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Original Research

First Year Student Pharmacists' Views on the Opioid Epidemic

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ABSTRACT

Objective

To determine first-year student pharmacists' views on the opioid epidemic.

Methods

First-year pharmacy students were asked to complete an online survey to assess their views and opinions on the current opioid crisis using Likert-scale type questions.

Results

Forty-four pharmacy students were surveyed, and all participants completed survey questions, 100% response rate. Majority of participants were female (N=34, 77.3%), with more than half of participants falling in the age range of 18-24 (N=25, 56.8%). Geographically, most of the participants home residences are in other states out of the DC, Maryland, Virginia (N=25, 56.9%). In addition, majority of participants worked before starting pharmacy school (N=42, 95.5%) and a majority had a pharmacy and health-related occupations before pharmacy school (N=36; 81.9%). Most study participants reported an annual income of less than $10,000 (N=17, 38.6%) and obtained a bachelor's degree (N=26, 59.1%). Majority of participants strongly agree that the opioid epidemic is becoming a severe crisis for society (N=42; 95.5%) and that opioid should be readily available when it is medically necessary to people (N=27; 61.4%). When asked if they know anyone personally who suffers from the opioid crisis, over three-quarter (N=34; 77.3%) said no. However, over two-third (N=29; 65.9%) of participants said that they have taken opioids in the past themselves to relieve pain. Although, almost all of them strongly agree that prescription opioids are addictive (N=42; 95.5.%); about eighty percent (N=35; 79.5%) agree that taking opioids is an effective way to alleviate severe pain.

Conclusion

Our results indicate that pharmacy students perceive the opioid epidemic as a crisis and despite their views that opioids are addictive and knowing someone who suffers from opioid use disorder, they believe opioids are a clinically effective way to alleviate pain.

Keywords

Survey; Opioids; Epidemic; Students; Pharmacy.

INTRODUCTION

The opioid use and overdose rates have climbed tremendously in the United States (U.S.). According to the Centers for Disease Control and Prevention (CDC), the opioid epidemic is a multilayered crisis that has escalated over the years.[1] In the 1990's there was a marked increase in prescription opioid overdose deaths due to a false perception that painkillers were not addictive, in 2010 there was an increase in heroin-related overdose deaths, and in 2013 there was a rise in synthetic opioid overdose deaths.[1] The leading drive of opioid addiction has been known to be prescription medications, primarily prescribed to patients for chronic pain.[2] However, data from 2018 to 2019 has shown that prescription opioid involved death rates decreased by nearly 7%, and synthetic opioid involved death rates have increased by 15%.[3] More than 36,000 people died from overdoses involving synthetic opioids in 2019.[4]

Currently, pharmacists play a vital role in mitigating the opioid crisis, they are the most accessible healthcare providers. Pharmacists can directly impact opioid misuse by educating patients on the risks associated with opioids, being vigilant of signs of opioid misuse by patients, utilizing available prescription drug monitoring programs (PDMPs), serving as advocates for patients, and increasing naloxone access.[5] Previous studies have shown that

pharmacists perceive the opioid pandemic as a crisis that has grown over the past decade despite increased regulation of prescription opioids to combat misuse and/or overuse.[6] Pharmacists along with other healthcare providers play a dynamic role in combating the opioid crisis, therefore it is important to understand their views in order to implement change and interventions. Student pharmacists have numerous opportunities throughout their schooling to participate in community outreach and programs contributing to the prevention of opioid use disorder. Most previous studies explore pharmacists' and physicians' perceptions of the opioid crisis, but very few studies include students. The purpose of this study was to explore incoming first-year student pharmacists' views on the opioid epidemic.

METHODS

This study enrolled 44 incoming first professional year students from Howard University College of Pharmacy. Of the 44 students enrolled in this study, all students submitted responses, 100% response rate. The survey was optional, it was distributed to students during a drug information course. All questions, demographics, and responses were analyzed using Qualtrics. Survey questions consisted of 8 demographic questions and 7 questions using the Likert scale (Strongly agree to strongly disagree). Demographic data, including age, gender, state you live in, work experience, annual income, and education was collected through the survey. All results were analyzed using IBM Statistical Package for the Social Sciences (SPSS) and statistical analysis was completed using cross-tab and Chi-square Pearson analysis, with a *p*-value of less than 0.05 considered significant.

RESULTS

Forty-four pharmacy students from Howard University Pharmacy School were surveyed and all participants answered the survey questions to completeness (100% response rate). The demographic data of participants are shown in Tables 1 and 2. The demographics of participants were as follows: majority of participants were female (N=34, 77.3%), with more than half of participants falling in the age range of 18-24 (N=25, 56.8%). Most of the participant's home residences are other states out of the DC, Maryland, Virginia (DMV) area (N=25, 56.9%). In addition, majority of participants worked before starting pharmacy school at Howard University (N=42, 95.5%) and majority had pharmacy and health-related occupations before pharmacy school (N=36; 81.9%). Most study participants reported an annual income of less than $10,000 (N=17, 38.6%) and obtained a bachelor's degree (N=26, 59.1%).

Table 1. *Demographics of Participants (N=44)*

		N (%)
Gender	Male	10 (22.7)
	Female	34 (77.3)
Age	18-24	25 (56.8)
	25-34	18 (40.9)
Home state before Howard	DC	4 (9.1)
	MD	12 (27.3)
	VA	9 (20.5)
	Others	19 (43.2)

Table 2. *Demographics of Participants (N=44)*

		N (%)
Have you worked before Howard	Yes	42 (95.5)
	No	2 (4.5)
Annual Income	<$10K	17 (38.6)
	$10-19K	7 (15.9)
	$20-29K	3 (6.8)
	$30-39K	8 (18.2)
	$40-49K	3 (6.8)
	>$49K	5 (11.4)
Type of Work	Pharmacy Related	27 (61.4)
	Non-Pharmacy Related	9 (20.5)
	Non-Pharmacy or Healthcare Related	7 (15.9)
How many years have you worked before Howard?	0	1 (2.3)
	<1 Year	7(15.9)
	1-3 Years	14 (31.8)
	4-5 Years	11 (25.0)
	>5 Years	11 (25.0)
Highest level of Education	Prerequisite	12 (27.3)
	Associate	2 (4.5)
	BA/BSc	26 (59.1)
	MS or higher	4 (9.1)

Table 3. *Frequency of Survey Responses (N=44)*

	Strongly Agree and Agree	Disagree and Strongly Disagree	*p* values
I am aware that the opioid epidemic is becoming a severe crisis for the society.	42 (95.5)	2 (4.5)	<0.001
I believe that opioids should be/are readily available when it is medically necessary to people who want to take them.	27 (61.4)	17 (38.6)	<0.001
I personally know someone (family member, a relative, a friend, etc.) who suffers from opioid crisis.	10 (22.7)	34 (77.3)	<0.001
I have taken opioids in the past for myself to relieve pain.	15 (34.1)	29 (65.9)	<0.001
I believe taking opioid is an effective way to alleviate severe pain.	35 (79.5)	9 (20.5)	<0.001
I would let my family or children use/take opioids for chronic pain.	19 (43.2)	25 (56.8)	<0.001
I am aware that prescription opioids are addictive.	42 (95.5)	2 (4.5)	<0.001

Survey responses were presented based on frequencies and *p*-values are displayed in Table 3. Majority of participants strongly agree that the opioid epidemic is becoming a severe crisis for society (95.5%) and that opioids should be readily available when it is medically necessary to people (61.4%). Most students do not personally know someone who suffers from the opioid crisis (77.3%) and (65.9%) of participants have taken opioids in the past to relieve pain. Most strongly agree that taking opioids is an effective way to alleviate severe pain (79.5%) and many strongly agree that prescription opioids are addictive (95.5.%). All survey responses were significant based on the *p*-values <0.001.

In Table 4 a Chi-square (χ^2) analysis was used to determine the significance of the association between demographics and students' opinions, defined as *p*-vale<0.05.

Table 4. *Demographic Variables in Association with Survey Responses*

	p values
Age vs. strongly agree that opioids should be/are readily available when it is medically necessary to people who want to take them.	0.018
Age vs. strongly agree that taking opioid is an effective way to alleviate severe pain.	0.035
Years worked vs. strongly disagree that I have taken opioids in the past for myself to relieve pain.	0.026
Education vs. strongly agree that I am aware that the opioid epidemic is becoming a severe crisis for the society.	0.018

A total of 44 entry-level pharmacy students were surveyed. The demographics of participants were as follows: majority of participants were female (N=34, 77.3%), with more than half of participants falling in the age range of 18-24 (N=25, 56.8%). Most of the participants home residences are other states out of the DMV area (N=25, 56.9%).

Most participants worked before starting pharmacy school at Howard University (N=42, 95.5%) and majority had pharmacy and health-related occupations before pharmacy school (N=36; 81.9%). Most study participants reported an annual income of less than $10,000 (N=17, 38.6%) and obtained a bachelor's degree (N=26, 59.1%).

Majority of participants strongly agree that the opioid epidemic is becoming a severe crisis for society (N=42; 95.5%) and that opioid should be readily available when it is medically necessary to people (N= 27; 61.4%). Most students do not personally know someone who suffers from the opioid crisis (N=34; 77.3%) and (N=29; 65.9%) of participants have taken opioids in the past to relieve pain. Most strongly agree that taking opioids is an effective way to alleviate severe pain (N=35; 79.5%) and many strongly agree that prescription opioids are addictive (N=42; 95.5.%). All survey responses were significant based on the *p*-values <0.001.

