 (0.96, 1.11)	0.44
Adjusted*	1.03 (0.96, 1.11)	0.43
Adjusted†	1.03 (0.96, 1.11)	0.39
Adjusted‡	1.03 (0.96, 1.12)	0.39

* Adjusted by age, sex; ** Adjusted by troponin level before PCI; *** Adjusted by age, sex, troponin level before PCI; $Adjusted by myelopero xidase level, troponin level before PCI; £ Adjusted by age, sex, myeloperoxidase level and troponin level before PCI; §Adjusted by troponin level before PCI; ∫ Adjusted by age, sex, troponin level before PCI; † Adjusted by troponin level and myeloperoxidase before PCI; ‡ Adjusted by age, sex, myeloperoxidase level and troponin level before PCI; CI: Confidence interval; PCI: Percutaneous coronary intervention

Despite the significant increase of troponin levels after PCI, the regression model did not show a significant relationship between troponin levels before and after PCI and the incidence of MACE. This is in contrast with a number of previous studies probably due to the very small sample size of our study.[21,22]

Fewer studies have examined the value of myeloperoxidase in predicting the incidence of MACE after PCI. In a study on 128 patients with ACS, Chang et al. measured myeloperoxidase levels during the hospital stay before primary PCI. They suggested serum concentration of myeloperoxidase to be significantly related with the incidence of MACE during the 30 days after PCI.[17] In contrast, Moldoveanu et al. evaluated 80 patients with ACS in terms of restenosis 1, 3, and 6 months after primary PCI. They measured myeloperoxidase, adiponectin, and lipoprotein-associated phospholipase A2 before PCI and immediately, 24, 48, and 72 h, and 1, 3, and 6 months after PCI. Their findings did not indicate a significant association between serum myeloperoxidase levels and the incidence of MACE. However, adiponectin was found to be significantly related with time of discharge and restenosis after 6 months.[14] Similarly, we failed to find a significant relation between myeloperoxidase levels before and after PCI and the incidence of MACE one month after PCI. In other words, although myeloperoxidase levels before and after PCI were significantly different, there was no significant difference between the groups with and without MACE in this regard.

Overall, we did not detect significant relations between troponin and myeloperoxidase levels before and after PCI and the incidence of MACE. A probable reason is a small sample size. Larger sample size and increased frequency of MACE provide the possibility of adjustments for other variables and finding significant relations. On the other hand, since many studies have found significant relations (especially in case of troponin) in long-term follow-up, increasing the duration of follow-up may reveal such relations. Another important factor is measuring cardiac biochemical markers, that is, measurement of cardiac troponin in several previous studies could have been responsible for the observed relations. Increased frequency of troponin and myeloperoxidase measurements can also reveal

significant relations between the incidence of MACE and one of these enzymes.

Conclusion

This study did not show significant relations between troponin and myeloperoxidase levels before and after PCI and the incidence of MACE. Further studies with larger sample size, increased number of measurements, and longer duration of follow-up are required for obtaining better, more reliable results. Other biochemical factors with probable relations with ischemia and clotting should also be evaluated.

Conflict of Interests

Authors have no conflict of interests.

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The sustainability of interventions of a community-based trial on children and adolescents' healthy lifestyle

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Original Article

Abstract

BACKGROUND: Sustainability is the core of a successful health-related intervention program. This study was conducted to evaluate the sustainability of interventions of the Heart Health Promotion from Childhood (HHPC) project, one of the 10 interventional projects of the Isfahan Healthy Heart Program.

METHODS: The evaluation of HHPC included administrating surveys to 500 elementary and middle, and 500 high school students. The study participants were randomly selected from all schools in Isfahan. The questionnaires were administered by interviews to evaluate the sustainability of interventions.

RESULTS: The results of interviews showed that interventions were sustainable in 100% of elementary school, 99% of middle school, and 87% of high school students. Training of healthy lifestyle behaviors was significantly higher in all-girls middle schools ($P < 0.001$). Daily morning exercise was more frequent in girls high schools ($P < 0.001$), while selling unhealthy food was more frequent in boys high schools ($P < 0.001$). The participants attributed the success of the program mostly to students' agreement and cooperation.

CONCLUSION: Even though 5 years have passed since the end of the HHPC project, many of the interventions have been continued at the schools, often because healthy behaviors have become institutionalized in the target population. However, now all schools have the same level of sustainability, especially the middle and high schools, and all-boys schools. Therefore, it is important for future projects to place additional emphasis on these institutions for future school-based interventions.

Keywords: Behavior, Community Health Planning, Institutionalization, Schools, Sustainability

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Introduction

The escalating rise of non-communicable diseases globally[1-3] has required swift concerted action, at various levels of decision making from international level to the community level.[4] Successful programs may not necessarily develop into a sustainable organizational strategy,[5] therefore evaluation of sustainability should be mainstreamed into the evaluation process. In addition, the organizations that sponsor the interventions implementation need to know whether funded programs should be continued.[6] Sustainability may refer to maintaining, endure or even support,[7] and it has became an important global target to achieve, while performing health, economic, ecologic or any other program that deals with development.[8] It was then, that sustainability became among the evaluation indicators of successful programs.[9]

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A program is considered sustainable when its relevant activities and resources continue in the direction of its primary objectives.[9] Crisp and Swerissen believe that program sustainability depends on the continuation of its implementation strategy, in terms of the organization concerned and program effects.[10] Others have reported that a program becomes sustainable after institutionalization in relevant organizations and empowerment of its recipients.[11,12] Most programs are evaluated on the basis of parameters such as feasibility, strategic planning, process, and outcomes. Thus, sustainability is not part of the evaluation process.[13] One of the best definitions reported for sustainability specifically in health programs is the one introduced by Shediac-Rizkallah and Bone.[14] They suggested three components for sustainability that include: (1) continued benefits to those who received health services when the program started and to new participants when the supporting funds are discontinued; (2) continued implementation of a program activities in an organization following the discontinuation of the program financial support, which is called "institutionalization" or "routinization"; and (3) community empowerment to improve their health by continuing the activities of a finished program.

In Iran, the Ministry of Health runs most health programs using its health system infrastructure and to some extent inter-sectoral collaboration; however, according to our knowledge, there has been no study conducted to evaluate the sustainability of these programs. Furthermore, there have been few comprehensive community-based programs planned, implemented and evaluated on non-communicable diseases (NCD) prevention and health promotion. "Isfahan Healthy Heart Program" (IHHP) was a comprehensive community-based interventional program that ran between 2000 and 2006 and aimed to prevent cardiovascular diseases (CVD), reduce their risk factors, and promote a healthy lifestyle.[15] The program comprised 10 interventional projects and covered different target groups.[16] Healthy nutrition, physical activity, and tobacco control were the main fields of interventions, while its main strategies were community education and empowerment, health professionals training, inter-sectoral collaboration, public-private partnership and policy enforcement or development. The managers of each project were among the beneficiary target groups or organizations. Different types of evaluation, including process, outcome and impact, were done to determine the optimum process of interventions.[15,16] The processes of implementing its interventions were extensively evaluated and applied to most activities.[17,18] The general results of these evaluations in adults showed that the interventions were effective in promoting health-related behaviors.[19-22] Furthermore, the mean level and the prevalence of physical and metabolic risk factors were improved.[23-25] One of the 10 IHHP projects entitled "Heart Health Promotion from Childhood" (HHPC) was implemented for children and adolescents, their parents, and health professionals in schools.[26]

The main target population of this project was children and adolescents attending schools and day care centers; in addition, parents and teachers, school staff, and healthcare providers were also targeted as intermediary population.[22] All groups were interviewed in this study; but only, the results of the survey related to schoolchildren (in all grades) are reported in this paper.

HHPC focused on healthy nutrition, physical activity, and tobacco control and were implemented between 2001 and 2005.[23]

Interventions were implemented by beneficiary organizations (Provincial Education and Training Office, Welfare Organization, Institute for the Intellectual Development of Children & Young Adults, and Provincial Health Center of Isfahan) and were integrated with their infrastructure in order to minimize the additional expenses and to be part of their staff daily work. The investigators and their collaborators supported these organizations in the design and implementation of interventions and advocate for policy and legislation enforcement or changes.

The whole HHPC project methods, sampling, target groups, intervention activities, types of evaluation and some short-term results were reported in earlier publications.[26,27]

The success or failure of these interventions was evaluated at the time of implementation by an internal process evaluation committee of IHHP,[17,18] while the whole program was evaluated by an external team from the National Institute for Health and Welfare of Finland.[28]

After finishing IHHP and evaluating its outcomes, the beneficiary organizations were given the option to continue with the interventions. In order to continue, the Isfahan Provincial Health Center collaborated with the Education and Training Office and 12 other organizations to integrate the lifestyle-modification interventions within their infrastructure in a program called "Student Health Mobilization".

According the importance of sustainability as an indicator for evaluating the success of health programs, in this study we presented the methods of assessing HHPC sustainability and its outcomes.

Materials and Methods

This study was conducted 5 years after the final phase of HHPC project. Considering the importance of continuing the interventions to promote a healthy lifestyle of children and adolescents, we evaluated their sustainability as an indication of the legacy of the IHHP projects.

Sustainability determinants

To develop tools for measuring the sustainability of HHPC project, we defined its determinants. A review of the literature was performed using keywords such as "sustainability," "institutionalization," "implementation," "health promotion program," "healthy lifestyle," and "health program" in PubMed and Google Scholar. All related publications were studied, and sustainability determinants and their definitions and evaluation methods were extracted.

From the literature review, the following sustainability determinants were identified for NCD community-based intervention programs prevention and healthy lifestyle promotion:

1. Continuity of funding.
2. Constant supervision and follow-up of the funding body.
3. Supporting human resources and volunteers.
4. Community preparation.
5. Involving the community in the design process.
6. Empowerment of the community.
7. Constant monitoring and modification of strategies.
8. Being dynamic.
9. Considering new needs.
10. Sustainability of outcomes.
11. Sustainability of institutionalization process.

On the basis of interventions, the results of process evaluation, and determinants extracted from review of literature, brief questions for key informant interviews were created to be used to conduct a small qualitative study with the aim of obtaining the HHPC sustainability concepts and its determinants.

