

Use, Knowledge and Perception About Ketogenic Diet Amongst University Students from Medical and Health Sciences Faculties

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(Submitted: 18 December 2020 – Revised version received: 26 December 2020 – Accepted: 27 January 2021 – Published online: 26 March 2021)

Abstract

Objectives This study aimed to determine the use, knowledge and perception amongst medical students at An-Najah National University.

Methods A cross-sectional study has been followed to collect data from students of Faculty of Medicine and Health Sciences using electronic questionnaire in October 2020. The questionnaire was consisted of 5 sections regarding; sociodemographic variables, dietary information, usage of KD, knowledge and perceptions toward KD. Differences between KD users and non-users and with associations to knowledge and perceptions were statistically analysed using Chi square. While independent samples *t*-test and ANOVA test were conducted to examine the differences for the total score of the KD knowledge.

Results Total respondent were 227 students with 71.8% were females. The mean age was 20 ± 3 and ranged from 18–24-year-old. More than half of the participants have used a kind of diet mainly for weight management with only 7.5 % were using KD for an average of 6 months, half of the students referred to social media as a source of nutritional information while only 25.6% of the participants has attended nutrition related courses at the university. Overall, the students' knowledge regarding KD was low 3.4 ± 3.6 out of 15. However, Faculty of Medicine, third and fourth year of study, KD-user and overweight/obese students have scored significantly higher. The majority of the participants have viewed KD as not easy to be followed and need medical supervision. The relationship between the knowledge score and the perception items has shown significant differences in all perception items. Meaning that positive perception has improved as knowledge has increased.

Conclusion The results have confirmed that knowledge amongst medical students with regard to KD was low. Sociodemographic variables were not associated with the knowledge scores however, having attended a nutrition course has improved both the knowledge and perception towards KD. Similar studies are warranted to implement nutritional courses in medical curriculum.

Keywords ketogenic diet, university students, knowledge, perception, weight management.

Introduction

Ketogenic diet (KD) is a high fat and protein diet with very restricted source of carbohydrates ($< 20 \text{ g d}^{-1}$ or 5% of total daily energy intake).¹ Biologically, it mimics the starvation or fasting state in the body. Historically, KD was used to alleviate the symptoms of epilepsy.² Currently, this type of diet is getting an increasing popularity due to its promise of weight management. Other uses of KD are for controlling of hyperglycaemia in Type 2 diabetics,³ maintaining of muscle strength for athletes⁴ decreasing the burden of metabolic syndrome⁵ and alleviating the symptoms of autism.

Weight loss through dieting and restriction of a macronutrient is a common approach for weight management, however, maintaining weight loss after the initial 5–10% decrease was reported to be low. Feeling hungry with low energy intake was thought to be the reason. This is a crucial issue especially for obese and overweight individuals, making it the main obstacle to adhere to any restrictive diet. More importantly, feeling hungry will not only cause the failure of weight loss but also facilitate the weight regain. Therefore, KD was recommended to control satiety and hunger in people conducting weight management. KD was reported to suppress appetite and people reported feeling 'more full' after the meal.⁶ Due to its mode of action on weight loss KD will provide ketone bodies that were found to affect the appetite through suppression of ghrelin hormone.

Moreover, KD was reported to have more lowering effect on body weight than low fat diet,⁷ also, KD tends to decrease total caloric intake.⁸

KD was reported to be beneficial for hyperglycaemic subjects. Adopting KD by type 2 diabetic individuals reduced the postprandial glucose and insulin secretion. Similar mechanism was proposed for such effect based on shifting the body metabolism towards production of ketone bodies. KD has been shown to improve insulinemia and insulin resistance as glucose level and glycaemia reduced.³ Hence, it was recommended for addressing the physiopathology of type 2 diabetes insulin should be reduced rather than increased.³ On the other hand, hyperinsulinemia was reported to be a risk factor for cardiovascular diseases, hypertension and renal problems.⁹ Dashti et al. (2003) have found that KD hasn't only acted as a therapy for obesity but also favourably decreased the risk factors for heart disease in obese subjects.¹⁰ Moreover, KD was found to be safe when tried by obese patients with mild kidney failure.¹¹

KD is a new and promising therapy for cancer. Few studies have shown that tumour cells growth was depressed with no alterations on normal cells.¹² Moreover, anticancer chemotherapy has become more effective for KD patients.¹³ Animal models studies have reported that dietary intervention against tumour cells have protected the animals against cancer cells

and reduced tumour cells growth after its initiation.¹⁴ Low blood level of glucose and hypoinsulinemia were proposed to be the mode of action of KD.