This table shows that when investigating whether age influenced whether participants believed opioids should be/are readily available when it is medically necessary to people who want to take them, majority of participants in the older age group (25-34) strongly agreed (N=15; *p*-value 0.018). Most of the study participants amongst both age groups (18-24, 25-34) strongly agree that taking opioids is an effective way to alleviate severe pain (N=34; *p*-value 0.035). The number of years worked influenced whether participants have taken opioids in the past to relieve pain; those who had 3 or fewer years of work experience strongly disagree compared to those who have over 3-years of work experience (0-3 years N=18 *vs.* >3-years N=11; *p*-value=0.026). Education level showed a significant association with majority of students in each subgroup strongly agreeing that the opioid epidemic is becoming a severe crisis for the society (BA/BSc or higher N=32 *vs.* prerequisite/associate N=10; *p*-value=0.018).

DISCUSSION

The opioid epidemic is a major widespread public health crisis that continues to rise at an alarming rate. Pharmacists play a vital role in the opioid crisis because of their accessibility, education, and their unique relationship with patients. Pharmacists have served to mitigate the opioid crisis through appropriate consultation of medications, educating patients on opioid risks, dispensing naloxone, and utilizing the prescription drug monitoring program. Nearly 1.6 million people had an opioid use disorder in the past year and 70, 630 people have died from a drug overdose in 2019.[7]

Overall, this study aimed to explore the opinions and views of student pharmacists on the opioid epidemic. In this study, we noticed that majority of participants strongly agree that the opioid epidemic has become a severe crisis for society (N=42, 95.5%), similar to opinions seen in research conducted by Skrabal et al.[8] Their study investigated pharmacy students' perspectives regarding opioid use, the opioid crisis, and pharmacy education related to both topics. In the Skrabal et al[8] study, 99% (N=147) of students

ranging from P1 to P4 agreed that there is an opioid crisis. The findings of this study confirm that despite demographics, study participants agree that the opioid epidemic is an issue that is affecting society.

Studies have been conducted reviewing the impact of the opioid crisis on the community. Numerous variables have fueled the increase of opioid abuse and overdose across communities in the U.S., variables including poverty, unemployment, over-prescription of drugs, and easier access to treatment facilities.[9] Opioid addiction and overdose have been studied for decades now, especially exploring opioid use trends and risk factors associated with demographics.

In our study, over one-third (N=17; 38.6%) of participants disagree that opioids should be readily available when it is medically necessary to people. All study participants are first-year pharmacy students who have yet to study the effects and benefits of opioids so this finding may be due to a lack of knowledge about opioids' place in therapy. This is reflective with the findings in Table 4 when exploring whether age influenced participants belief on opioids being readily available when it is medically necessary to people, it was noted that majority of participants in the older age group (25-34) strongly agreed (N=15; *p*-value 0.018).

Over three-quarter of the students said that they do not personally know someone who suffers from the opioid crisis (N=34; 77.3%). This outcome is contradictory to current data that shows nearly a third of Americans say they know someone who has suffered from an opioid addiction.[10] The findings of this study may not be an accurate depiction of this due to the limited sample size the young age range of the participants which can increase variability in results.

About two-third (N=29; 65.9%) of participants have not taken opioids in the past to relieve pain. Considering the limited sample size, these findings is much higher comparing to data for overall U.S. adult papulation which is about 5% who have taken opioids or some sort of prescription painkillers.[10] Although opioid therapy is an effective way to alleviate chronic and acute pain, some individuals are hesitant to initiate therapy due to the highly addictive nature of opioids. This is indicated in this study with majority strongly agreeing that prescription opioids are addictive (N=42; 95.5.%).

In this study, we also found that most participants strongly agree that taking opioids is an effective way to alleviate severe pain (N=35; 79.5%). Further analysis comparing demographics with survey responses also showed that most of the study participants amongst both age groups (18-24, 25-34) strongly agree that taking opioids is an effective way to alleviate severe pain (N=34; *p*-value 0.035). However, when investigating whether years worked influenced whether participants have taken opioids in the past for themselves to relieve pain, those who had 3 or fewer years of work experience have not taken opioids as much to relieve pain compared to those who have over 3-years of work experience (0-3-years N=18 *vs.* >3-years N=11; *p*-value=0.026).

Education level also showed a significant association with majority of students in each subgroup strongly agreeing that the opioid epidemic is becoming a severe crisis for the society (BA/BSc or higher N=32 *vs.* prerequisite/associate N=10; *p*-value=0.018). Advance education is believed to allow individuals to have more exposure to information and controversial issues in society. It is not alarming that more individuals with advanced degrees strongly agree that opioid misuse has become an issue comparing to their counterparts.

It should be noted that some of the results of this study showed no statistical significant association in the state where a student resided before joining Howard and the kind of occupation a student had, whether pharmacy related, non-pharmacy related, or non-pharmacy/non-health related.

There were various limitations in this study. One of the most vital limitations is that the sample size was relatively small (N=44) and the study participants were from one pharmacy school. Future studies conducted should have a larger sample size to increase generalizability and appropriately evaluate the views of professional students on the opioid crisis. In addition, all participants were entry-level first-year pharmacy students, and they may have limited knowledge of opioids. In the future, it will be beneficial to extend the study to all level pharmacy students to precisely depict the opinions based on knowledge and background of opioid use disorder.

CONCLUSION

Despite key health care providers working together to combat the opioid epidemic, the crisis is still growing with increases in opioid misuse and related overdoses. In this study, a survey was conducted to analyze the views of first-year pharmacy students on the current opioid epidemic. Majority of participants agreed that the opioid epidemic has become a severe crisis to society. Despite majority agreeing that opioids are addictive, they believe taking opioids is an effective way to alleviate severe pain.

Indicated by the findings of this study, participants believe that opioids are addictive but are an effective way to alleviate severe pain. Student pharmacists are in favor of allowing opioids to be readily available when it is medically necessary to people. Remarkably and unlike the data from the U.S., majority of participants said that they do not know someone who suffers from the opioid crisis.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

ETHICAL CONSIDERATIONS

This study has been approved by the Howard University (HU) Institutional Review Board (IRB)

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Lycopene for Hypertension and Factors Affecting Its Use: A Survey of Pharmacy Students

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ABSTRACT

Purpose

To better understand and assess the potential obstacles to the adoption of lycopene for treating high blood pressure.

Methods

A cross-sectional observational study was conducted by administering a survey to 42 Howard University College of Pharmacy students. Descriptive statistics and risk estimates were calculated using statistical package for social studies (SPSS) software.

Results

Only 33.3% of students had ever heard of lycopene, and lycopene knowledge score was poor among 88% of respondents. Non-D.C. residence, dietary supplement use and the belief that dietary supplements such as lycopene interact with prescription drugs and should be used cautiously, were all correlated with a lesser risk of having poor lycopene knowledge. Annual income >$40,000 was correlated with a greater risk of being in the poor lycopene knowledge group. Despite this data, 59.5% report that will incorporate more lycopene into their diet.

Conclusion

Lycopene knowledge is generally poor among the observed cohort; however, this does not seem to be a great obstacle in the path of adoption.

Keywords

Lycopene; Dietary supplement; Hypertension; Cardiovascular.

INTRODUCTION

Hypertension remains a leading risk factor for cardiovascular disease, estimated to affect over 40% of American adults.[1] Prescription drug therapies and dietary restrictions have been mainstays of therapy for those with hypertension however, there has been growing inquiry into the potential of food products and supplements to positively impact blood pressure. One such food product is lycopene, a phytochemical found in fruits and vegetables such as tomato, guava, grapefruit, carrot, and watermelon. Lycopene is a carotenoid antioxidant. By scavenging reactive oxygen species, it can mitigate cellular oxidative damage, which has been implicated in cardiovascular disease and inflammation. Research also suggests that lycopene may have a beneficial effect on several other pathologies including prostate and colorectal cancer, and diabetes, as well as having hepatoprotective and neuroprotective properties.[2]

Lycopene consumption has also been demonstrated to reduce systolic blood pressure. A double-blind placebo-controlled study investigating the effect of various daily doses of lycopene on blood pressure found that 15 mg and 30 mg lycopene treatment groups experienced a statistically significant reduction in mean systolic blood pressure after 8 weeks (-9.8 mmHg/-7 mmHg respectively; $p<0.01$).[3] A meta-analysis investigating the effect of lycopene supplementation on blood pressure using the pooled data from six studies also found that lycopene produced a statistically significant reduction in systolic blood pressure and suggests that >12 mg daily intake of lycopene may produce greater blood pressure reduction than lower doses.[4] While no explicit recommendation regarding lycopene intake is given, these studies suggest, an intake of approximately 15 mg of lycopene daily may have a beneficial effect on blood pressure. In addition, lycopene is not

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known to have significant drug-drug interactions or adverse effects, although some sources caution against taking lycopene in the weeks leading up to a surgery due to lycopene's antiplatelet effect, which is comparable to that of aspirin 81 mg.[5] There does not seem to be a consensus on the effect of lycopene supplementation in pregnant women. One study suggests that pregnant women avoid lycopene supplements due to an increased risk of premature birth and low birth weight,[6] while another suggests significantly improved perinatal outcomes in lycopene supplemented mothers.[7] In addition to this, it should be noted that no study that examines the effects of lycopene intake in pediatric populations exists. Despite these warnings, lycopene has consistently been found to have a favorable toxicity profile, even in cases of excessive ingestion.