We interviewed health decision makers, schoolchildren and their parents as well as school's principals or health educators. The sample size was determined based on the rule of data saturation in qualitative studies.[29]

The interviews were carried out to determine the sustainability or non-sustainability determinants from their points of view and based on the study objectives. The interviews were conducted with the permission of Education and Training Office. Consents of the interviewees were obtained. All interviews were recorded and transcribed, coded, and the main concepts and their determinants were extracted from the transcribed data. This part of the study was done according to qualitative studies standard methods.[29]

Continuing interventions, education, evaluation, motivation, changes in knowledge, attitude and practice as well as the obstacles and facilitators of sustainability were concepts extracted from interviews. All determinants of the qualitative part are presented in the full report.[30] The questionnaire was developed based on these concepts and determinants.

Data collection

The sample size of this survey was 1000 consisted of 500 elementary and middle school students and 500 high school students. Samples were selected using cluster random sampling. In each municipality areas in Isfahan, 100 students (50 from high school and 50 from elementary and middle school), were interviewed. The questionnaires were completed by trained interviewers at schools. The completed questionnaires were reviewed by an expert personal to check for correct completion and missing data.

In our analysis, we considered interventions to be sustainable when it were implemented at least on 60% of their target places.[9]

After completing the questionnaires, the collected data were managed, entered and analyzed using the Statistical Package for the Social Sciences (SPSS) software program (version 18, SPSS Inc., Chicago, IL, USA). Chi squared test was used to analyse the data based on sex in each school grade and P value < 0.05 was considered as significant.

Results

In total, 500 students from elementary and middle schools and 500 students from high schools were interviewed. Based on the pollution distribution of Isfahan, 50% female and 50% male students were selected for interviews. The mean ages of elementary, middle and high school students were 10.84 ± 0.84, 13.72 ± 0.99, and 16.38 ± 0.95 years, respectively.

Table 1 shows the determinates of sustainable interventions according to elementary school children responses. All participants responded

positively to the presence of healthcare staff and the existence of morning exercise. Boys were more satisfied with this exercise than girl's significantly (P = 0.002). All schools have a healthy snack bar services with boys reporting more satisfaction than girls (P < 0.001). Determinants like parental pressure or liking the food ranked as the highest among factors influencing compliance with schools' healthy food plans. Almost all girls and boys experienced improvement in their health after the HHCP implementation, students' acceptance, then authorities approval and family support were the most important reasons for continued interventions.

The determinants of sustainable interventions in middle schools and students' opinions on continued or discontinued interventions are presented in table 2. While all girls' schools have healthcare staff, only 48% of boys' schools had them. Training of healthy lifestyle behaviors was persisted in all and 88% of girl's and boy's schools respectively (P < 0.001). Training children during morning programs was the most frequent method used among girls and boys, but its frequency is significantly higher in girls schools (P < 0.001). Daily morning exercise and cafeterias selling healthy snacks were available in most schools. Boys believed more in the effect of HHCP interventions on their health and behavior changes than girls (P < 0.001). The frequency of boys satisfactied with snack bars services and daily morning exercise were significantly higher than girls (P = 0.002 for both). Authorities' approval for continuing interventions followed by the student's acceptance and integration into the school curriculum were the most frequent reasons for continued interventions. Discontinuation of interventions was higher among all boys schools (P = 0.010). The reasons for discontinued interventions were; other priorities considered by school staff, lack of rules in schools and lack of human resources.

Table 1. Sustainability determinants according to elementary students' responses based on sex

Determinants	Total	Girls	Boys	P
Presence of healthcare staff in schools	250 (100.0)	125 (100.0)	125 (100.0)	-
Training on lifestyle modifications in school	250 (100.0)	125 (100.0)	125 (100.0)	-
Extracurricular education	66 (26.4)	28 (22.4)	38 (30.4)	0.151
Education during morning programs	241 (96.4)	119 (95.2)	122 (97.6)	0.500
Education as part of curriculum	191 (76.4)	85 (68.0)	106 (84.8)	0.002
Education using training aids	205 (82.0)	97 (77.6)	108 (86.4)	0.070
Face-to-face education by teachers	34 (13.6)	17 (13.6)	17 (13.6)	1.000
Daily morning exercise in schools	250 (100.0)	125 (100.0)	125 (100.0)	-
Satisfaction with morning exercise	172 (68.8)	73 (58.4)	99 (89.2)	0.002
The existence of snack bars or cafeterias in schools	250 (100.0)	125 (100.0)	125 (100.0)	-
If yes				
Not selling unhealthy food in schools	250 (100.0)	125 (100.0)	125 (100.0)	-
Satisfaction with snack bars services	134 (53.6)	52 (41.6)	82 (65.6)	0.002
School plans for student food menus	157 (62.8)	78 (62.4)	79 (63.2)	0.896
Compliance with food plans	125 (79.6)	52 (66.7)	73 (92.4)	< 0.001
If yes				
Factors influencing compliance with food plans				
Liking the food	123 (98.4)	50 (96.2)	73 (100.0)	0.171
School forcing students to comply	7 (5.6)	2 (3.8)	5 (6.8)	0.698
Peer pressure	27 (21.6)	16 (30.8)	11 (15.1)	0.036
Parental pressure	88 (70.4)	29 (55.8)	59 (80.8)	0.002
Need for interventions	244 (97.6)	123 (98.4)	121 (96.8)	0.373
Experiencing improved health after interventions	240 (96.0)	115 (92.0)	125 (100.0)	0.002
If yes				
Reasons for implementing interventions				
Authorities' approval	190 (80.5)	88 (77.9)	102 (82.9)	0.328
Family support	180 (76.3)	72 (63.7)	108 (87.8)	< 0.001
Students' approval	216 (91.5)	103 (91.2)	113 (91.9)	0.843
Simplicity of implementation	148 (62.7)	65 (57.5)	83 (67.5)	0.114
Existence of legislations	120 (50.8)	44 (38.9)	76 (61.8)	< 0.001
Integration into school curriculum	164 (69.5)	71 (62.8)	93 (75.6)	0.033

Table 2. Sustainability determinants according to middle school students' responses based on sex

Determinants	Total	Girls	Boys	P
Instituting interventions to improve lifestyle in schools	247 (98.8)	124 (100.0)	123 (97.6)	0.247
Presence of healthcare staff in school	185 (74.0)	124 (100.0)	61 (48.4)	< 0.001
Training on lifestyle modification in schools	236 (94.4)	124 (100.0)	112 (88.9)	< 0.001
Healthy nutrition	222 (94.1)	123 (99.2)	99 (88.4)	< 0.001
Appropriate physical activity	213 (90.3)	121 (97.6)	92 (82.1)	< 0.001
Tobacco control	138 (58.5)	76 (61.3)	62 (55.4)	0.356
Methods to cope with stress	162 (68.6)	91 (73.4)	71 (63.4)	0.098
Training methods				
Extracurricular training	87 (36.9)	52 (41.9)	35 (31.3)	0.089
Training during morning programs	207 (87.7)	121 (97.6)	86 (76.8)	< 0.001
Training as part of school curriculum	166 (70.3)	103 (83.1)	63 (56.3)	< 0.001
Using educational materials	169 (71.6)	112 (90.3)	57 (50.9)	< 0.001
Face-to-face education by teachers	28 (11.9)	16 (12.9)	12 (10.7)	0.604
Daily morning exercise	233 (93.2)	122 (98.4)	111 (88.1)	< 0.001
Presence of snack bars or cafeterias in schools	225 (90.0)	99 (79.8)	126 (100.0)	< 0.001
Selling unhealthy food at snack bars	48 (21.3)	25 (25.3)	23 (18.3)	0.203
Behavior changes	208 (83.2)	101 (81.5)	107 (84.9)	0.463
Improvement of health	219 (87.6)	106 (85.5)	113 (89.7)	0.314
Necessity of interventions	224 (89.6)	109 (87.9)	115 (91.3)	0.383
Authorities prioritizing interventions	198 (79.2)	97 (78.2)	101 (80.2)	0.707
Student's opinion on improving interventions	70 (28.0)	47 (37.9)	15 (11.9)	< 0.001
Success of interventions	190 (76.0)	94 (75.8)	96 (76.2)	0.943
Reasons for success				
Authorities' approval for instituting interventions	143 (75.3)	85 (90.4)	58 (60.4)	< 0.001
Allocating appropriate budget to implement interventions	40 (21.1)	27 (28.7)	13 (13.5)	0.010
Family support	119 (62.6)	69 (73.4)	50 (52.1)	0.002
Students' acceptance	157 (82.6)	90 (95.7)	67 (69.8)	< 0.001
Ease of performance	92 (48.4)	59 (62.8)	33 (34.4)	< 0.001
Integration into school curriculum	114 (60.0)	70 (74.5)	44 (45.8)	< 0.001
Discontinuing interventions	47 (18.8)	14 (11.3)	33 (26.2)	0.010
Reason for discontinuation of interventions				
Lack of authorities' willingness	13 (27.7)	3 (21.4)	10 (30.3)	0.726
Lack of budget	6 (12.8)	1 (7.1)	5 (15.2)	0.653
Lack of need for interventions	13 (27.7)	5 (35.7)	8 (24.2)	0.486
Authorities' disapproval	6 (12.8)	3 (21.4)	3 (9.1)	0.344
Failure of interventions	9 (19.1)	5 (35.7)	4 (12.1)	0.102
Other priorities	24 (51.1)	9 (64.3)	15 (45.5)	0.238
Lack of rules in schools	12 (25.5)	8 (57.1)	4 (12.1)	0.003
Lack of human resources	9 (19.1)	6 (42.9)	3 (9.1)	0.013
Some interventions may lead to side-effects	4 (1.6)	2 (1.6)	2 (1.6)	1.000

The sustainable interventions in high schools and student's opinions on continued or discontinued interventions are presented in table 3. While integrating interventions was similar in girls' and boys' high school, only 22% of boy's schools have health care staff compared to 66% of girls schools (P < 0.001). High school children of both sexes referred to receiving training during morning programs as the most frequent method while face to face education by the teachers as the least used method. The frequency of boys trained for tobacco control was higher than girls (P < 0.001). Daily morning exercise was more frequent in girls schools (P < 0.001) while selling unhealthy food was more frequent in boys' high schools (P < 0.001). Students acceptance followed by authorities' approval, and family support were the most frequent reasons for success, while lack of related rules and the perception that interventions were not needed in schools were the most reasons for failure. Other priorities considered by school staff followed by lack of willingness of authorities were the main reasons for discontinued interventions according to students' opinions.