KD was also used to alleviate the symptoms of autism. El-rashidy et al. (2017) have reported significant improvements in speech, social and cognition parameters when applied modified Atkins diet on autistic children.¹⁵

Saying that, KD was reviewed by many researchers for its long-term effects. It was reported that LDL-cholesterol level has been increased by KD.¹⁶ Moreover, carbohydrates quality and source of fat were found to be major players in the all-cause-mortality in cohort studies, with fat from animal sources has been associated with higher risk.¹⁷ Other side effects of the KD were reported such as constipation, acidosis, dehydration, dyslipidaemias, growth retardation, kidney stones and osteoporosis.¹⁶

As the use of KD for therapeutic purposes is increasing healthcare providers should be aware about its applications and consequences. General practitioners and emergency worker may encounter subjects who already on KD. Students in medical disciplines are the future medical professionals and their knowledge about such practices also is crucial. Students themselves may enrol in any of the dietary regimens to lose weight prior to counselling. A study investigated the knowledge and perception of medical students with regard to KD, has found out that majority of students were not knowledgeable nor aware about KD applications and side-effects.¹⁸ Therefore, the current study aimed to determine the use, knowledge and perceptions toward KD amongst medical students at An-Najah National University.

The Methodology and Study Instruments

The study has followed a cross sectional design. The data were collected in October 2020 using an online questionnaire. All the students from Faculty of medicine and health sciences, were invited to participate in the study. The students were invited by distributing the questionnaire's link by their lecturers during the e-classes and through the university pages. Participants were informed that their participation was voluntary and the data will be collected for research purposes and will be treated confidentially. The study protocol was approved by Institutional Review Board of research ethics at An-Najah National University ref. no. 16-Nov-2020.

Subjects Characteristics

The study population has included all the students from the faculty of medicine and health sciences at An-Najah National university. Students were selected by random sampling. Participants were excluded if they didn't complete the questionnaires. Postgraduates students and whose age was less than 18 years old were also excluded.

The sample size was calculated using (Cochrane 1963) formula for prevalence studies. Prevalence of KD users was taken from previous similar study conducted¹⁹ to determine the knowledge about KD amongst KD users and non-users of university students. The author has found that prevalence of KD users was 18.1%. $n = (Z \alpha/2)^2 P (1 - P)/\Delta^2$, Δ assumed to be 5%. The calculated Sample size was 226. Considering 5% drop off, the required sample size was 237 and rounded to 240 participants.

Data Collection

The data was collected using a newly developed questionnaire. The questionnaire was consisted of 5 sections; section one: socio demographic characteristics of the participants such as age, gender, years of study, area of living and economic status, while section two: dieting related data, following diet before, reasons of following diet, source of dietary information, university courses in nutrition. Third section contained 3 items about the participants satisfaction of their weight, body shape and dietary habits in addition to self-report weight and height measurements. There was a section if the participant was using KD: reason of following KD, period and effectiveness.

Section four: contained 15 multiple choice questions about KD information. Section five: has included 10 items about the perception of KD with 3 level answers (agree, no opinion, disagree).

The Questionnaire Development

The questionnaire was developed by the researchers based on reviewing several studies conducted to determine the knowledge and perception regarding KD. In addition to the basic concepts and information about KD, the basic concepts and information were formulated as multiple-choice questions (MCQ). In the knowledge part composed of MCQ questions participants need to choose 1 correct answer for each question. The perceptions items were formulated depending on common believe about KD feasibility, safety and effectiveness.

The validation of knowledge questions and perception items was conducted by 8 experts in the field of nutrition (5 experts) and in the field of assessment (3 specialists). Based on their feedback 3 items were rephrased for clarity and to consider "I don't Know" as an option for the answers in the knowledge section. A pilot study including 30 students, was conducted to determine the reliability of the questionnaire using Cronbach alpha. Cronbach alpha was 0.864 for knowledge items and 0.73 for perception (after deleting 1 item), so the perception items remained as 9 items.