It is thought that Lycopene's anti-hypertensive effect is due its ability to mitigate oxidative damage to vascular endothelial cells and to promote the expression of endothelial nitric oxide synthase. Due to this antihypertensive effect, lycopene supplementation may hold use as an adjunct to mainstay therapy or as a non-prescription option for those with mildly elevated blood pressure. In the current body of literature, data specifically concerning the public knowledge and attitudes towards lycopene are scarce. To better understand obstacles to the adoption of lycopene use in this capacity, and to understand the demographic factors that affect the attitudes towards its use and lycopene knowledge, survey data was collected from Howard University College of Pharmacy students and analyzed.

METHODS

A survey was administered to 42 students attending Howard University College of Pharmacy. The survey questions were designed to collect information on demographics, personal lifestyle, opinions, and lycopene knowledge. All question responses were categorical in nature. Cross-tabulation was facilitated by recoding responses into two categories for each question. Descriptive statistics and relative risks were calculated using the statistical package for social studies (SPSS) software, version 28.0.1.0 (142). For relative risks, a 95% confidence interval that excluded 1 was considered statistically significant.

RESULTS

Demographics and Work Experience

The demographic and work experience data shows that 73.5% of survey respondents were under the age of 26, and more than two-thirds were female. Of those surveyed, 81% report having earned a bachelor of arts (BA) or bachelor of science (BSc). The proportion of respondents that reside outside of D.C., Maryland or Virginia (DMV) is 42.9%, while 31% reside in the DMV. The proportion of respondents that have worked either a full-time or part-time job is 88%. Two-thirds of respondents have worked in medical prescription (Rx) related or other healthcare jobs. The proportion of respondents that have worked for at least 1-year is 97.6%. The proportion of respondents that report having worked either part-time or full-time jobs is 88.1%, and 21.4% report that they are currently working. Lastly, 73.9% of respondents report an annual income of less than $40,000 (Table 1).

Table 1: *Frequency Table of Lycopene Survey Respondent Demographics (n=42)*

		N (%)
Patient's age (in years)	21-23	14 (33%)
	24-26	17 (40.5%)
	27-29	5 (11.9%)
	>29	6 (14.3%)
Gender	Male	15 (35.7%)
	Female	27 (64.3%)
Highest education attained	Some college	1 (2.4%)
	Associate degree	1 (2.4 %)
	BA/BSC	34 (81%)
	MSC/MA	4 (9.5%)
	PHD/Professional	2 (4.8%)
Place of residence	Washington D.C.	4 (9.5%)
	Maryland	13 (31%)
	Virginia	16 (16.7%)
	Other states	18 (42.9%)

Opinion-Based Survey Questions

Respondents were asked to rank their agreement with the above opinion-based survey questions on a 4-point scale (strongly agree/agree/disagree/strongly disagree). The responses to each question were then grouped into those who agreed and those who disagreed.

Table 2: *Frequency Table of Lycopene Survey Respondent Income and Work Experience (n=42)*

		N (%)
Work experience	Never worked	2 (4.8%)
	Short term	3 (7.1%)
	Part-time	16 (38.1%)
	Full-time	21 (50%)
Type of job worked	RX related	16 (38.1%)
	Other healthcare	12 (28.6%)
	Non-healthcare	13 (31%)
	Not applicable	1 (2.4%)
Annual income	<10,000	13 (31%)
	$10,001-$20,000	7 (16.7%)
	$20,001-$30,000	6 (14.3%)
	$30,001-$40,000	5 (11.9%)
	>$40,000	11 26.2%)
Years worked	Never worked	1 (2.4%)
	1-2-years	19 (45.2%)
	3-4-years	11 (26.2%)
	>4-years	11 (26.2 5%)
Currently working	Yes	9 (21.4%)
	No, But plan to soon	18 (42.9%)
	No, no plan to work	15 (35.7%)

Question 1 asks respondents to evaluate their own knowledge on dietary supplements. The proportion of respondents that claim to be comfortable in their dietary supplement knowledge is 59.5%, however, a still substantial proportion report not feeling comfortable. Question 2 asks respondents about their history interacting with patients as it relates to dietary supplements, and 66.6% of respondents report disagreement with this question. Question 3 asks respondents if they are currently taking dietary supplements, which saw an even split between agreement and disagreement. Question 4 asked if respondents had taken dietary supplements in the past, to which 69% indicated agreement. Question 5 asks if respondents are concerned about lycopene and potential drug interactions. Respondents overwhelmingly believe that lycopene interacts with prescription drugs, with 92.9% indicating agreement. Question 6 simply poll's respondents as to whether they have ever heard about lycopene, to which 33.3% report agreeing. Question 7 asks if respondents are comfortable with recommending lycopene and if it and other natural substances should be first line therapy for treating mild hypertension (HTN). The proportion of respondents that disagree with this statement is 59.5%, while a substantial minority agree. Finally, question 8 asks respondents whether they now personally have the intention of increasing their dietary lycopene intake for health purposes, to which 59.5% agreed and a substantial minority disagreed (Table 2).

Lycopene Knowledge Score

Respondents' lycopene knowledge score was measured by recording their responses to a series of three statements. Each respondent was awarded a score of 0-3 for each question depending on their level of agreement with each correct statement. The total lycopene knowledge score was the sum of the scores for each statement. The frequency table for each total score is recorded above. Thereafter, respondents were categorized into poor or good lycopene knowledge groups based on their total scores. If a respondent scored 6 or less, then they were placed in the poor knowledge group, and if they scored 7 or higher, then they were placed in the good knowledge group. Results show that 88% of respondents have poor lycopene knowledge (Table 3).

Risk Estimate

The relative risk of respondents being in the poor lycopene knowledge group between demographic categories and survey questions was calculated, along with the 95% confidence interval of the relative risk. Between all the demographic factors and survey responses collected, four were found to have statistically significant relative risks. The first of these significant relative risks is the relative risk of being in the poor lycopene knowledge category in the non-D.C. resident group compared to the D.C. resident group, and the relative risk was found to be 0.87. Next, the relative risk of being in the poor lycopene knowledge group in the >$40,000 income level compared to the <$40,000 income level was found to be 1.19. The relative risk of being in the poor lycopene knowledge group if a respondent agrees with the statement "*I am currently on some type of dietary supplements including vitamins*" compared to if they disagree with the statement was found to be 0.81. Finally, the relative risk of being in the poor lycopene knowledge group if a respondent agrees with the statement "*I believe dietary supplements such as lycopene interact with prescription medicines and should be used cautiously*". Compared to those who disagreed with the statement was found to be 0.87 (Table 4).

DISCUSSION

Although respondents report feeling confident about their dietary supplement knowledge, and report taking dietary supplements, their lycopene knowledge remained low. This mismatch between self-reported confidence and lycopene knowledge may be explained from two possible angles. It may be that the respondents

Table 3: *Frequency Table of Lycopene Survey Question Responses (n=42)*

Survey Questions	Strongly Agree/Agree	Disagree/Strongly Disagree
1. I am Comfortable in my knowledge of dietary supplements	25 (59.5%)	17 (40.5%)
2. I have been involved in counseling or interacting with patients discussing dietary supplements	14 (33.3%)	28 (66.6%)
3. I am currently on some type of dietary supplements including vitamins	21 (50.0%)	21 (50%)
4. I have taken dietary supplements in the past for various reasons	29 (69.0%)	13 (38.1%)
5. I believe dietary supplements such as lycopene interact with prescription medicines and should be used cautiously	39 (92.9%)	3 (7.1%)
6. I have heard about lycopene before	14 (33.3%)	28 (66.7%)
7. I feel comfortable recommending lycopene for a patient with HTN. Natural substances such as lycopene should be the first line in treating mild HTN	17 (40.5%)	25 (59.5%)
8. I will now start eating more foods containing lycopene for my own personal health	25 (59.5%)	17 (40.4%)

Table 4: Lycopene Knowledge Scores

1	2	3	4	5	6	7	8	9
1 (2.4%)	1 (2.4%)	3 (7.1%)	5 (11.9%)	13 (31%)	14(33.3%)	3 (7.1%)	0 (0%)	2 (4.8%)
Poor knowledge (≤70%)	Good knowledge (≥70%)							
37 (88%)	5 (11.9%)							

are legitimately knowledgeable about dietary supplements generally, but that lycopene is too obscure, and so they have not been exposed to research about its potential benefits. This hypothesis is supported by the fact that 66.6% of respondents disagreed that they had heard about lycopene before. Another explanation may be that the self-reported dietary supplement knowledge is inaccurate, and that respondents are not as knowledgeable as they believe themselves to be. This possibility would be congruent with findings from other studies that tested general dietary supplement knowledge. A study conducted by Alqrache et al[8] found that the student body of the Abdulaziz University in Saudi Arabia had low dietary supplement knowledge. Another peculiar finding was that 50% of respondents report currently taking dietary supplements, despite the young age of the cohort. This figure is similar to another study conducted by Samreen et al[9] at King Saud University College of Pharmacy, which found that 46.8% of pharmacy students used dietary supplements. Alqrache et al[8] also found that half of the male students who reported taking dietary supplements did so to improve body image and muscle bulk. It may be that young male cohorts have different motivations for taking dietary supplements, preferring to use them for body-image purposes rather than health reasons.