Table 3. Sustainability determinants according to high school students' responses based on sex

Determinants	Total	Girls	Boys	P
Instituting interventions to improve lifestyle in schools	433 (86.6)	220 (88.0)	213 (85.2)	0.358
Presence of healthcare staff in schools	222 (44.4)	165 (66.0)	57 (22.8)	< 0.001
Training on lifestyle modification in schools	412 (82.4)	208 (83.2)	204 (81.6)	0.639
Healthy nutrition	270 (65.5)	134 (64.4)	136 (66.7)	0.632
Appropriate physical activity	307 (74.5)	150 (72.1)	157 (77.0)	0.259
Tobacco control	214 (51.9)	82 (39.4)	132 (64.7)	< 0.001
Methods to cope with stress	261 (63.3)	160 (76.9)	101 (49.5)	< 0.001
Training methods				
Extracurricular training	97 (23.5)	57 (27.4)	40 (19.6)	0.062
Training during morning programs	339 (82.3)	180 (86.5)	159 (77.9)	0.022
Training as part of school curriculum	231 (56.1)	131 (63.0)	100 (49.0)	0.004
Using educational materials	257 (62.4)	133 (63.9)	124 (60.8)	0.508
Face-to-face education by teachers	29 (7.0)	14 (6.7)	15 (7.4)	0.805
Daily morning exercise	287 (57.4)	188 (75.2)	99 (39.6)	< 0.001
Presence of snack bars or cafeterias in schools	498 (99.6)	248 (99.2)	250 (100.0)	0.156
Selling unhealthy food at snack bars	130 (26.1)	13 (5.2)	117 (46.8)	< 0.001
Behavior changes due to interventions	292 (58.4)	118 (47.2)	174 (69.6)	< 0.001
Necessity of interventions	449 (89.8)	214 (85.6)	235 (94.0)	0.002
Improvement of health due to interventions	373 (74.6)	177 (70.8)	196 (78.4)	0.051
Authorities prioritizing interventions	318 (63.6)	143 (57.2)	175 (70.0)	0.003
Student's opinion on improving interventions	83 (16.6)	58 (23.2)	29 (11.6)	< 0.001
Success at performing interventions	251 (50.2)	107 (42.8)	144 (57.6)	< 0.001
Reasons for success				
Authorities' approval for instituting interventions	183 (72.9)	88 (82.2)	95 (66.0)	0.004
Allocating appropriate budget to implement interventions	56 (22.3)	33 (30.8)	23 (16.0)	0.005
Family support	163 (64.9)	76 (71.0)	87 (60.4)	0.081
Students' acceptance	193 (76.9)	92 (86.0)	101 (70.1)	0.003
Ease of performance	116 (46.2)	56 (52.3)	60 (41.7)	0.094
Integration into school curriculum	115 (45.8)	57 (53.3)	58 (40.3)	0.041
Reasons for failure				
Disapproval of some authorities	24 (28.6)	8 (21.6)	16 (34.0)	0.211
Lack of budget	28 (33.3)	14 (37.8)	14 (29.8)	0.437
Lack of need to implement interventions	32 (38.1)	13 (35.1)	19 (40.4)	0.620
Families'disapproval	5 (6.0)	1 (2.7)	4 (8.5)	0.378
Students' disapproval	33 (39.3)	9 (24.3)	24 (51.1)	0.013
Lack of necessary rules in schools	31 (36.9)	17 (45.9)	14 (29.8)	0.128
Lack of human resources in schools	17 (20.2)	5 (13.5)	12 (25.5)	0.173
Discontinuing interventions	180 (36.0)	98 (39.2)	82 (32.8)	0.199
Reason for discontinuation of interventions				
Lack of authorities' willingness	74 (41.1)	39 (39.8)	35 (42.7)	0.695
Lack of budget	39 (21.7)	26 (26.5)	13 (15.9)	0.083
Lack of need for interventions	56 (31.1)	31 (31.6)	25 (30.5)	0.869
Authorities' disapproval	32 (17.8)	20 (20.4)	12 (14.6)	0.313
Failure of interventions	53 (29.4)	29 (29.6)	24 (29.3)	0.962
Other priorities	89 (49.4)	44 (44.9)	45 (54.9)	0.182
Lack of rules in schools	62 (34.4)	31 (31.6)	31 (37.8)	0.385
Lack of human resource	52 (28.9)	30 (30.6)	22 (26.8)	0.577
Some interventions may lead to side-effects	9 (1.8)	2 (0.8)	7 (2.8)	0.176

Discussion

In this study, we evaluated the sustainability of HHPC interventions 5 years after the completion of the project by conducting qualitative and quantitative studies. The results obtained from the qualitative study constitute the variables used to develop questionnaires that were later administrated in the surveys. The survey conducted on schoolchildren of all grades showed that most of the interventions were sustainable in 100% of elementary schools, 99% of middle schools, and 87% of high schools. The

frequency of sustainable interventions was higher in girls' than in boys' schools.

NCDs are on the rise trend[31] and community-based interventions that improve health and lifestyle can reduce the morbidity and mortality rates of these diseases.[4] Policy makers and financial sponsors as well as the society are interested in determining what constitutes a successful program and more importantly, what will happen to these programs after the research phase is completed and the financial support is withdrawn.[6]

Despite these facts, our knowledge on the sustainability of community-based intervention programs for health improvement is limited. One of the problems in evaluating the sustainability of such programs is the need to wait for at least 3 years after the termination of these projects to start evaluating its sustainability, a fact that was considered in our study.[32]

In HHPC project, different types of evaluations were done to assess the implementation of interventions and their short- and long-term results.[16] The results showed that the prevalence of hypercholesterolemia, hypertriglyceridemia, and high levels of low-density lipoprotein (LDL)-cholesterol decreased significantly among children and adolescents after interventions. While overweight and obesity decreased significantly in girls, it was increased in boys at the same grades.[26] This project, like the other projects under the IHHP, ended in 2006 while most of its interventions were integrated in the collaborating organizations.[28]

The present study included a qualitative part that was done on HHPC target groups to extract the sustainability concepts and its determinants from their point of view. Its results that are presented, beside a literature review on the same topic consist the variables used to develop the questionnaire used in the surveys. The surveys assessed how far HHPC intervention activities were sustainable and ongoing 5 years after the completion of its research phase in 2006.

Among 19 studies that were reviewed by Scheirer, 18 reported its continuity, 6 reported continued benefits, and 2 reported continued community capacity.[9] Shediac-Rizkallah and Bone study showed that sustainability is influenced by the manner in which the program is designed and institutionalized, the factors involved in the performance of the program in related places and the characteristics of the environment and target population.[14] While our study showed that the main reason for sustainable interventions according to the schoolchildren view points in all grades were their acceptance of the intervention followed by authorities approval and their families support. One of the important reasons that led to the sustainability of HHPC interventions is the fact that IHHP projects were performed simultaneously[22] which helped to increase the dose of interventions and had a booster effect.[26] Furthermore, the managers of each project involved the directors or chiefs of cooperating offices or organizations in the planning, implementation, and evaluation of interventions, a strategy that later helped in institutionalizing these interventions and saving the study funds to perform the research part of the whole program.[28]

Most of the studies on sustainability have evaluated only the outcomes and maintenance of health results. Cene et al. studied the level of risk factors, lipid profile, and blood pressure 1 year after program completion to evaluate the level of sustainability of community-based interventions.[33] Smith-DiJulio and Anderson studied the sustainability of women's behavior changes 5 years after implementing an interventional program to prevent CVD.[34]

In HHPC, all target groups, behaviors were evaluated annually.[13] While, other cardiometabolic risk factors were evaluated after 4 years of interventions. Some behaviors and risk factor levels were improved to some extent and some were not. Changes differed based on age and sex.[26]

Pluye et al. performed a complete evaluation of the level of sustainability of a health-related interventional project 13 years after project termination in seven centers. Their results showed that only three centers continued to conduct the activities completely.[35] The New Jersey Health Initiatives Expecting Success: Excellence in Cardiac Care (NJHI-ES) program funded health-promotion projects in 10 hospitals in New Jersey. After the financial support stopped, the sustainability results showed that only three projects were completed.[36]

Among community-based interventional programs for NCD prevention and healthy lifestyle promotion, programs for children and adolescents are of special importance. The prevalence of some risk factors, especially overweight and obesity, are rising in this age group.[37] Because most of the children can be reached in schools, school-based studies are especially important, and financial sponsors fund such programs easier than adult ones.[38] However, there are limited studies on the sustainability of such programs in children. Health policymakers are interested in finding out how

effective and sustainable the interventions that they funded are.[39]

HHCP interventions are among limited projects that remained sustainable after 5 years. During the HHPC, Isfahan Provincial Health Center and Provincial Education and Training Office had close cooperation. Since the chiefs of both organizations were HHPC directors, they integrated several of its interventions in their daily activities. Apparently, such cooperation has substantially increased the sustainability of the HHPC. They are performing a healthy lifestyle program with expanded areas of interventions and have added the evaluation, follow-up of interventions and continuous reporting as part of their activities.

HHPC was an intervention project that was conducted in schools and kindergartens, aiming to improve lifestyle habits and to prevent and control CVD risk factors. The target groups who were trained on healthy nutrition, tobacco control measures and physical activity include children and adolescents, their parents, school staff, and health care providers. Our results of school children showed that the sustainability of health-promoting interventions in elementary and middle schools of Isfahan was high as currently 100% of elementary schools and 99% of middle schools have integrated the interventions, including educational programs, morning workouts and ban of unhealthy food sales like snacks including chips and cheese balls.

The number of interventions integrated in girls' middle schools was 100%, however it was less in boys' middle schools, and the least in boys' high schools. For example, sales of unhealthy food reached 46.8% in boys' high schools. Furthermore, only 39.6% of boys in high schools did morning exercise. We considered interventions to be sustainable if they were implemented in at least 60% of target places, therefore, the interventions in high school boys were often non-sustainable. Lack of need of these interventions was the response provided by 41% of boys in middle and high schools.