Statistical Analysis

Statistical analysis was carried out using the Statistical Package for Social Sciences (SPSS) software, version 21.0. An alpha level of (0.05) was considered for all the statistical tests used in the study. Two-sided *P* values of (0.05) and (80%) power was considered to be statistically significant. Before the analysis, the data were cleaned from missing data for the primary outcome variables i.e., knowledge, perception and the use of KD. The outliers were checked and only 1 extreme value was deleted from the BMI (49 kg/m²).

Normality test was checked for all of the continuous variables using Shapiro-Wilk Test Descriptive analysis including the means and the standard deviations were used to analyse the data pertaining continuous dependent and independent variables. The categorical data were described by percentages. The Independent samples *t*-test and ANOVA test were conducted to examine the differences for the total score of the KD knowledge due to selected independent variables at alpha <0.05. Chi-square test was used to determine the association between the categorical variables.

The Results

Participants Characteristics

Sociodemographic Characteristics

The estimated number of the invited students was 1200 students from the faculties of medicine and health sciences, only 227 respondents filled the online questionnaire and included in the final analysis, with response rate around 19%. The majority of the students (71.8%) were female. The mean age (20 ± 3) ranged from 18–24 years old. The sociodemographic characteristics are presented in Table 1.

Nutritional Status and Dieting Related Data

According to body mass index categories, the majority of the students 139 (61.2%) were normal weight, 22 (9.7%) underweight, 42 (18.5%) over weight, while 13 (5.7%) were obese. More than half of the participants (55.5%) reported that they have previously followed a type of diet. Amongst those who have followed a diet, the reasons of following the diet were 7.5% due to medical reasons and 63% were for weight management (decrease weight) and the rest were for becoming healthier. The self-satisfaction; dietary habits, body weight and body shape satisfaction are presented in Table 2. Participant's satisfaction regarding body weight and body shape are: 40.1% and 46.3% respectively, while it is only 24.2% for dietary habits satisfaction.

As depicted in Table 3 more than half of the students referred to social media as a source of nutritional information

Table 1. Sociodemographic characteristics of the participants presented in frequency and (%)

Sociodemographic parameter		Frequency	%
Gender	Male	64	28.2
	Female	163	71.8
Academic year	First	94	41.1
	Second	82	36.1
	Third	37	16.3
	Fourth + fifth	14	6.2
Faculty	Medicine	63	27.8
	Nursing	103	45.4
	Others (pharmacy + medical lab)	61	26.9
Living location	City	100	44.1
	Village + camp	127	55.9
Living status	With Family + relatives	201	88.5
	Students hostels	26	11.5
Marital status	Single	226	99.6
	Married	1	0.4
Family income/ month	<1500 NIS	35	15.4
	1500–3000 NIS	90	39.6
	3000–5000 NIS	56	24.7
	More than 5000 NIS	46	20.3

Table 2. Participants satisfaction dietary habits, body weight and shape satisfaction presented in frequency and (%)

Self-satisfaction		Frequency	%
Body weight satisfaction	Yes	91	40.1
	Some how	69	30.4
	No	67	29.5
Body shape satisfaction	Yes	105	46.3
	Some how	79	34.8
	No	43	18.9
Dietary habits satisfaction	Yes	55	24.2
	Some how	125	55.1
	No	47	20.7

Table 3. Nutrition information sources and attended nutrition courses presented in frequency and (%)

Nutrition information		Frequency	%
Source of reliable nutrition information	Nutritionist	22	9.7
	Health care workers	38	16.7
	Books	10	4.4
	Social media	122	53.7
	Mixed	35	15.4
Nutrition course during study	Yes	58	25.6
	No	169	74.4

while only 25.6% of the participants attended nutrition related courses at the university.

KD Related Data

The percentage of the KD users was 7.5% of the total participants, among those who used or were using KD 12 participants followed KD for weight loss, 4 participants to control Diabetes mellitus, and 1 to protect against cancer. The period of following the KD ranged from 1 month to 1 year with a mean of 6 ± 3.5 months. With regard to self-reported effectiveness of the KD, 9 participants reported that they were satisfied with the effectiveness of the KD.

