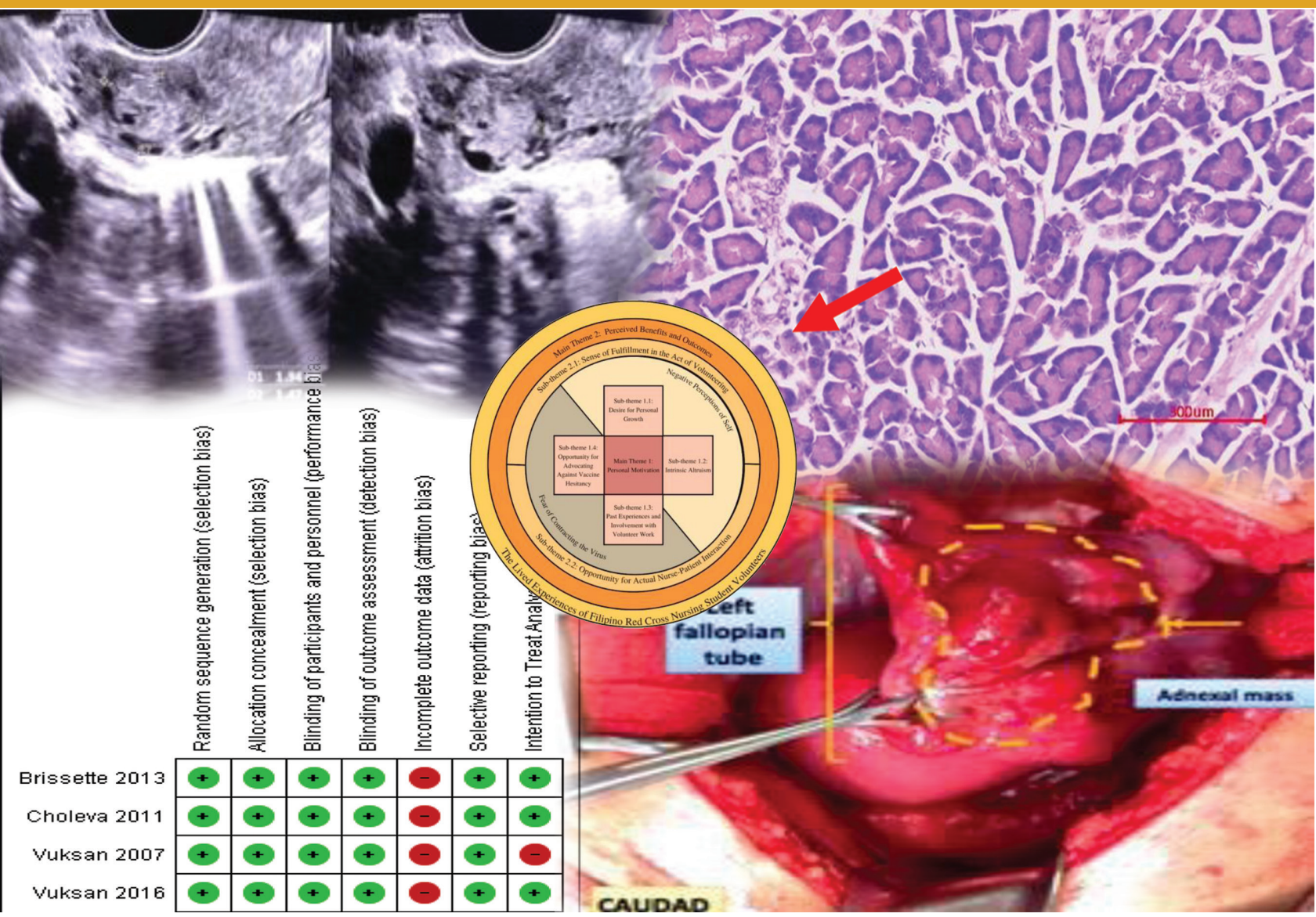
Vol. 11 No. 2 July-December 2022

UERM
Memorial Medical Center, Inc.
Research Institute for Health Sciences

Health Sciences Journal

ISSN 2244-4378 e-ISSN 2408-302X

From the desk. To the bench. To the bedside.



The HEALTH SCIENCES JOURNAL

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Contents

Determination of the efficacy of okra seed powder in aqueous solution as a glucose lowering agent compared to acarbose in STZ diabetic rats

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Abstract

Introduction Okra is reported to have anti-diabetic effects, but the literature shows conflicting results. The experiment aimed to determine the efficacy of three doses of okra seed powder suspension as a glucose lowering agent on streptozotocin-induced diabetic rats and its cellular effects on the liver and pancreas.

Methods Twenty-five Sprague Dawley rats that were given streptozotocin 60 mg/kg intraperitoneally were randomly allocated to one of five treatment groups: okra seed powder at 100 mg/kg, 150 mg/kg and 200 mg/kg, acarbose (positive control) and vehicle only (negative control). The treatments were given as a 1.5 mL oral gavage daily for 21 days. Significant differences in blood glucose were determined between treatment groups in terms of relative change from baseline, using One-Way ANOVA with Dunnett's method with acarbose as the referent group. Repeated measures ANOVA was used to analyze the blood glucose levels across the time point collections (baseline, T1 and T2). Histopathologic changes on the liver and pancreas were described using counts and proportions.