Differences in childrens' perception might be one of the reasons of the results in this study, however, questions with large sex-based differences were direct and objective like whether they have a healthy snack bar services in their schools or whether they received educational sessions or not. Furthermore, the principals of girls school are usually women and boys' ones are men in Iran, a fact that may lead to better results among girls, as women pay more attention to health behaviors.[40,41] Another reason might be related to girls attitude and behaviors, because girls in this age are more concerned about their body shape and health, which may lead them to do more physical activity and eat healthier food.[42,43]

Taking the opportunity of morning programs to teach students and conduct daily exercise might be effective. Morning programs are conducted daily in all schools in Iran. In this program, different issues about life, society, religion, family, and environment are discussed. Because all students took part in these programs, schools can take advantage of this opportunity to educate all students about the interventions. Furthermore, policy makers, school teachers, and principals have used this opportunity as the most important way to teach students programs. In addition, daily exercise is done in 100% of elementary schools and most of middle and high schools. Another advantage of the morning programs is the participation of principals and some teachers beside students in these programs. It seems that students will be encouraged to have a healthy behavior when they see their principals' exercise or modify their lifestyle.

When tobacco control is considered, boys' school's were more successful in continuing their activities than girls' schools. The difference was significant in this regard. It may be related to the higher frequency of tobacco use among boys than girls and the early age of starting tobacco among boys in Iran[44] (Table 3).

HHPC sustainable interventions may also be related to improved knowledge and practice of the target population, together with the school childrens' acceptance, feeling of necessity for the interventions by policy makers, proper planning and implementation, developing rules/legislation, training of the teachers and principals, frequent evaluations and application of their results, and use of appropriate opportunities and available facilities.

Considering the results obtained and the fact that the implementation of these interventions does not need extra financial and human resources, it can be applied in other countries in the region because of the similarity in culture, socioeconomic status, and religious beliefs.

The strengths of our study are that it included qualitative component beside a comprehensive literature review to extract the determinants that constitute the variables related to sustainability to be included in the survey questionnaires; that school children in different grades and both sexes; and that our study was conducted 5 years after project completion.

Conclusion

Although 5 years have passed since the final phase of HHPC project, its interventions still continues at schools and in some cases, outcomes in lifestyle change have been sustained in populations. The sustainability is higher in elementary and middle schools than high schools and in girl school more than boy school. Therefore, it is important for future projects to put additional emphasis in these institutions for future school-based interventions to ensure intervention sustainability.

What's New

Although there are several studies on healthy lifestyle promotion or NCD prevention, few studies have examined the sustainability of their interventions. Such studies may need a combination of qualitative and quantitative components which can make the study complicated and hard to conduct. This study was done not only on school children at all grades, but on their parents and teachers, it consisted of qualitative and quantitative parts and was done 5 years after the completion of the original study.

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Conflict of Interests

Authors have no conflict of interests.

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Pediatric patients with renal disease and cardiovascular complications: A literature review

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Review Article

Abstract

The cardiovascular burden of end stage renal disease (ESRD) in children has recently received more attention, and some authors have recommended that the origins of the increase in cardiovascular morbidity and mortality be found in childhood. In this comprehensive review of the literature, we aim to review the main and most recent studies evaluating cardiovascular risk factors in pediatric kidney disease patients. The literature suggests that ESRD, even in the pediatric population, is associated with a high rate of cardiovascular morbidity and mortality, and needs serious attention. Unfortunately, there is extreme scarcity of data on the efficacy of preventive strategies on cardiovascular morbidity and mortality in pediatric patients with renal disease. Therefore, authors of the current article recommend future studies to be directed to find beneficial and/or potential harmful effects of different interventions conventionally used in this population, including lifestyle modifications and pharmaceutical therapy on cardiovascular indices. Moreover, the effects of these drugs on the renal function of children with minimal kidney disease should be evaluated.

Keywords: Cardiovascular Complication, Children, Kidney Disease, Pediatrics

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Introduction

It is a well-known fact that kidney disease can adversely affect cardiovascular health in the general population.[1] The importance of the issue, however, increases when evidence suggests that the largest share of mortality in renal disease patients is related to cardiovascular insults.[2] Although the issue has been broadly discussed in the adults, there is no mention whether similar connection exists in the pediatric population. In the current literature review, we focus to find potential connections between these two entities in patients of childhood age, and to find the extent of such associations.

The first part of the current review article reviews the existing evidence on potential association between renal disease in children and cardiovascular mortality. In the second part, factors which are potentially connected to cardiovascular mortality in pediatric patients with kidney disease will be evaluated. In the third part, associations between arterial hypertension and kidney disease in children will be reviewed. The forth part discusses functional and anatomical insults to the left ventricle. And in the last part, preventive and therapeutic are described.

Epidemiology of Pediatric Kidney Disease and Cardiovascular Mortality

It is a well-established fact that end stage renal disease (ESRD) induces a high rate of mortality, especially in adult patients compared with that in the general population. Moreover, several studies have suggested that the majority of these patients' mortality is associated with cardiovascular disease that complicates the original renal disease.[2] On the other hand, recent evidence indicates decreasing rates of cardiovascular morbidity and mortality in these patients.[3] Cardiovascular burden of ESRD in children has recently received more attention, and some authors have recommended that the origins of the increase in cardiovascular morbidity and mortality are better to be found in childhood.[4] Cardiovascular disease has been established as the leading cause of morbidity and mortality in adults with childhood-onset ESRD,[5] and the mortality rate of children with ESRD compared to that in the

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general population is 10 times larger than that in their adult counterparts.[6] Table 1 summarizes major data on the cardiovascular causes of death in pediatric patients with ESRD.

Table 1. Major studies evaluating cardiovascular cause of death in pediatric renal disease patients

Authors (references)	Cohort follow-up (year)	Main findings	Sample size
Groothoff et al.[7]	Up to 20	Overall 5-, 10-, and 20-year survival after ESRD onset was 87%, 82%, and 78%, respectively with cardiovascular disease accounted for most deaths (41%). In the whole group, LVH, aortic valve calcification, and arterial wall stiffening were highly prevalent. LVH was associated with hypertension at the time of assessment. Aortic valve calcification was strongly associated with a long total duration of peritoneal dialysis	249
Kramer et al.[8]	Up to 10	For young adults starting dialysis in childhood, the average life expectancy was 63 years for those with a functioning graft and 38 years for those remaining on dialysis	1777
Lin et al.[9]	Up to 10	The overall 1-, 5-, and 10-year survival rates for peritoneal dialysis (PD) patients were 98.1%, 88.0%, and 68.4%, respectively, and were 96.9%, 87.3%, and 78.5% for hemodialysis (HD) patients. The death rate was 24.66/1000 dialysis patient-years. Cardiovascular disease (13%) was the second death reason succeeding the infection (23.4%)	475
US Renal Data System[3]	5	In 2005–2009, the 1-year adjusted cardiovascular mortality rate in children age 0–9 was 28.5/1000 patient years, 4.8 and 2.5 times higher, respectively, than for ages 10–14 and 15–19. Children on hemodialysis have higher cardiovascular mortality than those on peritoneal dialysis (23.2 vs. 17.5), while children with a transplant have the greatest survival advantage, with a mortality rate of 2.3	US National data
Parekh et al.[6]	7	Evaluating the risk of cardiac death in children and young adults, of 1380 deaths recorded, 311 (23%) were due to cardiac causes. Percentage of cardiac deaths varied by age and was higher among black patients (0–4 years, 36%; 5–9 years, 18%; 10–14 years, 35%; 15–19 years, 22%; 20–30 years, 32%) than white patients (18%, 12%, 17%, 14%, and 23%, respectively). Among black patients, cardiac deaths occurred in 34% (21.4/1000 patient-years) of dialysis patients, and among white patients 25% (20.5/1000 patient-years)	USRDS
McDonald et al.[10]	Median 9.7	The most common cause of death was cardiovascular disease (45%). Cardiovascular causes accounted for 57 percent of deaths among children receiving hemodialysis, 43% among those receiving peritoneal dialysis, and only 30 percent among those with a functioning renal transplant	1634
Groothoff et al.[11]	Up to 20	Cardiovascular deaths accounted for 41% of the mortality, which was the leading cause of mortality both in patients under dialysis (45% of mortality) and transplant patients with a functioning graft (36%)	251
Chavers et al.[5]	6	Cardiac deaths accounted for 38% (13.7/1000 patient years) of the mortality, representing the leading cause of death in the population. There was no significant difference in cardiac mortality by age or sex. Cardiac deaths were significantly increased among blacks (4.5 vs. 2.1% whites, 1.5% other, P = 0.03)	1454

ESRD: End stage renal disease; LVH: Left ventricular hypertrophy; USRDS: United states renal data system

Risk Factors for Cardiovascular Disease in Pediatric Kidney Disease

While cardiovascular diseases and their unfavorable consequences in the general population generally matters adults and elderly, there is presumptions even among professionals that cardiovascular complications of ESRD in children is minimal. However, speaking based on scientific evidence, the prevalence of cardiovascular disease in pediatric kidney disease is astonishingly high, and is associated with several risk factors. One of the major risk factors associated with a higher cardiovascular disease in ESRD children is patients' gender, with males at higher risk.[7,12] However, there are studies suggesting controversial data with females representing the highest rate of developing cardiovascular complications (including cardiomyopathy, arrhythmia and valvular heart disease.[5] Race is another major playing factor with blacks at highest risk for cardiovascular disorders.[5,6] Obesity has been shown to be highly more prevalent among is proposed as a potential risk factor for cardiovascular complications in childhood, but there is controversy on its role.[4] There are also some other cardiovascular risk factors which are especial to ESRD children, with no evidence for any major effects for them in the general population. The most important of them is impaired calcium-phosphorus metabolism, which is supposed to lead to vascular calcification. ESRD, either in adult individuals or in children, is associated with a secondary hyperparathyroidism that effectively impairs calcium-phosphorus metabolism in this population.[13] However, it is not the end of the story. Treatment of secondary hyperparathyroidism with calcium-containing phosphate binders and vitamin D analogs can result in hypercalcemia as well as increased levels of calcium-phosphorus product, which produce broad calcifications in soft-tissue, with the most clinically dangerous feature in the coronary arteries.[14] It has been suggested that although calcium accumulation begins pre-dialysis, but it is the induction of vascular smooth muscle cell apoptosis in dialysis that is the key event in disabling vascular defense mechanisms and leading to overt calcification.[15] The major studies on the coronary calcification of children with ESRD are listed in table 2.