Knowledge and Perception about KD

Table 4 showed the knowledge items and the percentage of the correct and wrong answers. The mean of the total score of the correct answers was 3.4 ± 3.6 out of 15, ranged from 0–15 points, which revealed very low level of knowledge. Item no. 4 (The KD increases the utilization of fatty acids) has scored the highest percentages of the correct answers. While item no. 11 (Muscle cramps and pain are common during KD, it is recommended to take the following supplementations) has scored

Table 4. Frequencies and percentage of student's answers responded to knowledge questionnaire

No.	Question		Correct answers %	Wrong answer/ I don't know %
1	The medical indication for KD is for	Epilepsy Diabetes mellitus Autoimmune I don't know	12.3	87.7
2	The following is among the characteristics of KD	High fat very low CHO Balanced diet diet without bread or rice I don't know	29.5	70.5
3	The ketone bodies are formed from (in human body)	CHO Fatty acids Animal protein I don't know	33.9	66.1
4	The KD increases the utilization of fatty acids	Yes No I don't know	40.5	59.5
5	The following organ depends on ketones as energy source during hypoglycaemia	Brain Muscle All the body organs I don't know	16.7	83.3
6	The ketones body increase during	Prolonged fasting After meals Between meals I don't know	30.8	69.2
7	Ketogenic diet is safe and suitable for older adults	Yes No I don't know	19.8	80.2
8	Following KD increase the risk of acidosis	Yes No IDK	24.7	75.3
9	The following among the common side effect of KD	Headache and fatigue Intestinal motility Hypotension I don't know	32.6	67.4
10	The ketogenic increase the risk of dyslipidaemia	Yes No I don't know	17.2	82.8
11	Muscle cramps and pain are common during keto diet, it is recommended to take the following supplementations	Calcium + vit D Magnesium Potassium I don't know	4.4	95.6
12	Fruit consumption during the keto diet	Allowed Fresh fruits are allowed while dried are not Fruits are forbidden I don't know	9.7	90.3
13	The amount of rice allowed during the keto	100 gm bread or rice/day Rice and bread are not allowed in any amount I don't know	19	81
14	The main precautions you need to know about keto diet	Long term safety is not confirmed No risk or precaution The side effect disappear with time	17.6	82.4
15	Keto diet help to control the hunger sensation	Yes No I don't know	29.5	70.5

Table 5. Participants perceptions about KD

No.	Question	Response	(n)%
1	KD is popular and many people follow	Agree	66 (29.1)
		No opinion	90 (39.6)
		Disagree	71 (31.3)
2	I believe that following KD is reliable method for weight loss	Agree	70 (30.8)
		No opinion	103 (45.4)
		Disagree	54 (23.8)
3	I believe KD has many good health effect	Agree	65 (28.6)
		No opinion	121 (53.3)
		Disagree	41 (18.1)
4	I believe KD is easy to follow	Agree	22 (9.7)
		No opinion	115 (50.7)
		Disagree	90 (39.6)
5	I believe that KD is suitable for life long life style	Agree	16 (7)
		No opinion	117 (51.5)
		Disagree	94 (41.4)
6	I believe that KD leads to certain nutrients deficiency	Agree	92 (40.5)
		No opinion	113 (49.8)
		Disagree	22 (9.7)
7	I believe that KD must be followed under medical supervision or by nutritionist	Agree	121 (53.3)
		No opinion	90 (39.6)
		Disagree	16 (7)
8	I believe that ketogenic diet needs long term clinical research to documents the side effects	Agree	102 (44.9)
		No opinion	107 (47.1)
		Disagree	18 (7.9)
9	I believe that following KD increase the risk of CVD	Agree	49 (22)
		No opinion	138 (60.8)
		Disagree	39 (17.2)

the lowest percentages of the correct answers. The rest of the items showed variable percentages of correct and wrong answers. With regard to the perception towards KD, item no. 8 (the need of long-term clinical trial) and item no. 7 (the need for medical supervision to follow KD) relatively have scored the highest agreement amongst the participants with 53.3% and 44.9%, respectively. While the highest scores of disagreements were item no. 4 (KD is easy to follow) with 39.6%, and item no. 5 (KD is suitable for long life) with 41.5% Table 5.

Differences Between Users and Non-users of KD

All sociodemographic variables; gender, age, area of living, living status and family income have shown no association with using KD ($P > 0.05$ using chi square test). With regard to the study discipline, being a medicine student has shown a significant association with using KD ($P < 0.05$ using chi square test) compared with other faculties. Similarly, the body weight and shape satisfaction in addition to satisfaction about dietary habits have shown no significant association with being a KD user or non-user.