Several factors were found to have a statistically significant effect on lycopene knowledge. Firstly, non-D.C. residents were found to have a 13.2% lesser risk of being in the poor lycopene knowledge group compared to D.C. Residents. This indicates that lycopene knowledge is poorer among D.C. residents than residents of other localities.

Those with an annual income of >$40,000 were found to have 19.2% greater risk of being in the poor lycopene knowledge group compared to those with <$40,000 income. This result at first seems to be counter intuitive, however it may be that those with lower income tend to be more interested in natural products and other products that could be seen as over the counter (OTC) health promoting and disease preventing measures.

Respondents who agreed with the statement "*I am currently on some type of dietary supplement including vitamins*" had a 19% lesser risk of being in the poor lycopene knowledge group. This is not a surprising result, as it is likely that those who takes supplements may be more aware of the landscape of different natural health products and may have had more exposure to information about lycopene.

Respondents who agreed with the statement "*I believe that dietary supplements such as lycopene interact with prescription medications and should be used cautiously*" had a 12.9% lesser risk of being in the poor lycopene knowledge group. This type of caution with regards to anticipating drug interactions may be an artifact of pharmacy school education, which may prime students to expect an interaction. There are indeed many examples of dietary supplements that interact with prescription medications, and so agreement with this statement may indicate a higher level of general knowledge about lycopene and dietary supplements more broadly.

Lastly, an important finding is that, despite the previously mentioned poor lycopene knowledge among respondents, 59.5% of respondents report that they will consume more lycopene containing foods to promote their own personal health. It therefore seems that poor knowledge was not and overwhelming obstacle to respondents' willingness to use lycopene.

If the effects of lycopene on blood pressure revealed by the works of Wolak et al[3] and Li et al[4] are considered, then the potential for public benefit by its supplementation cannot be overstated. While previous studies by Algrache et al[8] and Samreen et al[9] have assessed demographic factors surrounding general dietary supplement use and attitudes, data specifically about lycopene, particularly in an American context, have not been collected. This present study narrows its focus and demonstrates the lack of lycopene knowledge among pharmacy students, and in doing so reveals possible obstacles to the public benefit that could be offered by the adoption of lycopene supplementation.

CONCLUSION

While lycopene knowledge is generally poor, most respondents report willingness to increase their dietary intake of lycopene. Educating health students and the public may be prudent to improve their receptivity to this promising natural antihypertensive agent. More studies with greater reach must be conducted to learn how to achieve this goal more efficiently.

LIMITATIONS

The limitations of this study include its relatively low sample size, the demographic skew of its respondents towards young people and females, and the fact that all respondents were pharmacy students at a single university. These factors damage the external validity of study results, as they may not be representative of the general population of interest.

INSTITUTIONAL REVIEW BOARD

This study has been approved by the Howard University (HU) Institutional Review Board (IRB).

CONSENT

Obtained.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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DIABETES RESEARCH

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Editorial

Dual Action Mechanism of Insulin Resistance and Insulin Secretion by Imeglimin for Diabetic Treatment

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ABSTRACT

Imeglimin (Twymeeg) is novel oral hypoglycemic agent (OHA) developed in the glimin category. It has dual action mechanisms of reducing insulin resistance and increasing insulin secretion. Trials of imeglimin for efficacy and safety 1 (TIMES 1), TIMES 2 and TIMES 3 were performed with significant clinical efficacy. Among them, HbA1c decrease for 52 weeks showed single imeglimin -0.46%, combined therapy of dipeptidyl peptidase-4i (DPP-4i)-0.92%, Glucagon-like peptide-1 receptor agonists (GLP-1RA)-0.12% and insulin -0.63%. From physiological and pharmacological points of view, the mechanism may include the enhancement action of glucose-stimulated insulin secretion (GSIS). For GSIS progress, transient receptor potential melastatin 2 (TRPM2) channel is activated.

Keywords
Imeglimin; Twymeeg; Trials of imeglimin for efficacy and safety 2 (TIMES 2); Glucose-stimulated insulin secretion (GSIS); Transient receptor potential melastatin 2 (TRPM2) channel.

For non-communicable disease (NCD), diabetes has been crucial medical and social problem worldwide. Medical and health care for diabetes has been managed by International Diabetes Federation (IDF). IDF reported the increased prevalence of diabetes and undiagnosed diabetes mellitus (UDM).[1] Furthermore, latest standard guideline for diabetes was pronounced by American Diabetes Association (ADA) in Jan 2022.[2] It presents recommendation of medical care in diabetes.[3] Recent topics include some types of pharmacological treatment for diabetes. Among them, clinical effect of glucagon-like peptide-1 receptor agonist (GLP-1RA) has been known.[4] GLP-1RA has been recently prescribed more. Cases of 932 type 2 diabetes mellitus (T2DM) were 63.8-years in average and used dulaglutide (65.7%) or liraglutide (29.1%).[5] Hemoglobin A1C (HbA1c) decreased for 6-months from 8.3% to 7.8%, and ratio of HbA1c<7.0% increased from 14.4% to 22.9%. Clinical efficacy of liraglutide and dulaglutide in real world was compared for 179 T2DM patients.[6] HbA1c decreased 8.9% to 7.4% in liraglutide, and 8.7% to 7.5% in dulaglutide for 12-months. Both effects were actually comparable. Thus, GLP-1RA would be in focus for injectable agent for diabetes in the medical practice.

On the other hand, oral hypoglycemic agents (OHAs) have played main role of treating diabetes for long. Metformin has been widely prescribed for first-line medicine with desirable pharmacokinetics. Similar to metformin, a novel OHA has been recently developed, that is imeglimin associated with a triazine ring.[7] It is in the glimin category, which has tetrahydrotriazine-containing agent.[8] The characteristic function shows the dual action mechanism of reducing insulin resistance for peripheral organs and also increasing insulin secretion from beta cell in the pancreas.[9] Imeglimin has been introduced to clinical application, and authors have prescribed the adequate T2DM patients who had successful effects.[10] In our report, T2DM case showed HbA1c decrease from 8.6% to 5.7% in 8-weeks.[11]

From clinical practice points of view, three series of investigations were carried out. They are trials of imeglimin for efficacy and safety 1 (TIMES 1), TIMES 2 and TIMES 3. For TIMES 1, double-blind, randomized, parallel-group, placebo-controlled phase 3 trial was conducted in 30 sites in Japan.[12] Protocol included imeglimin group (2000 mg/day, n=106) and placebo (n=107) for 24-weeks. As a result, HbA1c change from baseline was -0.87% at

24-weeks.

Regarding TIMES 2, clinical efficacy of the combination of imeglimin and other antidiabetic agents for 52-weeks was investigated.[13] It was a phase 3, pivotal, open-label trial including 714 T2DM patients. They were provided 1000 mg of imeglimin twice a day for single therapy or combined therapy of other agents. The primary endpoint was set for maintaining the safety such as adverse events, laboratory results or electrocardiography (ECG). The results showed the following: single imiglimin -0.46%, sulfonyl urea -0.56%, glinide -0.70%, biguanides -0.67%, α-GI -0.85%, thiazolidine -0.88%, sodium/glucose cotransporter-2 inhibitors (SGLT2i) -0.57%, dipeptidyl peptidase-4i (DPP-4i) -0.92% as OHAs, and GLP-1RA -0.12% as injection.

As TIMES 3, combined therapy of imeglimin and insulin was performed for 35 multi-center study. The protocol was double-blind, randomized, parallel-group phase 3 trial with 215 cases.[14] As a result, mean difference in HbA1c between study and control group was -0.60 to -0.64% during 16-52-weeks. Thus, Imeglimin revealed a novel option for add-on therapy (AOT) to insulin therapy.

Among these, impressive comparison would be the combined therapy of DPP-4i (-0.92%), GLP-1RA (-0.12%) and insulin (-0.63%).[13] Common pathway of pharmacological mechanism action has been recognized in the DPP-4i and GLP-1RA. As a matter of fact, however, the clinical effect showed much difference. The efficacy of additional insulin revealed the middle value of those of DPP-4i and GLP-1RA.[14] Possible reason for this phenomenon includes the different pathway of action mechanism of these agents and dual function of imeglimin through mitochondria metabolism.