Hypertension in Pediatric Kidney Disease

Hypertension maybe the most common cardiovascular risk factor that develops in young patients with ESRD, which not only accelerates kidney disease course to ESRD, but it induces high cardiovascular burden.[16] The interesting thing about hypertension is that it is, perhaps, the most modifiable risk factor of all; so it is very logical to pay a tremendous amount of attention to control this risk factor. Despite the high relevance of the subject, it has only recently taken attention for research.[17] One of the first major studies surveying the subject was conducted by Mitsnefes et al.[18] who reported from a large cohort of 3743 dialysis children. In this study, authors reported a 77% prevalence of hypertension in their population, and regression analysis showed associated risk factors include: baseline hypertensive status, use of antihypertensive medications, young age, acquired cause of renal failure, black race, initiation of dialysis therapy in 1992 to 1997, and hemodialysis as a mode of renal replacement therapy. In another major study by Flynn et al.[19] reporting from the chronic kidney disease in children (CKiD) prospective cohort study, authors showed that 54% of children with chronic kidney disease (CKD) had hypertension (defined as measured blood pressure (BP) >95th percentile and/or history of antihypertensive medication). Characteristics associated with elevated BP reported by CKiD included black race, shorter duration of CKD, absence of antihypertensive medication use, and elevated serum potassium. Another major study on the subject was conducted by Chavers et al.[20] on 624 American ESRD children revealed an appalling prevalence of hypertension, with 79% having hypertension and 62% under antihypertensive pharmacotherapy. Nevertheless, a more recent study by Halbach et al.[21] showed some improvement in the mentioned factors' epidemiology with 68% of patients representing hypertension, and 58% were prescribed antihypertensive medications. The same study reported that more recent year of dialysis commencement was associated with a higher use of antihypertensive medication and lower systolic BP and diastolic BP z-scores. Other factors associated with higher BP included black race, glomerular disease, younger age, hemodialysis (for systolic BP only), and antihypertensive use. Moreover, patients on hemodialysis or those with glomerular diseases represented the highest percentage of uncontrolled hypertension.[21] In the sole major European study available in the literature, Kramer et al.[22] recently showed that hypertension was present in 69%, 68%, and 67% of hemodialysis, peritoneal dialysis, and

Table 2. Major studies investigating coronary artery and cardiac calcification in children with end stage renal disease (ESRD)

Authors (References)	Diagnosis method	Main findings	Sample size
Goodman et al.[23]	Electron-beam tomography	None of the 23 patients who were younger than 20 years of age had evidence of coronary-artery calcification, but it was present in 14 of the 16 patients who were 20–30 years old	39
Civilibal et al.[24]	Spiral CT scan	CAC was present in 15% of patients (3/15 hemodialysis (HD) patients, 3/24 peritoneal dialysis (PD) patients, and 2/14 kidney transplants). The patients with CAC had longer duration of total dialysis, had higher time-integrated serum phosphorus, calcium-phosphate (CaxP) product, iPTH, vitamin B (12) levels, the amount of cumulative calcium-containing OPBs, and calcitriol intake, and had lower serum hemoglobin level. A stepwise logistic regression analysis revealed that serum phosphorus (P = 0.018) and the cumulative exposure to calcium-containing OPBs (P = 0.016) were the most significant independent predictors in the development of CAC	53
Lumpaopong et al.[25]	Electron-beam tomography	Coronary calcification was observed in 64% patients. The mean daily dose of calcitriol was significantly higher in patients with calcification; but the mean daily dose of total calcium, triglyceride level, and calcium/phosphorus products did not reach a significant level. Using Spearman multivariate correlation, authors found a correlation between the coronary calcium scores and mean daily doses of total calcium and calcitriol (r = 0.750, P =0.008 and r = 0.869, P = 0.001, respectively)	11 renal transplant patients
Shroff et al.[26]	Spiral CT scan	Patients with calcification had lower fetuin-A and higher osteoprotegerin than those without calcification. On multiple linear regression analysis and fetuin-A and osteoprotegerin predicted cardiac calcification (P = 0.02, beta = −0.29 and P = 0.014, ss = 0.33, respectively, model R (2) = 32%)	61 children on dialysis
Gruppen et al.[27]	Echocardiography	110 patients had received a transplant and 30 patients were on dialysis. 27 (19%) had aortic valve calcification. Multiple regression analysis revealed that aortic valve calcification was associated with prolonged peritoneal dialysis (beta = 0.36, P < 0.001)	140 young adults with childhood onset ESRD
Shroff et al.[28]	CT scan	Cardiac calcification score was correlated with iPTH (r = 0.39, P = 0.03), serum PO_4 levels (r = 0.34, P = 0.03) and vitamin D dosage (2.8 fold higher dosage than that in no calcification group; r = 0.28, P = 0.02). Significantly, patients with iPTH levels greater than twice the upper limit of normal had greater cardiac calcification	85 children on at least 6 months dialysis

CAC: Coronary artery calcification; OPBs: Oral phosphate binders; CT: Computed tomography iPTH: Intact parathyroid hormone; ESRD: End stage renal disease

renal transplant patients, respectively. BP values above the 95th percentile were significantly more prevalent in very young patients (under 3 years) compared with 13–17-year olds (odds ratio 2.47), during the 1st year compared to over 5 years of renal replacement therapy (odds ratio 1.80), and in patients on hemodialysis compared to transplant recipients or those on peritoneal dialysis (odds ratios of 2.48 and 1.59, respectively). Over time, mean BPs decreased in both hemodialysis and transplant patients, but not in peritoneal dialysis patients.[22] Besides the prevalence of hypertension among children with kidney disease, maybe the more important issue is the cardiovascular effects of hypertension in this population. In the adult patients, the cardiovascular morbidities of hypertension are well-recognized. However, in the very particular subpopulation of pediatric kidney disease patients, one may rightly think that there might be some substantial differences. Table 3 summarizes data of major studies on the cardiovascular consequences of hypertension in children with kidney diseases.

Structural and/or Functional Abnormalities of the Left Ventricle in Children with Kidney Disease

Structural anomalies have been consistently reported by different studies on pediatric ESRD patients; but the interesting thing is that even when there is minimal renal disease, these abnormalities began to develop and progress through the renal disease advancement.[29,30] A recent report from CKiD study,[31] demonstrated that left ventricular hypertrophy (LVH) has overall prevalence of 17% in pediatric kidney disease patients, while this rate in the International Pediatric Peritoneal Dialysis Network registry,[32] on 507 patients was 48%. Moreover, LVH is more frequently observed in children with clinic measured hypertension, than that defined by ambulatory measures.[33] Although data from CKiD study indicates that children with sustained and masked systolic or diastolic hypertension have higher rates of LVH,[31] Bakkaloglu et al.[32] in a very recent study reported that this is systolic hypertension, and not diastolic that predicts LVH in pediatric kidney disease patients. It has also been proposed elevated parathyroid hormone as a contributing factor in the progression of LVH in higher stages of kidney disease in children.[34]

Data on the ESRD children who undergo renal transplantation also indicates a high rate of LVH. A Midwest Pediatric Nephrology Consortium study,[35] showed that the prevalence of LVH among ESRD children who undergone kidney transplantation was 40% 1-year post-transplant. Most of the studies show the persistence of cardiac hypertrophy and ventricular dysfunction,[36-38] although some evidence also suggest improvement post-transplantation.[39,40]

Impaired left ventricular (LV) filling and compliance early or later in the progression of pediatric kidney disease has been reported overwhelmingly.[41] More the kidney disease progresses, the higher LV dysfunction advances,[42] with the highest prevalence of diastolic dysfunction in patients undergoing maintenance dialysis.[43] There are also several reports documenting subtle alterations in LV wall mechanics in children on maintenance dialysis. The most significant of these alterations are decreased shortening at the myocardial mid-wall,[44,45] diminished contractile reserve during stress,[46] and acute reductions in global and segmental myocardial blood flow simultaneous with an increase in myocardial stunning.[47]

Preventive Strategies to Reduce Cardiovascular Risk

Because risk factors, which contribute in cardiovascular injuries in kidney disease patients are multiple, and they mostly have conjoined contribution in inducing their ominous effects, strategies to risk reduction in this patient population should be complex and perhaps different for each individual patient, based on his/her risk profile. Unfortunately due to the very limited data available in the literature on the treatment and prevention strategies in the pediatric population of kidney disease, herein, we briefly review data on the mentioned strategies in adult kidney disease population.

Lifestyle and nutritional status intervention

Lifestyle modifications, is the most common and probably the most effective intervention in these patients. Although there is data scarcity on the effectiveness of undertaking these strategies in pediatric kidney disease patients, overwhelming data suggests them as effective methods for risk reduction in the general population. Weight loss programs, prevention of smoking, diet modifications, and encouragement to regular exercise are probably the most effective and implementable strategies physicians can prescribe for their patients. Weight loss in obese people has been shown to decrease BP. In 50% or more of individuals, the average decrease in BP is 1–4 mm Hg systolic and 1–2 mm Hg diastolic per kilogram of weight reduction up to the normalization of BP.[48]

Table 3. Data of major studies on the cardiovascular consequences of hypertension in children with kidney diseases