With regards to BMI categories, using KD was significantly associated with being overweight or obese ($P < 0.05$ using chi square test). The difference in the knowledge regarding KD scores between users and non-users was significant, the mean score of knowledge regarding KD amongst users was 7.5 ± 2.3 while amongst non-users was 3.1 ± 3.4 ($P < 0.01$ using independent sample t -test). Regarding, the perception of KD, users of KD have shown significant positive agreement to all

perception items except to item no. 4 (I believe that KD is easy to use) and item no. 8 (the KD must be followed under medical supervision or by a nutritionist) ($P > 0.05$ using chi square test).

The Relationship Between KD Knowledge and Other Variables

The score of KD knowledge has shown no significant relationship with the sociodemographic variables. Students in their third and fourth years of medicine, scored higher in the KD knowledge ($P < 0.05$ using one way ANOVA) compared with other faculties. With regard to the source of nutritional information, there was a significant higher score of the KD knowledge amongst participants who have received nutrition courses and who referred to nutritionists as nutritional information sources ($P < 0.05$ using independent sample t -test). The relationship between the knowledge score and the perception items has shown significant differences in all perception items taking into account the mean of each answer (agree, no opinion and disagree). For example, the participants who answered agree or disagree have scored significantly higher than participants who answered no opinion in all items. Meaning that the perception toward KD has been significantly affected by the level of knowledge either if the perception was with agreement or disagreement.

Discussion

As mentioned before KD is becoming very popular and its more likely that any health practitioner or healthcare provider

will encounter some patients who are adopting KD. Therefore, shedding light about the importance of being aware and knowledgeable about such and alike restrictive regimens, would be highly valuable. In particular for medical students who will be working in different health levels.

No doubt that KD has jumped from being a special diet for certain cases such as epilepsy and seizure to be a therapeutic approach for weight management, cancer treatment, heart support and antihyperglycaemia.

In the current study the representative sample characterisations have shown no differences between the sociodemographic variables and the sample has covered all faculties of health sciences. This was important for this study to have a clear picture about the knowledge of medical students towards KD. BMI of the students has revealed that only 61% were on the normal range, meaning that a large number of students is likely to be under risk of problems related to weight. We hypothesised that these students with weight problems will be involved in some kind of dietary intervention. A recent study in Brazil has found that 1 out of 4 students was practicing low-carb diet, although the participants BMI average was normal (23.56 kg/m²).²⁰ While in a nearby country like Lebanon unhealthy dieting was reported to be uncommon practice amongst the university students.²¹ The authors urged that awareness about healthy eating, realistic healthy weight and improved self-image were highly recommended. Although, in this study we didn't report dieting based on gender other studies have reported that female students were significantly higher to practice a type of diet such as low-carb diet.²² As our sample contained 71.8% females and 55.5% of the total participants have reported that they have followed a kind of dieting, we expect that the majority of dieters will be from females. This is consistent with previously mentioned studies. However, the main concern was about ketogenic users who represented 7.5% of the total sample. Many studies have investigated the dietary patterns amongst the university students, of which a study has shown that 18.1% of respondent students were using KD mainly from male students.¹⁹ This higher result may be due to the nature of the selected sample as this study has covered health and non-health related disciplines. Moreover, the level of KD popularity is expected to be higher in the developed countries.

In the current study, the main reason of following a diet in general and KD in particular was weight management. This was in line with a similar study conducted on Pakistani medical students where 76.4% of the participants have known KD as weight loss therapy.¹⁸ In the present study, almost, 1 out of 5 students was not satisfied about body weight, body shape or dietary habits. Such level of dissatisfaction can be a strong drive for students to seek information with regard to dieting. More than half of the students has relied on social media to get nutritional information. This can be advantageous as it is easy to access however, it should be taken cautiously as not all information is reliable. Moreover, the lack of professional guidelines with regard to KD as a therapeutic approach²³ may limit medical students' sources about KD. Lack of information can be detrimental and a major contributor to unhealthy nutrition.²⁴ Medical students like other university students already have access to the media however, the message with regard to healthy eating hasn't been delivered from reliable sources. This has a negative consequence either by adopting fad diet which can affect the individual health or can negatively shape the students' perception towards efficiency of diet in health care

system. General practitioners and medical professionals would look to deliver a message about nutrition-related health issues to their patients, however, the quality and reliability of such message is questionable.²⁵ In the current study only 25% of the participants has been attendant to a nutrition course during study. Leeman et al. (2011) have addressed the low attention in medical education paid nutrition and the effect of long-term dieting. They found that diet/health relationship from medical point of view is highly affected by cultural/national status rather than medical status especially for professionals from Germany, Italy and France who consider food as an enjoyable item rather than as a health behaviour.²⁵