From basic physiological and pharmacological points of view, imeglimin has been characteristic dual mechanisms.[8] It has an ability for increasing insulin secretion, decreasing β-cell dysfunction, and preventing epithelial cells death.[15] The complete physiological mechanism of imeglimin has not been clarified yet. However, it is suggested for the enhancement action of the glucose-stimulated insulin secretion (GSIS). Concerning GSIS progress, the channel of the transient receptor potential melastatin 2 (TRPM2) is activated, and then it will promote the depolarization of plasma membrane as non-selective cation channel (NSCC) of the β-cell.[16] By the experiment using wild-type and TRPM-knockout type mice, imeglimin shows the action through NSCC. This process will bring the insulin secretion. Consequently, imeglimin may proceed the TRPM changes activation in the beta cells. Its mechanism is through nicotinamide adenine dinucleotide (NAD(+))/Cyclic adenosine diphosphate ribose (cADPR) production, which leads to potentiation of GSIS. Moreover, imeglimin would be involved in the calcium mobilization, that proceeds to the amplification function for insulin secretion.[17]

The mechanism mentioned above would be probable insulin secretion by imeglimin. Other pathways were known to be involved in the insulin secretion.[18] One is the stimulation by glucose, which leads to cyclic adenosine monophosphate (cAMP) activation, exchange protein by cAMP2A (exchange protein directly activated by cAMP 2 (Epac2A)) and TRPM2. These pathways bring the first phase of insulin secretion. Another is the stimulation by GLP-1, exendin-4 and glucose-dependent insulinotropic polypeptide (GIP), that may activate cAMP production as the same route of glucose pathway.

From these basic pharmacological mechanisms, imeglimin can contribute much for actual diabetic practice. As to chronic kidney disease (CKD), pharmacokinetic (PK) characteristics were studied.[19] Consequently, usual doses of 1000 mg of imeglimin twice daily can be given for case with estimated glomerular filtration rate (eGFR)>45 mL/min/1.73 m^2, and 500 mg twice is recommended for case with eGFR 15-45 mL/min/1.73 m^2. Study of imeglimin for patient with hepatic impairment was conducted by area under the curve (AUC) and maximum observed plasma concentration (C_{max}). The result showed 50% higher AUC and 30% higher C_{max}, indicating safe and well-tolerated administration of imeglimin for hepatic impairment.[20] Meta-analysis investigation was performed for 1555 cases from 8 studies. As a result, Imeglimin group showed decreased HbA1c and no significant changes in homeostasis model assessment-estimated insulin resistance (HOMA-IR), triglyceride, and HDL-C.[21] In summary, this article will be hopefully useful reference in the future diabetic research.

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Case Report

Improved Insulin Resistance and Glucose Variability by Super-Low Carbohydrate Diet

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ABSTRACT

Background
Diabetes mellitus (DM) has been more prevalent. American Diabetes Association (ADA) proposed the Standards of Medical Care in Diabetes-2022. For nutritional therapy, low carbohydrate diet (LCD) has been recognized for its benefits. Authors have continued diabetic research concerning LCD and meal tolerance test (MTT).

Case Presentation
The case is 61-year-old male with type 2 diabetes mellitus (T2DM) for years. His hemoglobin A1c (HbA1c) increased to 7.8% in autumn 2021, and further evaluation and treatment was conducted including LCD, daily check of meal and carbohydrate amount, 75 g OGTT, glucagon stimulation test (GST) and others.

Results
He was on super-LCD method including 12% of carbohydrate. His carbohydrate intake amount and 45-minutes post-prandial blood glucose showed significant correlation. The results of 75 g OGTT twice in May 2020 and December 2021 showed that similar pattern of glucose and insulin responses and insulinogenic index (IGI). In contrast, they showed decreased fasting immuno-reactive insulin (IRI) and Homeostasis model assessment insulin resistance (HOMA-R). For GST, C-peptide showed normal response.

Discussion and Conclusion
Judging from the results of MTT, OGTT, GST and IGI, he seems to show rather decreased insulin resistance by LCD associated with preserved insulin secretion ability to some degree. Further investigation would be required from pathophysiological point of view.

Keywords
Super-low carbohydrate diet (LCD); Meal tolerance test (MTT); Type 2 diabetes mellitus (T2DM); Insulinogenic index (IGI); Glucagon stimulation test (GST); Homeostasis model assessment insulin resistance (HOMA-R).

INTRODUCTION

Diabetes mellitus (DM) has been more prevalent across the world according to the epidemiological report of International Diabetes Federation (IDF).[1] Among them, undiagnosed DM (UDM) in adult is gradually increasing in developed and developing countries.[2] American Diabetes Association (ADA) proposed the latest guideline in Jan 2022, which is the Standards of Medical Care in Diabetes-2022.[3]

For the diabetic therapy, nutritional treatment would be the fundamental strategy including low carbohydrate diet (LCD).[4] Clinical efficacy of LCD has been gradually recognized for improving glucose variability and weight reduction.[5] Authors and collaborators have continued diabetic research and practice for long.[6] Their clinical fields include LCD, continuous glucose monitoring (CGM), Glucagon-Like Peptide 1 receptor agonist (GLP-1RA), meal tolerance test (MTT) and others.[7,8]

Concerning LCD investigation, historical changes for nu-

tritional therapy were observed. Calorie restriction (CR) was the standard method for diabetic diet therapy in previous period. After that, LCD method was introduced to medical and health care field by Atkins et al.[9] LCD was evaluated to be clinically effective by Dietary Intervention Randomized Controlled Trial (DIRECT) study.[10] Successively, LCD was generally defined as related with several diet methods.[11] On the other hand, authors et al. initiated LCD in Japan and developed LCD medically and socially through the activity of Japan LCD Promotion Association (JLCDPA).[12] Among our various activities, three representative methods of LCD were widely informed to general people. They are petite LCD, standard LCD and super LCD.[13] These LCD nutritional options were applied to many obesity patients, and the results showed that 25% subjects achieved >10% of weight reduction.[14]

As to MTT, standardized liquid meal was ingested and assessed for β-cell function in diabetic patients.[15] Similar to MTT, widely applied popular method includes oral glucose tolerance test (OGTT).[16] Authors have developed MTT research, and proposed the simple method using breakfast.[17] The standard meal is made from Japanese style standard breakfast including 70 g of carbohydrate.[18] Applying this meal, the responses of blood glucose, insulin and C-peptide were investigated.[19]

By combination of the research of LCD and MTT, we have continued clinical diabetic studies. Among several patients with type 2 DM (T2DM), we have experienced a case of impressive characteristic aspects. In this case report, general outline of clinical course and treatment will be introduced.

CASE PRESENTATION

Family and Past History

The current case is 61-year-old man. Regarding his family history, there was unremarkable disease involved, such as diabetes mellitus, hypertension, coronary heart disease (CHD), cerebral vascular accident (CVA) or malignant disease.

For his previous medical history, he was born without any health problem. When he was born, his weight was 3500 g. It was much heavier than average baby weight. Her mother was not diabetic or did not have any medical problems during pregnancy. He did not have significant disease or impaired function until 54-years-old.

Medical History and Status

The current case is 61-year-old T2DM male patient who has diabetic history of 4-years. He has become gradually rather obese after 55 years old and then he was diagnosed for T2DM. Then he was advised to reduce the weight, and he tried to continue mild LCD for a few years. He received 75 g OGTT in May 2020, in which it showed delayed pattern of glucose and insulin. The HbA1c value maintained about 6.1-6.4% for a few years. During summer 2021, he felt general malaise and weight loss and then received medical check. Consequently, he was pointed out to have exacerbated T2DM and to start strict LCD at once. Consequently, he and his wife have started to evaluated carbohydrate amount of his daily meal. Consequently, HbA1c and blood glucose decreased, associated with lower post-prandial blood glucose.

His physical status showed unremarkable findings, including consciousness, vital signs, lung, heart, abdomen and neurological examination. His stature, weight and body mass index (BMI) was 181 cm, 89 kg and 27.2 kg/m^2, respectively. His laboratory examinations revealed that HDL-C 65 mg/dL, LDL-C 142 mg/dL, TG 100 mg/dL, GOT 22 U/L, GPT 28 U/L, r-GTP 25 U/L, BUN 17 mg/dL, Cr 0.8 mg/dL, UA 3.9 mg/dL, WBC 8600 /μL, RBC 508×10^6 /μL, Hb 16.2 g/dL, Plt 21.1×10^4 /μL, CRP 0.02 mg/dL. Urinalysis showed pH 6.0, protein (-), glucose (+), urobilinogen (+/-), occult blood (-) and ketone body (+). Other tests showed negative for chest X-P and electrocardiogram (ECG). Pulse wave velocity (PWV) test showed normal range results, where ankle brachial index (ABI) was 1.08/1.09 and cardio-ankle vascular index (CAVI) 10.0/10.0 for right/left.

Clinical Course

This case has applied strict LCD that has been known as super-LCD method. It means that carbohydrate ratio in calorie calculation would be 12%. He actually continued to decrease carbohydrate as possible.[20] Then, his daily profile of blood glucose became normalized and HbA1c values decreased from 7.8% to 6.3% for 3-months. He felt no remarkable complaints, symptoms, signs or abnormal biomedical exams during 4-months. During his clinical course, he received 75 g OGTT and continued taking daily meal data by digital camera associated with calculating carbohydrate amount and calorie included. Especially, 45-minutes post-prandial glucose of dinner was continued to check for months.[21] Furthermore, the insulin response was investigated for endocrinological stimulus by glucagon test.

RESULTS

During the period of LCD, several data such as carbohydrate amount and calorie were checked and analyzed (Table 1). Table 1 revealed Western and Japanese styles of dinner provided. Blood glucose value was measured as 45-minutes post-prandial point of each dinner. Further, relationship between carbohydrate amount and 45-minutes post-prandial blood glucose was investigated, which was analyzed in Figure 1. It shows significant relationship between them. The formula for the regression curve is shown, which was $y=1.9084x+104.76$, $R^2=0.5789$, $p<0.05$.