Authors (references)	Main findings	Population size
Johnstone et al.[49]	No correlation was found between BP and LVH in children on dialysis	32 CRF, 10 peritoneal dialysis, 30 renal transplants (age < 27 year)
Mitsnefes et al.[50]	Multiple logistic regression analysis revealed hemodialysis versus peritoneal dialysis as a significant independent predictor for severe LVH, while higher systolic BP remained in the final model was found to be an independent predictor with lower significance level	64 (< 22 year)
Chinali et al.[44]	Systolic dysfunction was most common (48%) in patients with concentric hypertrophy and associated with lower hemoglobin levels	130 pre-dialysis children (< 18 year)
Mitsnefes et al.[51]	Multiple regression analysis showed that baseline LVMI (P = 0.005) and interval change in indexed systolic BP (P = 0.027) were independent predictors for LVMI changes	29 children at the initiation of dialysis (age < 18 year)
Chavers et al.[5]	The most common cardiovascular "events" were arrhythmias, valvular disease, and cardiomyopathy; cardiac deaths accounted for just 9% of all reported events	1454
Mitsnefes et al.[34]	Lower initial LVMI and hemoglobin level and interval increase in iPTH and nighttime systolic BP load during a follow-up independently predicted interval increase in LVMI	31
Sinha et al.[33]	Patients with LVH had consistently higher BP values than those without. Multiple linear regression demonstrated a strong relationship between systolic BP and LVMI. Clinic measured systolic BP showed a stronger relationship than ambulatory measures	49 non-hypertensive children (all below 95th percentile)
Matteucci et al.[52]	After restrict control of hypertension for at least 1 year, LVH prevalence decreased significantly from 38% to 25%. Changes in LVMI were restricted to patients with LVH at baseline (−7.9 g/m$^{2.7}$; P < 0.02). In multivariate analysis, improvement in myocardial function was associated with reduction in BP (r = −0.4; P < 0.05), independently of LVMI reduction	84
Shamszad et al.[53]	Post-dialysis hypertension was associated with elevated LVMI (OR = 2.9, 95% CI = 1.5–5.5)	63 (mean age: 14.1 year)
Bakkaloglu et al.[32]	Systolic (but not diastolic) hypertension (OR = 1.93, 95% CI = 1.25–2.98), high body mass index, use of continuous ambulatory peritoneal dialysis, renal disease other than hypo/dysplasia, and hyperparathyroidism were identified as independent predictors of LVH	507 peritoneal dialysis patients (age < 19 year)

CRF: Chronic renal failure; OR: Odds ratio; CI: Confidence interval; BP: Blood pressure; LVH: Left ventricular hypertrophy; LVMI: Left ventricular mass index; iPTH: Intact parathyroid hormone

In a recent and very extensive meta-analysis of 13 studies on the effects of weight loss in kidney disease patients, Navaneethan et al.[54] reported that a decrease in body mass index (BMI) with nonsurgical interventions was associated with a significant decrease in proteinuria [Weighted mean difference (WMD) −1.31 g/24 h; 95% confidence interval (CI) −2.11 to −0.51] and systolic BP with no further decrease in glomerular filtration rate (GFR) during a mean follow-up of 7.4 months. In morbidly obese individuals (BMI >40 kg/m^2) with glomerular hyperfiltration (GFR >125 ml/min), surgical

interventions for weight loss resulted in a decrease in GFR (WMD −25.56 ml/min; 95% CI −36.23 to −14.89), albuminuria, and systolic BP.[54] Diet modification is probably the most efficient intervention method in CKD patients, due to overwhelming data on the survival effects of malnutrition in this patient population. In a 2-year cohort of an American hemodialysis population of as large as 53,933 patients, Shinaberger et al.[55] have reported that a decrease in protein intake during the first 6 months in patients was associated incrementally with greater death risks in the subsequent 18 months, whereas an increase in protein-nitrogen appearance tended to correlate with reduced death risk. In contrary, Kalantar-Zadeh et al.[56] in a prospective cohort of 122 hemodialysis patients reported an increase in hospitalization rate and mortality in patients undergoing protein-nitrogen appearance and/or albumin level normalizations. On the other hand, in a more recent study, Shinaberger et al.[57] in a 3-year trial showed that restricting protein intake in order to control hyperphosphatemia may lead to greater mortality. They reported that a simultaneous decrease in phosphatemia and protein nitrogen appearance is associated with the worse survival rate compared to other combinations of the two factors. Hemoglobin is also an important marker for nutritional status. Regidor et al.[58] in their study have reported that having hemoglobin levels within the range of the recommended Kidney Disease Quality Outcomes Initiative hemoglobin target (11–11.5 g/dl) for hemodialysis patients was associated with a higher death risk compared with the 11.5–12-g/dl range. A decrease or increase in hemoglobin over time was also associated with higher or lower death risk, respectively, independent of baseline hemoglobin. Moreover, use of erythropoiesis stimulating agents in these patients was associated with better survival.[58] Although there are controversies on the survival advantage of effects of erythropoiesis stimulating agents in dialysis patients.[59,60] However, similar findings to Fort et al. have also been reported from other societies.[61]

Pharmacological intervention

Due to the multifactorial nature of the kidney disease and its associations with cardiovascular morbidities, pharmacological interventions to address them are very extent and efficacy of several of them has already been confirmed. Hence, here, we focus on the most recent major studies evaluating pharmacological intervention, especially controversial ones, to reduce cardiovascular risk factors in kidney disease patients.

Rosuvastatin is a statin whose effectiveness in reducing cardiovascular events has been proved in the general population; however in the kidney disease, patient's data has only been published recently. Fellstrom et al.[62] conducted an international, multicenter, randomized, double-blind, prospective trial involving 2776 patients, 50–80 years of age, who were undergoing maintenance hemodialysis, and after 3 months of initiation of rosuvastatin, the mean reduction in low-density lipoprotein (LDL) cholesterol levels was 43%. However, rosuvastatin had no effect on individual components of the cardiovascular end point. There was also no significant effect on mortality.[62] Ezetimib is a Niemann–Pick C1-like 2 protein blocker that potently prevents the absorption of cholesterol from the gastrointestinal tract.[63] Simvastatin is also a potent statin that has the same effect on lipid profile. In the Study of Heart and Renal Protection trial,[64] Baigent et al., for the first time evaluated the effects of simvastatin and ezetimib on the cardiovascular outcome of kidney disease patients on 9438 (3023 on dialysis) kidney disease patients. During a median follow-up of 4.9 years patients treating with simvastatin plus ezetimibe experienced a 17% proportional reduction in major atherosclerotic events than patients taking placebo (11.3% vs. 13.4%; rate ratio: 0.83, 95% CI: 0.74–0.94; log-rank P = 0.0021).[64] However, the second United Kingdom Heart and Renal Protection study[65] revealed that there is no statistically significant effect for the addition of ezetimibe to simvastatin on triglyceride or high-density lipoprotein cholesterol levels in kidney disease patients. Potential effects of oral 1α-hydroxy vitamin D3 has also been examined on the cardiovascular mortality of hemodialysis patients, and has been shown to be associated with reduced risk for cardiovascular death in this cohort of ESRD patients.[66]

The power of renal protective effects of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB) is also controversial. A comprehensive meta-analysis of 49 studies showed that the effects of ACEI and ARB in reducing proteinuria was similar to each other, but combination therapy by both of the agents induced a higher effect.[66,67] In the very recent and large Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, Rahman et al.[68] reported no difference in cardiovascular mortality, coronary heart disease, cardiovascular disease, stroke, or ESRD in participants with an estimated GFR <60,

between using chlorthalidone and amlodipine, or chlorthalidone and lisinopril. Because there are several valuable review articles in the literature on the subject, we refer interested readers to them.[69]

Conclusion

Evidence suggests that ESRD even in the pediatric population is associated with a high rate of cardiovascular morbidity and mortality, and needs high levels of attention. Unfortunately, there is scarcity of data on the efficacy of preventive strategies on cardiovascular morbidity and mortality in pediatric patients with renal disease. This limitation of data exists both in pharmacological and non-pharmacological interventions in childhood kidney disease population. We recommend future studies to be directed to find therapeutic effects of different agents on various cardiovascular indices, including structural and functional measures, as well as adverse effects associated with those drugs. Moreover, the effects of these drugs on the renal function of children with minimal kidney disease should be evaluated.

Conflict of Interests

Authors have no conflict of interests.

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A rare case of stenting of spontaneous dissection of Shepherd's Crook right coronary artery

Laxman Dubey[1]

Case Report

Abstract

BACKGROUND: Spontaneous coronary artery dissection (SCAD) is a rare cause of acute coronary syndrome (ACS) and sudden death. It usually occurs in young women during the peripartum period; however, it had also been reported in older aged males having risk factors for atherosclerotic coronary artery disease.

CASE REPORT: This case describes a 69-year-old male patient who presented with manifestations of ACS due to a spontaneous dissection of the Shepherd's Crook right coronary artery (RCA), which was successfully managed with percutaneous coronary intervention (PCI) and stenting. At the 6th month follow-up, the patient remained chest pain free.

CONCLUSION: Patients with SCAD in the presence of ongoing ischemia can be treated with PCI and stenting.

Keywords: Acute Coronary Syndrome, Percutaneous Coronary Intervention, Shepherd's Crook Right Coronary Artery, Spontaneous Coronary Artery Dissection

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Introduction

Spontaneous coronary artery dissection (SCAD) is a rare but important cause of acute coronary syndrome (ACS). The spectrum of clinical presentation can range from unstable angina, acute myocardial infarction, and sudden death.[1-3] The population-based incidence of SCAD is unknown; however, the overall incidence of SCAD in angiographic series has been reported to 0.1–1.1%.[4] The exact etiological mechanism of SCAD remains unclear. There is a female preponderance and tendency to occur in pregnancy, making a hormonal influence likely. SCAD had also been reported in older aged males having risk factors for atherosclerotic coronary artery disease. This case highlights a 69-year-old male patient who presented with manifestations of ACS due to a spontaneous dissection of the Shepherd's Crook right coronary artery (RCA), which had been rarely reported in the literature. Patient was managed successfully with percutaneous coronary intervention (PCI) and stenting of the RCA.

Case Report

The case we present here is about a 69-year-old male patient who presented to our hospital with substernal chest pain associated with shortness of breath of 10 days duration and one episode of loss of consciousness one day back. The patient denied chest trauma, fever, or chills. He was a past smoker and taking medicines for systemic hypertension, type-2 diabetes mellitus, and long-standing atrial fibrillation. He was on aspirin, atorvastatin, atenolol, amlodipine, and metformin. In the emergency room, his systolic blood pressure was found to be of 170/90 mmHg with heart rate of 45 beats/min. Family history was unremarkable for any cardiovascular illness. Patient was conscious with no focal neurological deficit. Physical examination was within normal limits except for a soft systolic murmur at the apex. Complete blood count and serum biochemistry were within normal limits. Electrocardiography showed atrial fibrillation with slow ventricular response and ST segment depression of 3 mm in leads V2 and V6 with T-wave inversion. Laboratory studies did not show any elevation in cardiac enzymes. A computed tomography scan of the head showed normal findings. He was taken to the cardiac catheterization laboratory for the placement of a temporary pacemaker and coronary angiography (CAG).