As revealed from the results the total knowledge score with regard to KD was very low. This is expected as the majority haven't had specific course in nutrition and their information about KD based on the social media. However, the basic information about the KD which was the utilisation of fatty acids was found to be well-known by the majority of the participants. Students were not familiar with some side effects of the KD. This is consistent with Butt et al. (2020) who found that although ¾ of students have heard about KD only 1/5 of them could differentiate between KD and fasting. Similarly, few were aware about the side effects of KD.¹⁸ This would emphasise the fact that, although the awareness about nutrition and health is increasing a proper knowledge is lacking. Moreover, nutritional knowledge or declared knowledge may not be translated into behaviour or skills that are essential for healthier food intake or dietary decisions.²⁶ Well-designed studies are required to address the relationship between dietary habits, healthier life style and knowledge, as most of literature studies based on questionnaires and self-declared information.

With regard to perception towards KD, almost half of the respondents has agreed about the need for long-term clinical trial and the need for medical supervision to monitor users of KD. Also, with regard to KD compliance and easiness to adopt KD there was disagreement amongst the students. The majority have believed that KD was difficult to adhere to or to maintain. Such beliefs were found in other studies such as Butt et al., (2020) and²⁷ researchers have suggested a pre-KD counselling approach to improve the adherence to KD. For example, involvement of family and the person in-charge of purchasing food, information about, planned treatment and anticipated side effect will enhance the adherence to KD by a potential user.²³⁻²⁸

There was no difference between KD users and non-users with regard to their sociodemographic variables, meaning that the randomisation of the sample selection was effective. It could be an advantage to have neutral sociodemographic factors because this will help developing nutritional education based on modifiable variables such as BMI, faculties and source of nutritional information. With regard to BMI, KD users were more knowledgeable about KD however, their mean of BMI was overweight/obese. This can be explained by the fact that the main purpose of using KD was the weight loss. The average of period on KD was 6 months for KD users which was around the period that was reported to be the peak of weight loss on the KD.⁸ However, most importantly is to sustain such loss as reports have shown that weight regain was more likely on the long term of using any diet. A long-term study conducted on obese subjects has been lasted for 24 weeks.²⁹ The authors have claimed that KD was safe with no side effects in the patients with possible longer period of adopting.

Finally, knowledge scores have been significantly higher for students in their 3rd and 4th year, attending faculty of medicine and have had nutritional course. This emphasises the importance of nutritional education to improve the knowledge especially amongst medical students. In addition, the perception towards KD has been significantly associated with knowledge. A study conducted on adolescents has found that there was a relationship between knowledge and nutritional habits.³⁰ Moreover, a study based on face-to-face interviews has found a high association between high quality diet and nutritional knowledge,³¹ with consumption of fruits and vegetables²⁶ and with nutritionally essential groups other than fruits and vegetables.³²

Conclusion

This study has revealed a low level of knowledge amongst medical students towards the KD. The study has shown that KD users were more knowledgeable, however, their BMI was higher as well. Students' perception was associated with their knowledge. The score of knowledge was higher if a student has attended a nutrition course which also has improved the perception towards KD. Other sociodemographic variables were ineffective in the knowledge score.

Declarations

Ethics Approval and Consent to Participate

This project acquired an ethical approval from the Institution review Board for Ethical approval from An-Najah National University. The research procedures were conducted in accordance with the principle expressed in the Declaration of Helsinki. Electronic signature for the consents has been collected from all participants prior to data collection.

Consent for Publication

Not Applicable.

Availability of Data and Materials

The dataset used and analysed in this study is available from corresponding Author on reasonable request.

Competing Interest

The authors declare they have no competing interests.

Funding

The authors declare that no external financial support was received for this study.

Authors' Contributions

The authors have contributed in the manuscript as the following; Manal Badrasawi: the principle investigator has written the study proposal and protocol and supervise the data analysis. Mohammad Altamimi: participate in the study protocol revision and write the first draft of the manuscript. Bayan Khaled: has the responsibility for the research data management. All authors have read and approved the final manuscript.

Acknowledgments

We would like to acknowledge the lecturers who helped the researchers in the data collection. We would like to express our gratitude to students who agreed to participate in this study. Thanks, are also to all co-researchers and fieldworkers involved in this study.

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