Regarding the ability of insulin secretion, 75 g OGTT was conducted (Figure 2). Figure 2 includes totally four results of 75 g OGTT, in which Figures 2a and 2b are from the first author of current T2DM case in May 2020 and December 2021 (case 1), Figure 2c is from the second author without any diseases (case 2) and Figure 2d is from the third author with T2DM (case 3). Case 1 showed delayed response of glucose and immuno-reactive insulin (IRI) for T2DM. Case 2 showed normal response of glucose and IRI for normal subject. Case 3 showed hyperglycemia in which glucose increased to 240 mg/dL in 120-minutes. Related to 4 data of Figure 2, detail biomarkers of diabetes mellitus were summarized associated with detail background of case 1-3 in Table 2. Case 1 showed elevated fasting IRI, homeostasis model assessment insu-

Table 1: *Dinner Content with Carbohydrate Amount and Post-Prandial Blood Glucose*

Dinner	Ingredient	Each Carbo (gram)	Total Carbo (gram)	Total Calorie (kcal)
A 	Tempura	21.2	48.2	656
	Fish	4.0		
	White rice	19.0		
	Miso soup, etc.	4.0		
B 	Fried chicken	28.0	33.4	652
	Cauliflower	0.1		
	Vegetables	0.1		
	Miso soup, etc.	5.4		
C 	Hot pot shabu-shabu	0.1	10.8	445
	Beef	0.3		
	Tofu	0.4		
	Vegetables	10.0		
D 	Chili pepper soup	7.9	30.0	205
	Pork	0.2		
	White radish	2.4		
	Vegetables	19.5		

Figure 1. *Relationship between Carbohydrate Amount in the Dinner and 45-minutes Post-prandial Blood Glucose*

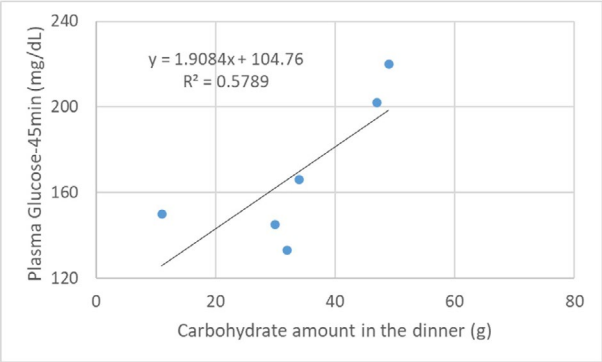
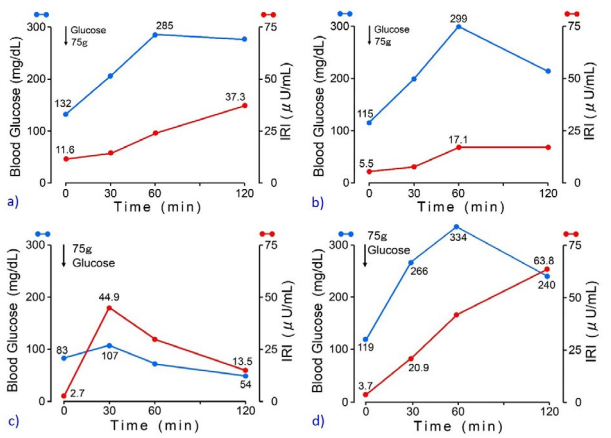


Table 2: *General Background, HOMA Values and IGI in Three Cases*

Case	Age/ Sex	Diagnosis	Test date (Mo/Year)	FPG (mg/dL)	IRI (μIU/L)	HOMA-R	HOMA-13 (%)	IGI	Figure
Case 1	61 M	T2DM	May 2020	132	11.6	3.78	60.5	0.04	Figure 2a
Case 1	61 M	T2DM	Dec 2021	115	5.5	1.56	38.1	0.03	Figure 2b
Case 2	65 M	Normal	Jan 2022	83	2.7	0.55	48 .6	1.76	Figure 2c
Case 3	56 F	T2DM	Feb 2022	119	3.7	1.09	23.8	0.12	Figure 2d

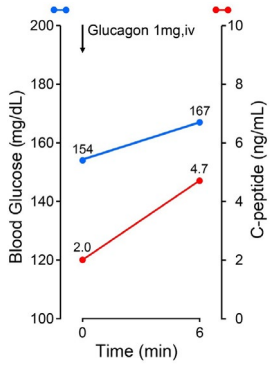
Case 1 is the first author who works in the administration section of the hospital.
Case 2 is the second author who specializes diabetes mellitus as a physician.
Case 3 is the third author who has worked in the out clinic as a hospital nurse.

Figure 2. *Responses of Blood Glucose and IRI in 75 g OGTT for Case 1-3*



Case 1 is the first author who works in the administration section of the hospital.
Case 2 is the second author who specializes diabetes mellitus as a physician.
Case 3 is the third author who has worked in the outclinic as a hospital nurse.

Figure 3. *Response of C-peptide for Glucagon Stimulation Test*



lin resistance (HOMA-R) in May 2020 and almost normal range of IRI and HOMA-R in December 2021. His insulinogenic index (IGI) values remained low during the period. Case 2 is 65-year-old physician and showed normal range of all biomarkers. Case 3 is 56-year-old nurse and showed normal range of HOMA-R and Homeostatic model assessment of β-cell function (HOMA-β), and decreased IGI. For detection of insulin secretion, glucagon stimulation test (GST) was conducted. As a result, c-peptide value increased from 2.0 ng/mL to 4.7 ng/mL during 6-minutes (Figure 3).

DISCUSSION AND CONCLUSION

The current case has T2DM, and HbA1c value has been elevated for years. Regarding the pathophysiological aspect, both of insulin resistance and insulin deficiency has been present to some degree from his history and biomedical examination results. BMI is currently 27.2 kg/m^2, but once it weighed 100 kg with 30.5 kg/m^2 of BMI. In this case report, detail investigation for several aspects is conducted, which are summarized in tables and figures. Discussion and perspectives would be described in this order.

In this case, super low carbohydrate diet (super-LCD) was applied and continued.[13] It includes 12% of carbohydrate in calorie ratio, associated with normalized HbA1c and glycemic fluctuation. Along with super-LCD, he successfully continued meal diary every day and blood glucose profile perfectly (Table 1). We have continued to research and clinically apply LCDs for long. Among them, the clinical effect of LCD was found in many patients, and the cases of remarkable weight loss were also observed.[20] There are actually three methods for LCDs, which are petite-LCD, standard-LCD and super-LCD. The carbohydrate content in calorie ratio is 12%, 26% and 40%, respectively.[13] From recent reports on LCD, various beneficial effects have been observed.[22]

For evaluating clinical LCD trials, carbohydrate ratio in the meal has been on discussion.[17] A standard classification shows that high-carbohydrate diet (>45%), moderate carbohydrate diet (26-45%), LCD (10-25%), and very low-carbohydrate ketogenic diet (VLCKD) (<10%).[18,19] As carbohydrate ratio is lower, glucose-lowering efficacy is larger for T2DM.[20] However, it has been not clear whether more carbohydrate restriction can bring the cardiovascular risk reduction or not.[19]

Meal tolerance test (MTT) was performed in advance to examine post-prandial blood glucose 30-minutes, 45-minutes, and 60-minutes for the case. As a result, 45-minutes post-prandial glucose was the highest.[21] Then, post-prandial timing was de-

cided 45-minutes for this case. Significant correlation was found between carbohydrate amount and 45-minutes post-prandial glucose in the dinner (Figure 1). We can calculate using the regression curve. When 20 g of carbohydrate is input, glucose value becomes 142 mg/dL, and when 50 g is input, it becomes 199 mg/dL. The measurement seems to be more or less consistent with actual carbohydrate intake and post-prandial glucose in T2DM patients.[18] MTT and OGTT are often compared for simple and convenient in the clinical practice.[23] Both are suitable methods to evaluate physiological β-cell ability for long-term.[24] Comparative investigation revealed that MTT showed stronger response of β-cell than OGTT,[24] and represented reproducible and reliable way of analyzing biomarkers of β-cell function.[25]

OGTT exams were checked twice, which were compared between in May 2020 and December 2021 (Figure 2). His weight was 95 kg *vs* 88 kg and his fasting IRI was 11.6 μIU/mL *vs* 5.5 μIU/mL. From these data, the degree of insulin resistance may be reduced. The pattern of glycemic and IRI for 75 g OGTT seems to be similar, and unremarkable change in insulin secretory reserve was observed. As a comparative control, case 2 showed rather low glucose on 120-minutes. Case 2 is healthy physician and usually on standard LCD, which may be involved in lower glucose on 120-min after 75 g OGTT. Case 3 has T2DM for more than 15-years, and is currently on petite LCD for better glucose variability. It showed delayed insulin response and blood glucose increased from 119 mg/dL to 334 mg/dL (215 mg/dL increase). From pathophysiological point of view, T2DM patient is reported to show 3 mg/dL of glucose increase per 1 g intake of carbohydrate. When calculating as 75 g×3=225, this result seems to be similar to actual data.[21] OGTT has been widely used for investigating glucose tolerance and insulin secretion in clinical practice.[26] Estimation of β cell function by OGTT shows more physiological responses of glucose and insulin than those of frequently sampled intravenous glucose tolerance tests (FSIVGTT) and hyperglycemic clamp.[27]

HOMA-R, HOMA-β and IGI in case 1 suggested that insulin resistance was slightly reduced for 19-months, but insulin secretory capacity was similar (Table 2). Regarding the pathogenesis of all types of DM, increased insulin resistance and reduced insulin secretion would play a major role.[26] It is rather difficult to obtain complete pathophysiology of diabetic metabolism because glucose and insulin have been influenced through various complex process. However, some metabolic indices are appropriate for investigate clinical diabetic situation, which are HOMA-R, HOMA-β and IGI. Regarding these biomarkers, the standard values widely used so far are HOMA-R<2.5, HOMA-β>30%, and IGI>0.4-0.5.