Temporary pacemaker was inserted via right

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femoral vein and kept in the right ventricle. CAG was performed via right femoral artery approach. Selective cannulation of the left coronary artery revealed a normal left main coronary artery bifurcating into the left anterior descending (LAD) and the left circumflex artery (LCX). There were non-obstructive lesions in the mid-LAD as well as at the first diagonal branch. LCX had minor atherosclerotic plaques. RCA was hooked with Judkins right catheter 3.5 × 6 French (Cordis). Selective cannulation of the RCA revealed a dissection within the proximal segment of an uplifted tortuous (Shepherd's Crook morphology) RCA with the normal flow down the distal vessel (Figures 1 and 2).

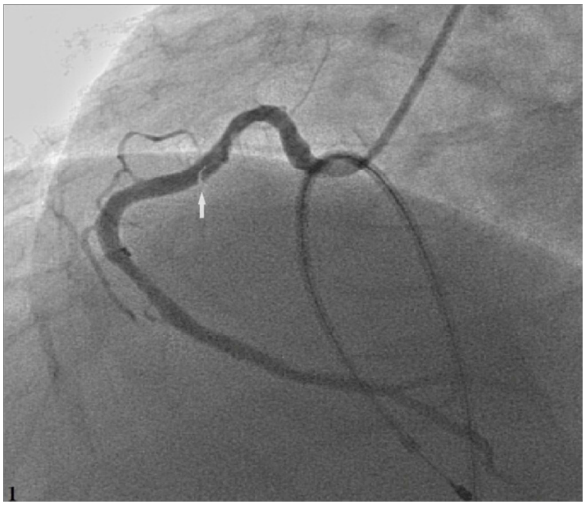

Figure 1. Coronary angiography in left anterior oblique projection showing Shepherd's Crook right coronary artery with a clear angiographic flap (arrow) indicating dissection

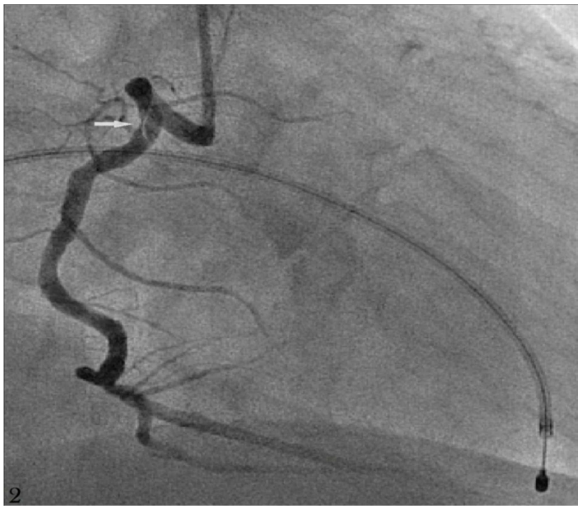

Figure 2. Right anterior oblique projection showing clear angiographic flap (arrow) in the right coronary artery

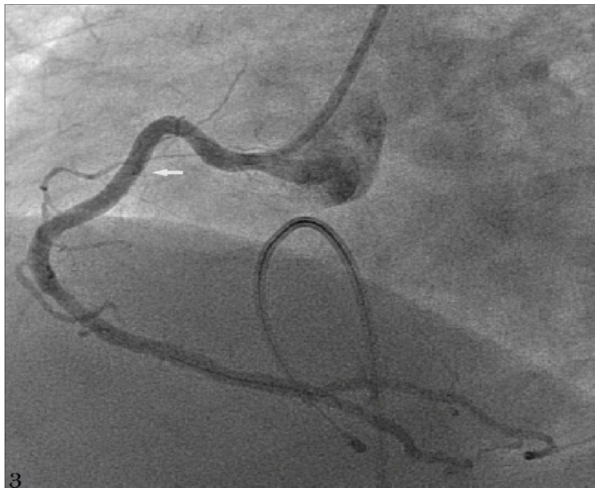

Figure 3. Final result after stenting shows disappearance of the dissection (arrow)

The dissection was treated by direct stenting (3.5 mm × 24 mm, Partner Sirolimus Eluting Stent, Lepu Medical), after which the dissection disappeared (Figure 3). Three days later, his heart rate was in a range of 60–70 beats/min and temporary pacemaker was removed. His subsequent stay in the hospital was uneventful and discharged free of symptoms on the 5th day. At 6 month follow-up, patient remained chest pain free.

Discussion

The earliest report of SCAD was published in 1931 during autopsy findings in a 42-year-old woman who died after presenting with chest pain.[5] SCAD is a relatively uncommon condition that usually presents as an ACS or sudden cardiac death, with a reported mortality of 80%.[6] The reported incidence of SCAD varies from 0.1% to 1.1% by angiography.[4] Until now, approximately 500 cases have been documented in the medical literature due to a significant number of SCAD presenting with sudden death.[7] The Western Denmark Heart registry reported 22 cases of SCAD out of a total of 11,175 ACS patients, and 77% of them were women.[8]

SCAD has been reported most commonly in young women of whom approximately 30% of cases occur in the peripartum period.[9] The increased incidence of SCAD in pregnancy and the postpartum period is thought to be due to decreased collagen production or enhanced degradation in the intima and media of the vessel wall in the postpartum period, increased shear stress on the arterial wall due to augmented cardiac output, inherent hypercoagulability in peripartum

state, and hemorrhagic disruption of vasa vasorum.[10] It may also be associated with autoimmune and collagen vascular diseases, Marfan's syndrome, Ehlers-Danlos syndrome type IV, systemic lupus erythematosus, or intense physical exercise.[11] The presence of an eosinophilic infiltrate in adventitia had also been described, particularly in non-atherosclerotic SCAD.[12] SCAD had also been reported in the older aged males having risk factors for atherosclerotic coronary artery disease,[13] as in our case. Atherosclerosis, coronary vasospasm, and coronary artery ectasia were also thought as the main reasons for dissection. In atherosclerotic arteries, increased density of vaso vasorum due to atherosclerotic plaque may cause bleeding and rupture of nidus that can lead to dissection of adventitia from media and subsequent rupture of intima or primary event is an intimal tear progressing into media by the force of arterial pressure.[13]

The most common localization of involvement is the LAD artery (80%) followed by the RCA; in a few cases the LCX may be affected.[14] CAG is the gold standard in the diagnosis of SCAD; however, other imaging techniques such as computed tomography, magnetic resonance imaging, intravascular ultrasound, and transesophageal echocardiography may be helpful in both the diagnosis and follow-up.[13-15]

Management of SCAD remains controversial and mostly depends on the clinical presentation, location of the dissection, the number of vessels involved, and the coronary flow status; however, there are no guidelines regarding optimal treatment of this condition. PCI and stenting is reasonable in acute cases with proximal dissection with arterial occlusion as well as in cases with an ongoing ischemia in order to restore the coronary perfusion and hemodynamic stability.[14] However, conservative medical therapy is reasonable in cases with no evidence of ongoing ischemia or hemodynamic instability. Surgical revascularization is usually restricted to hemodynamically unstable cases where PCI is failed or not possible.[16]

Conclusion

SCAD is a rare but a fatal condition, although, commonly reported in young women that do not carry any known risk factors, can be seen in the middle and older aged males having risk factors for atherosclerotic coronary artery disease. PCI may be the treatment of choice in patients with ongoing ischemia. We presented PCI and stenting of spontaneous dissection of the Shepherd's Crook RCA that had been rarely reported in the literature.

Conflict of Interests

Authors have no conflict of interests.

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Pulmonary hypertension due to a pulmonary artery leiomyosarcoma: A case report

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Case Report

Abstract

BACKGROUND: Primary pulmonary artery sarcomas are very rare and their histologic type called leiomyosarcoma is even rarer. These tumors are frequently misdiagnosed as pulmonary thromboembolism in clinical settings. Many patients receive anticoagulant therapy without response, and many are diagnosed postmortem only. Most of the tumors reported in the literature have involved the right ventricular outflow tract and the main pulmonary trunk, often extending into the main pulmonary artery (MPA) branches.

CASE REPORT: A 64-year-old woman presented with weakness, fatigue, malaise, dyspnea, and marked elevation of pulmonary artery pressure was admitted to our hospital. She was initially diagnosed with chronic pulmonary thromboembolism, and chest computed tomography (CT) scan revealed lobulated heterogeneous left hilar mass extended to precarinal and subcarinal space. Magnetic resonance imaging (MRI) demonstrated a polypoid lesion at the trunk with extension to left MPA and its first branch. The patient was operated, and a yellowish-shiny solid mass in pulmonary trunk was seen intra-operation and pulmonary endarterectomy was performed. Her tumor was pathologically diagnosed as pulmonary artery leiomyosarcoma.

CONCLUSION: Clinicians must consider pulmonary artery sarcoma when making the differential diagnosis for patients with pulmonary artery masses. The clinical prediction scores and the CT and MRI findings can help identifying patients with pulmonary artery sarcoma.

Keywords: Hypertension, Leiomyosarcoma, Pulmonary Artery, Pulmonary Embolism

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Introduction

Primary pulmonary artery sarcomas are very rare, and their histologic type called leiomyosarcoma is even rarer.[1] The incidence of primary pulmonary artery tumors is 0.001–0.03%, and are nearly always highly malignant and typically obtain their origin from the intima.[2] The underlying pathophysiology of these tumors of the pulmonary arteries is still unclear.[2,3]

These tumors are frequently misdiagnosed as pulmonary thromboembolism in clinical settings. Many patients receive anticoagulant therapy without respond, and many are diagnosed postmortem only.[4] Most of the tumors reported in the literature have involved the right ventricular outflow tract and the main pulmonary trunk, often extending into the main pulmonary artery (MPA) branches.[5]

Case Report

The patient was a 64-year-old woman presented with progressive generalized weakness and dyspnea for 6 months. She had no risk factors for thromboembolism. She had a history of headache, weight loss, and nonproductive cough prior to the admission and one episode of pre-syncope last year. Her vital signs at the time of admission were, temperature of 38°C, blood pressure of 120/70 mmHg, pulse of 80 beats/min and respiration rate of 24 breaths/min with O_2 saturation of 99%. On physical examination, no clinical evidence of deep vein thrombosis was found, and in cardiac auscultation, a systolic murmur (grade III/VI) was heard in lower left sternal border. Chest X-ray showed moderate enlargement of the right atrium and dilatation of right descending pulmonary artery (Palla's sign).