The standard range of HOMA-R cannot be clearly defined, where 2.5 has been often used in usual situation. The cut-off point of HOMA-R was studied in reference to the definition of IDF and Adult Treatment Panel III (ATPIII) criteria.[28] The method included the analysis of area under the curve (AUC). As a result, the optimal cut-off of HOMA-R was 1.775 for diagnosis of Metabolic syndrome (MetS) in non-DM patients, 4.325 and 3.875 for diagnosis of DM in MetS patients for IDF and ATPIII, respectively. Consequently, MetS or diabetes can be diagnosed from various patients with or without diabetes in applying this optimal method. HOMA-β has been one of the useful static assessments of β-cell function.[29] It is simple and widely applied in epidemiologic investigation. However, it has some limitation because only one point of glucose and insulin cannot represent complex situation of glucose-insulin feedback axis.[30]

Regarding IGI, lower results were found in case 1 and 4, and normal in case 2 (Table 2). Case 1 has weight reduction compared to 19 months ago, leading to decreased fasting IRI and HOMA-R. However, the capacity of insulin secretion did not change. IGI has been widely used to quantify the response of β-cell for the changes in blood glucose. It is calculated for delta-IRI (0-30min) (μIU/mL)/delta-glucose (0-30-minutes) (mg/dL).[24] It is also applied in the case of MTT trials.[31] Compared IGI for GTT and MTT has been studied.[32] Authors have studied insulin and C-peptide immunoreactivity (CPR) responses for MTT and presented clinical efficacy of MTT.[19,21] From several reports, β-cell function seems to be higher during MTT than OGTT, suggesting that several function parameters would be influenced by some composition in the meal.[24]

Glucagon stimulation test (GST) has been applied for the investigation of insulin-secreting ability from β-cell in the pancreas. Formerly, the purpose was evaluation of residual β-cell function,[33] in which subjects were 17 insulin-dependent diabetes mellitus (IDDM) patients. C-peptide elevation was measured after meal ($p<0.01$) and after intravenous glucagon ($p<0.001$). Both responses showed correlation ($p<0.005$), suggesting possible prediction of glucagon test for the responsive ability of β-cells during usual daily life. In the current case, GST revealed that pancreatic β-cell function was preserved (Figure 3). Based on his data for clinical course, 75 g OGTT, HOMA-R, HOMA-β, IGI and glucagon tests were comprehensively analyzed totally. LCD continuation had successfully brought weight reduction, decreased HbA1c, moderately reduced insulin resistance. Furthermore, it seems to maintain secretory capacity against strong endocrinological stimulation. On the other hand, OGTT seems to be rather weaker stimulation compared to GST. IGI values by 75 g OGTT did not improve.

There are some limitations for this report as follows: i) super LCD was continued, but any food has carbohydrate to some degree for elevating blood glucose, ii) correlation between carbohydrate amount and post-prandial glucose was found, but the study of MMT cannot predict complete suggested glucose values due to ingestion the meal per OS, iii) OGTT twice showed delayed IRI responses, which may suppose persisting impaired insulin secretion and increased insulin resistance, iv) current glucose-insulin situation will be possible changed due to clinical course in the future, then detail follow-up the glucose variability would be required.

In summary, this case report described a male patient with T2DM and gave some discussion from several points of view. He successfully continued daily check of meal with carbohydrate amount and post-prandial blood glucose. Diabetic biomarkers including 75 g OGTT, HOMA-R, HOMA-β, IGI and GST were analyzed for evaluating current pathophysiology. Current information will become hopefully some reference for diabetic practice and research in the future.

ETHICAL CONSIDERATIONS

Current investigation was conducted along the Declaration of Helsinki, that was previously revised in 2013 for the WMA Fortaleza General Assembly. In addition, several commentaries were added by the ethical guidelines for medical research. They are notified by the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan and Ministry of Health, Labour and Welfare (MHLW), Japan. This study in detail was explained to the patient. Authors have obtained the written document agreements from the patient. Current study was discussed in the professional ethical committee. The committee involves several professionals including president, director, doctors, nurses, pharmacists, dieticians, and a professional legal specialty.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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Dietary Supplements: A Survey of the Opinion of First-Year Professional Pharmacy Students

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ABSTRACT

Introduction
Pharmacists need to be at the forefront in advising consumers of dietary supplements (DS) about quality, claims, labeling, safety, efficacy, DS-drug interactions, and other aspects. Yet, the knowledge base of pharmacists and pharmacists-in-training about DS appears to be below expectation.

Objective
The goal of the study is to evaluate pharmacy student opinions about DS.

Methodology
A survey questionnaire was developed, tested, and distributed among students who were enrolled in the Drug Information class, which is a 2-credit hour mandatory course for all first professional pharmacy students at Howard University, College of Pharmacy. The data was analyzed using SPSS statistical analysis software.

Results
A total of 42 students (15 male, 27 female) participated in the survey. Of these, 25 respondents (59.5%) felt comfortable about their knowledge of DS, while only 14 (33.4%) reported participation in counselling (p=0.0281). Most respondents (29; 69%) had used DS in the past, while 21 (50%) claimed they used DS at the time of the survey. To a specific query in the questionnaire regarding lycopene-containing food items, 28 (66.7%) agreed they would use such foods in the future for health benefits. Analysis of the survey data revealed no statistical differences between the responses of male and female students (p>0.05 for all the five questionnaire items).

Conclusion
In a survey of 42 pharmacy students at Howard University College Pharmacy, over half (59.5%) felt comfortable about their knowledge of DS. About one-third students (33%) reported they were involved in patient counseling and interaction. Over two-third respondents (69%) took DS in the past, while half were taking DS at the time of the survey.

Keywords
Dietary supplements; Knowledge; Counseling; Use; Lycopene.

INTRODUCTION

The Dietary Supplement Health and Education Act (DSHEA) was enacted by US Congress with the purpose of regulating dietary supplements (DS) in the United States. Formulations of botanicals, vitamins, minerals, and amino acids constitute DS. They do not require pre-market approval by the Food and Drug Administration (FDA).[1] Manufacturers of DS are allowed to make structure-function claims, with a disclaimer that the latter have not been evaluated by FDA. They are also required to include a statement that a DS is not intended to diagnose, treat, cure, or prevent any disease.[2] The semantics adds to the confusion of interpreting claims. As of 2014, there were more than 85,000 diverse DS products in the market.[1] The quality and safety of DS continue to be of much concern.

A positive role cab be played by pharmacists in selecting appropriate DS not only for their own use, but also for public consumers who seek their advice. Pharmacists need to be at the forefront in advising consumers of DS about quality, claims, label-

ing, safety, efficacy, DS-drug interactions, and other aspects.[1] Yet, the knowledge base of pharmacists and pharmacists-in-training about DS appears to be below expectation. According to a study by Shah et al,[3] pharmacy students felt their knowledge about herbal supplements was inadequate, with 95% of the survey participants reporting a need to learn more about herbal supplements. In a systematic review of the literature by Kwan and colleagues, it was shown in 1990 that about 50% of surveyed pharmacists perceived they have some knowledge about DS.[4] The review reported similar results in five more studies. However, the actual knowledge level of pharmacists was even lower than 50%.[4] Data gathered from 41 academic pharmacists in US pharmacy schools indicated a use rate of 54% in the past, with 16 (39%) reporting taking DS at the time of the study.[5] In a survey of 179 pharmacy students by Axon et al,[6] it was reported 52% used at least one dietary supplement in their lifetime.[6] In a similar manner, another study which surveyed 70 pharmacists showed a majority (52.9%) reported taking dietary supplements.[7] In a 2017 survey, Hailemeskel et al[8] reported about 53% use rate among HU first year pharmacy students.[8] For this survey, several herbs were presented to the participants as a part of the survey. The herbs are listed alphabetically (Table 1) and by the diseases states they are intended to be used (Table 2) as shown below.

Table 1: *Dietary Supplements Included in the Study*

Dietary Supplements	Indications/Use
Alpha lipoic acid	Multiple sclerosis
	Liver disease
Berberine	Diabetes mellitus
Bitter melon	High blood pressure
Citicoline	Parkinson's disease
Coenzyme Q10	Hypertension
Curcumin	Hyperlipidemia
Fenugreek	Diabetes
Flaxseed	Hyperlipidemia
Garlic	High blood pressure
Ginkgo biloba	Parkinson's disease
Glutathione	Multiple sclerosis
Grape seed extract	High blood pressure
Hawthorn	High blood pressure
L-arginine	Hypertension
	Diabetes mellitus
L-Carnitine	Parkinson's disease
Low dose naltrexone	Opioid addictions
Lycopene	High blood pressure
Magnesium	Fibromyalgia
Melatonin	High blood pressure
Mucuna Purines (Velvet Beans)	Parkinson's disease
NADH	Parkinson's disease
OMEGA-3 (DHA/EPA)	Parkinson's disease
Phosphatidylserine	Parkinson's disease
Resveratrol	Hyperlipidemia
Sea weeds	Hypertension
Taurine	High blood pressure
Tocotrienol	Hyperlipidemia

Table 2: *Dietary Supplements by the Respective Disease States Claimed to be Useful*

Disease States	Dietary Supplements
Diabetes mellitus	Fenugreek
	L-carnitine
	Berberine
Fibromyalgia	Magnesium
High Blood Pressure	Bitter melon
	Garlic
	Grape seed extract
	Hawthorn
	Lycopene
	Taurine
	Coenzyme Q10
	L-arginine
	Sea weeds
Hyperlipidemia	Curcumin
	Flaxseed
	Resveratrol
	Tocotrienol
Liver disease	Alpha-lipoic acid
Multiple sclerosis	Alpha lipoic acid
	Glutathione
Opioid addictions	Low dose naltrexone
Parkinson's disease	Citicoline
	Ginkgo biloba
	Mucuna purines (velvet beans)
	NADH
	OMEGA-3 (DHA/EPA)
	Phosphatidylserine
	L-Carnitine

The current survey was carried out to evaluate the opinion of first year pharmacy students at Howard University (HU), College of Pharmacy regarding their knowledge, counseling roles, their own past and current use of DS. It is hoped the survey results would help HU College of Pharmacy address any deficits.

METHODS

After receiving approval from Howard University Institutional Review Board (IRB), the study voluntarily enrolled 45 incoming first professional year pharmacy students at HU College of Pharmacy for the year 2021. The survey was conducted as part of a Drug Information course, which is a 2-credit hour course in the college. Of these, 42 (93.3% response rate) completed the survey. Demographic data were collected on age, gender, education, residence, work-related items, and annual income. Five opinion questions were also included in the survey questionnaire. A 4-point Likert scale (1=strongly agree; 2=agree; 3=disagree; 4=strongly disagree) was used to collect responses. In cases where a "yes" or "no" answer was inferred, the strongly agree and agree responses were considered as a "yes" while the disagree and strongly disagree responses were considered "no". Mean Likert score were used to

place the levels of aggregate agree and disagree responses. Statistical methods were used to calculate confidence intervals and significance. A two-tailed Fisher's exact test was utilized to determine *p* values by comparing responses based on gender.

RESULTS

As shown in Table 3, most survey respondents (27; 64.3%) were female students. Thirty-four (81%) had a bachelor's degree prior to starting the pharmacy program. Respondents scored 2.14, 2.17, 2.38 and 2.43 on the mean Likert scale in three of the opinion

Table 3: *Demographic Characteristics of Respondents*

Characteristics	Respondents (n, %)	95% CI (% range)
Age (years)		
21-23	14 (33.3)	19.1-47.6
24-26	17 (40.5)	25.6-55.3
27-29	5 (11.9)	2.1-21.7
>29	6 (14.3)	3.7-24.9
Gender		
Male	15 (35.7)	21.2-50.2
Female	27 (64.3)	49.8-78.8
Education		
Some college	1 (2.4)	0.0-7.0
Associate Degree	1 (2.4)	0.0-7.0
BA/BSc	34 (81)	69.1-92.8
MSc	4 (9.5)	2.7-22.6
PhD/Professional	2 (4.8)	0.0-11.2
Residence		
Washington, D.C.	4 (9.5)	0.7-18.4
Maryland	13 (31)	16.9-44.9
Virginia	7 (16.7)	5.4-27.9
Other States	18 (42.9)	27.9-57.2
Working Now		
Yes	9 (21.4)	9.0-33.8
No	33 (78.6)	66.2-90.9
Work Experience		
Never worked	2 (4.8)	0.0-11.2
Short-term	3 (7.1)	0.0-14.9
Part-time	16 (38.1)	23.4-52.8
Full-time	21 (50)	34.9-65.1
Type of Job		
Pharmacy related	16 (38.1)	23.4-52.8
Other healthcare	12 (28.6)	14.9-42.2
Non-health related	13 (31)	16.9-44.9
Not applicable	1 (2.4)	0.0-7.0
Annual Income		
< USD 10,000	13 (31)	16.9-44.9
10,001-20,000	7 (16.7)	5.4-27.9
20,001-30,000	6 (14.3)	3.7-24.9
30,001-40,000	5 (11.9)	2.1-21.7
>40,000	11 (26.2)	12-9-39.5
Years Worked		
None	1 (2.4)	0.0-7.0
1-2	19 (45.2)	30.2-60.3
3-4	11 (26.2)	12.9-39.5
>4	11 (26.2)	12.9-39.6

CI=Confidence interval; Normal approximations of binomial exact values.

questions, which is close to the designated agree score of 2.

One questionnaire item scored a mean of 2.76, which is close to the disagree level on the scale (Table 4). A total of 25 respondents (59.5%) felt comfortable in their knowledge DS (mean Likert score=2.38±0.70). Fourteen (33.3%) were involved in counseling consumers of DS (mean Likert score=2.76±0.88). Most of the respondents (29; 69%) had taken DS in the past, while 21 (50%) used DS at the time of this survey (Table 4).

Gender-based sub-analysis of the data did not show statistical differences in the responses to the five opinion questions (p>0.05). The most difference was noted in the response to the question on past use of DS, which favored females (21 of 27 [77.8%]) *vs* males (8 of 15 [55.3%]), p=0.1635 (Table 5).

DISCUSSION

In a survey of 179 students by Axon et al,[6] 52% had used at least one DS in their lifetime. Our survey showed a higher user rate (69%) when such use in the past was inquired. In another survey of 70 pharmacists, a majority (52.9%) reported taking dietary supplements,[7] which agrees with our finding. Furthermore, in a survey of 41 pharmacy faculty and professional staff, Murphy et al[5] found a prior user rate of 54%, lower than our finding. In our survey, current user rate was 50% compared to 39% reported by Murphy et al.[5] Analysis of the response pattern to the five questions in our questionnaire based on gender did not show statistical difference. Most respondents in our study (59.5%) felt comfortable about their knowledge of DS, yet only 33% were involved in counseling, which indicated a statistically significant discrepancy (p=0.0281).

CONCLUSION

In a survey of 42 pharmacy students at Howard University College Pharmacy, 25 (59.5%) felt comfortable about their knowledge of DS. Fourteen students (33%) reported they were involved in patient counseling and interaction. A total of 29 respondents (69%) took DS in the past, while 21 (50%) were taking DS at the time of the survey. Twenty-eight respondents (66.7%) agreed they would consume lycopene-containing foods in the future to derive some health benefits.

CONSENT

Yes.

INSTITUTIONAL REVIEW BOARD PERMISSION

Yes.

Table 4: *Questionnaire Items and Answers of Respondents on a 4-point Likert Scale*

Questionnaire Items	Strongly Agree (n, %)	Agree (n, %)	Disagree (n, %)	Strongly Disagree (n, %)	Mean Likert Score (SD)
Are you comfortable in your knowledge of dietary supplements (DS) (n=42)	3 (7.1)	22 (52.4)	2 (35.7)	5 (4.8)	2.38±0.70
I have been involved in counseling and interaction with patients on DS (n=42)	4 (9.5)	10 (23.8)	20 (47.6)	8 (19.1)	2.76±0.88
I have taken DS in the past for several reasons (n=42)	10 (23.8)	19 (45.2)	10 (23.8)	3 (7.1)	2.14±0.87
I am currently on some type of DS including vitamins (n=42)	9 (21.4)	12 (28.6)	15 (35.7)	6 (14.3)	2.43±0.99
I will start eating foods containing lycopene for my own personal health (n=42)	9 (21.4)	19 (45.2)	14 (28.6)	2 (4.8)	2.17±0.82

Mean Likert score was calculated by multiplying each score by the number of responses, adding up the total and then dividing by the number of respondents; SD=Standard Deviation

Table 5: *Breakdown of Responses Based on Gender*

Survey Items	Gender	SA	A	DA	SDA	Ag A's	Ag DA's	p value
Are you comfortable in your knowledge of dietary supplements (DS)?	M (n)	2	7	6	0	9	6	0.7464
	F (n)	1	15	9	2	16	11	
I have been involved in counseling and interaction with patients on DS	M (n)	1	5	7	2	6	9	0.5159
	F (n)	3	5	13	6	8	19	
I have taken DS in the past for several reasons	M (n)	3	5	7	0	8	7	0.1635
	F (n)	7	14	3	3	21	6	
I am currently on some type of DS including vitamins	M (n)	4	4	4	3	8	7	1.0000
	F (n)	5	8	11	3	13	14	
I will start eating foods containing lycopene for my own personal health	M (n)	3	8	4	0	11	4	0.7337
	F (n)	6	11	8	2	17	10	

Abbreviations: SA=Strongly agree; A=Agree; DA=Disagree; SDA=Strongly disagree; Ag A's=aggregate agrees; Ag DA's=aggregate disagrees; M=Male; F=Female
p values were determined by using a two-tailed Fisher's exact test; values>0.05 are considered not significant.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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