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No abnormality was seen in her electrocardiography. Transthoracic echocardiography (ECG) showed a severe pulmonary artery hypertension (the predicted pulmonary artery pressure was 120 mmHg) with severe right ventricular hypertrophy, severe dysfunction, and moderate to severe tricuspid valve regurgitation. MPA was occupied by a large non-homogenous mass with very small flow from the left side of MPA and significant stenosis (peak gradient = 55 mmHg).

A contrast-enhanced computed tomography (CT) scanning of the chest showed lobulated heterogeneous left hilar mass occupying the precarinal and subcarinal space and invaded into left MPA and pulmonary trunk. Right ventricle and right atrium strain and enlargement, mild pericardial effusion and right sided pleural effusion were seen. Furthermore, magnetic resonance imaging (MRI) revealed a polypoid lesion at the trunk of pulmonary artery with extension to left main and the first branch (Figure 1).

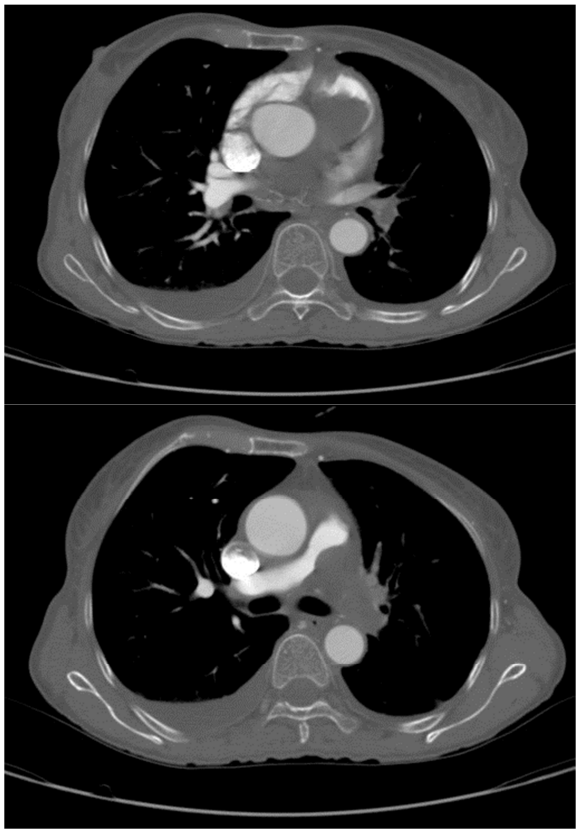

Figure 1. Magnetic resonance imaging reveals a polypoid lesion at the trunk of pulmonary artery with extension to left main and the first branch

No obvious extra-luminal extension was detected. With the primary diagnosis of the main pulmonary thromboembolism, the patient was operated through mid-sternotomy. On opening the pulmonary artery, a soft yellowish-shiny mass was found. Gross examination showed creamy to gray color irregular tissue fragments with elasticus consistency and hemorrhagic change totally measured 7 × 6 × 1.5 cm.

Microscopically, the tumor was composed of spindle shaped cell with pleomorphism and ovaloid hyperchromatic to spindle nuclei was found. A pattern of tumor growth was observed in the lung parenchyma: tumoral cells arranged in parallel with whirling appearance forming storiform pattern.

Mitotic activity was evaluated as the number of mitotic figures per 10 high-power fields (HPF) was about 5–6 and bizarre cell and tumoral giant cells were present. Many cleft like vascular channel in addition to hemorrhagic myxoid and necrotic changes were present. Pathological diagnosis confirmed leiomyosarcoma confined to the excised pulmonary (Figures 2–4).

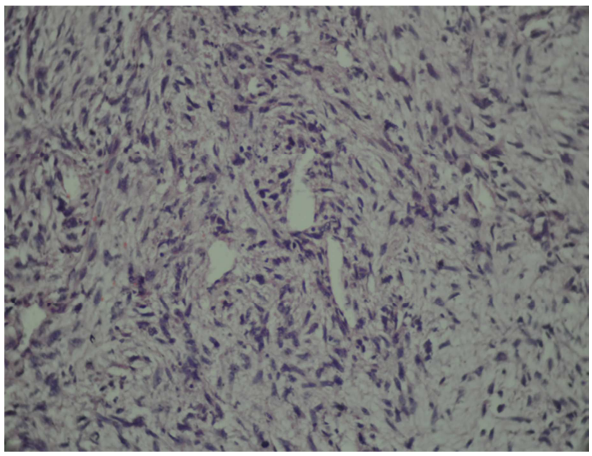

Figure 2. The intimate relationship of the tumor cells with the vessel walls is a clue to the diagnosis of leiomyosarcoma

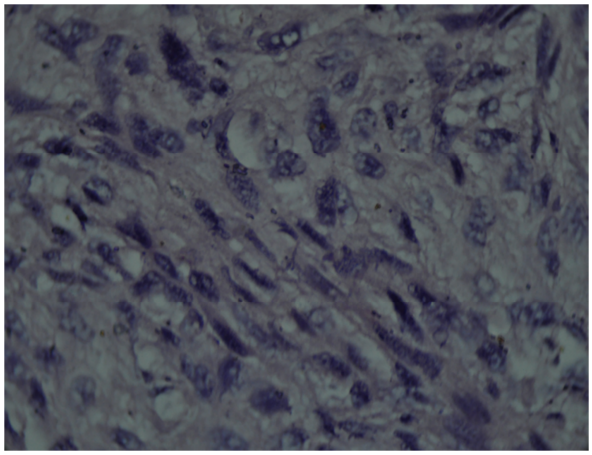

Figure 3. Cytologic features of leiomyosarcoma showing eosinophilic cytoplasm and blunt-ended nuclei

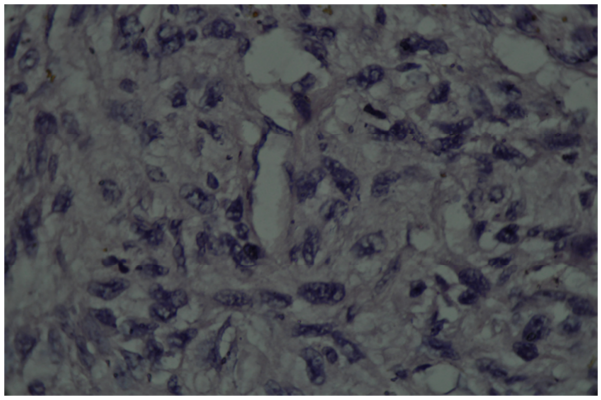

Figure 4. Cytologic features of leiomyosarcoma showing perinuclear vacuoles

Immunohistochemical staining was positive for smooth muscle actin, a marker for mesenchymal neoplasms. Immunohistochemical staining for factor 8, HMB45 and cytokeratin were negative while it was focally positive for CD68 and 5100. Tumor differentiation score was 2.3 with mitosis count of 13 per 10 HPF and score of 2.3.

Tumor necrosis: < 50% score: 1.2

And total score: 5.9. Grade: II.

The patient underwent pulmonary thromboendarthrectomy surgery with suspicion to pulmonary thromboemboly and a yellowish-shiny solid mass in pulmonary trunk was seen intra-operation and pulmonary endarthrectomy performed. Complete tumor resection was performed, and finally, the pathology result confirmed primary pulmonary artery sarcoma with smooth muscle differentiation compatible with leiomyosarcoma (i.e., intimal sarcoma).

Discussion

Primary leiomyosarcoma cases of the pulmonary artery are extremely rare, and most of them are initially misdiagnosed as pulmonary thromboembolism with symptoms of dyspnea, chest pain, cough, and hemoptysis.[6,7] Both diseases are typically detected between the ages of 40 and 60, and women are involved twice as often as men. Physical examination, ECG and the chest X-ray may not reveal abnormal findings. However, cardiomegaly and radiological signs of a peripheral hypoperfusion can be present if a large tumor mass is obstructing a MPA vessel.[8]

Atypical features such as lack of predisposing factors for thromboembolism, persistence of symptoms or recurrence despite adequate anticoagulation, and unilateral distribution of a massive perfusion defect may evoke the diagnosis of tumoral obstruction.[9]

The differential diagnoses include pulmonary artery sarcoma, thromboembolism, and lung cancer. The symptoms of the pulmonary embolism are nonspecific, and laboratory findings have a low diagnostic specificity and chest radiograph is generally nondiagnostic.[4]

The median survival time of the pulmonary artery leiomyosarcoma patients has been reported to be 1.5 months. It is believed that early and primary surgical resection is the best treatment of choice and can prolong the patient's life to 10–12 months.[7,10]

The role of adjuvant therapy has not been yet clearly defined in the literature. The limited experience of any center in the treatment of these neoplasms makes it difficult to evaluate the relative importance of surgical excision and adjuvant therapy. Some investigators are in favor of adjuvant therapy and describe encouraging results.[11,12]

Scores derived from explicit prediction rules that combine clinical findings at presentation with predisposing factors have proved useful in determining the clinical or pretest probability of pulmonary embolism. Three scores have been recommended as diagnostic criteria.[4]

Our patient experienced only a slight dyspnea before admission, and her physical examination on admission produced no findings suggestive of pulmonary embolism. It is suggested that pulmonary artery sarcomas should be strongly suspected in cases who present with mass lesions in the pulmonary arteries, but score low on the clinical prediction indexes. Several indicators on CT and MRI favor the diagnosis of pulmonary artery sarcoma over chronic thromboembolic disease.[13] Chest X-ray showed moderate enlargement of the right atrium and dilatation of right descending pulmonary artery and MRI revealed a polypoid lesion at the trunk of pulmonary artery with extension to left main and the first branch.

Differential diagnosis also included primary and metastatic lung cancer. Our patient never smoked, and her serum tumor markers were all within normal ranges. It is said that the actual prevalence of pulmonary artery sarcoma is much higher than the estimated prevalence because of difficult diagnosis and often going unidentified without autopsy. The prognosis for patients with pulmonary artery sarcoma is poor, and in most cases, the mean survival time is < 2 years. Effect of chemotherapy or radiation therapy on prognosis is unclear and radical surgical resection seems to provide the only hope of long-term survival.[14]

Conclusion

Clinicians must consider pulmonary artery sarcoma when making the differential diagnosis for patients with pulmonary arteries masses. The clinical prediction scores and the CT and MRI findings can help identifying patients with pulmonary artery sarcoma.

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Conflict of Interests

Authors have no conflict of interests.

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