Results Mean blood glucose values increased from baseline to T2 in all treatment groups. Increasing trend was observed only up to T1 in the 150 mg/kg and the 200 mg/kg okra seed treatment groups. Comparing okra treatment groups to acarbose, the percentage increase of mean blood glucose from baseline to T2 was lowest in the 200 mg/kg okra group ($p = 0.040$). The okra-treated rats had no fatty change and a dose-dependent decrease in cellular degeneration in the liver and none for the 200 mg/kg treatment group.

Conclusion The 200 mg/kg okra suspension has a potential lowering effect on blood glucose and a hepatoprotective effect. A longer period of observation with higher doses of okra suspension is recommended to study these effects further.

Key words: Okra, diabetes mellitus, STZ-diabetic rat

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Dr. Fernando S. Sanchez Research and Publication awardee, 24th Annual Research Forum, UERMMMCI Research Institute for Health Sciences, November 23, 2022

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Diabetes mellitus is a condition diagnosed based on either fasting blood glucose levels greater than 125 mg/dL, a random blood glucose level greater than 200 mg/dl, or a glycated hemoglobin glucose level greater than 6.5%.[1] Type I diabetes is caused by total absence of insulin secretion by the beta cells of the pancreas, while Type II is due to a lack of response to insulin or insulin resistance. The rising prevalence of this disease globally, the continued increase of its prevalence in the Philippines, and that diabetes and its complications rank 9th among the leading causes of premature death among Filipinos – despite the availability of free medicines – underscore the importance of treating the disease.[2,3] Reduction of premature death due to non-communicable diseases such as diabetes is included as one of the targets under Sustainable Development

Goal #3 by all member nations of the WHO, including the Philippines.[4]

Diabetes increases the risk of hypertension, ischemic heart disease, stroke and also causes end stage renal disease. These many complications have made the management of diabetes very expensive. The financial burden of the disease is reported to have increased by more than 100% from 2007 to 2017 in the USA.[5] In the Philippines, this is USD 205 million and for Filipino patients, more than 85% of this cost is an out-of-pocket expense.[6,7] The rising cost of pharmacologic treatments for diabetes and the compounded adverse effects of taking multiple medicines emphasize the need to search for possible alternative or complementary medicines.[8]

Many plants, such as bitter melon, onion, cinnamon, and neem have been reported to have a glucose lowering effect involving several mechanisms.[9-12] Okra, also known as "lady's finger", has also been reported by several studies to have promising glucose-lowering activity: the seed, seed coat and whole fruit have been reported to lower blood glucose in animal studies.[13-16] Thanakosai and Phuwapraisirisan were first to report that the okra seeds contain chemicals that inhibit alpha glucosidase, and thus inhibit absorption of simple sugars through the intestinal wall.[17] Sabitha reported that okra seed powder at 100 mg/kg and 200 mg/kg were effective in lowering blood glucose of streptozotocin (STZ) diabetic Wistar rats, and even a dose of 2000 mg/kg did not result in toxic effects.[14] These studies reported on the glucose lowering effect of okra but none compared okra with a standard glucose lowering agent with a similar mechanism of action.[13-16]

In the local literature, the studies of Almeda (2010), Alingod (2015), and Magbitang and Samaniego (2016) involved human subjects, but these reported conflicting results on the effect of okra on diabetes.[18-20] The evidence from the human clinical trials regarding the use of okra as a blood glucose lowering agent is inconclusive because the studies either did not use the same part of the okra fruit, did not use comparable doses of okra based on the animal studies, or did not compare the okra with a drug with a similar mechanism of action. Since no insulin levels were reported in the study of Magbitang and Samaniego, where the subjects involved were healthy people with normal insulin secretion, the absence of an effect by okra on blood glucose levels could not be definitely established.[20] For this reason, it would be necessary to do more animal studies to address these issues.

This research compared the effect of okra seed powder to a drug with a similar mechanism of action when the effect of insulin is controlled or removed by the action of streptozotocin in order to determine if the effects are comparable. The effect of three different concentrations of okra seed powder were compared to the effect of a standard dose of acarbose (positive control) on the blood glucose levels of rats as compared to a group that received only the vehicle solution (negative control). The differences in the mean change of the blood glucose levels of these groups were also compared. The possible adverse effects of the treatments on the liver and pancreas were also determined by identifying the histopathologic changes in these organs and comparing them between groups.

Methods

The proposal for this experiment was approved by the Manila Central University-Institutional Animal Care Use Committee (MCU-IACUC) prior to submission for funding and the necessary permit for its implementation was obtained from the Bureau of Animal Industry.

This research used an experimental design to determine the effects of the independent variable (treatments: okra seed powder at three concentrations, acarbose, and vehicle) on the dependent variable blood glucose expressed as a mean blood glucose change between and within treatment groups at baseline and post treatment at Day 12 (Time 1) and Day 22 (Time 2), and the histopathologic changes in liver and pancreas after a 21-day treatment period as shown in Figure 1.

Following a two-week quarantine period as per IACUC protocol during which time the in-house veterinarian regularly checked for signs of potential illness prior to the experiment (hair coat, nasal passages and eyes), 25 male 8- to 10-week-old Sprague Dawley rats were obtained from the Research and Biotechnology Group of the St. Luke's Medical Center. They were rendered diabetic with a single intraperitoneal injection of streptozotocin (STZ) at 60 mg/kg which selectively eliminated beta cells (Figure 2).[14,21,22] Hyperglycemia was confirmed (FBG > 200 mg/dL) 24 hours after STZ injection by checking the blood glucose levels using the tail vein sampling method.

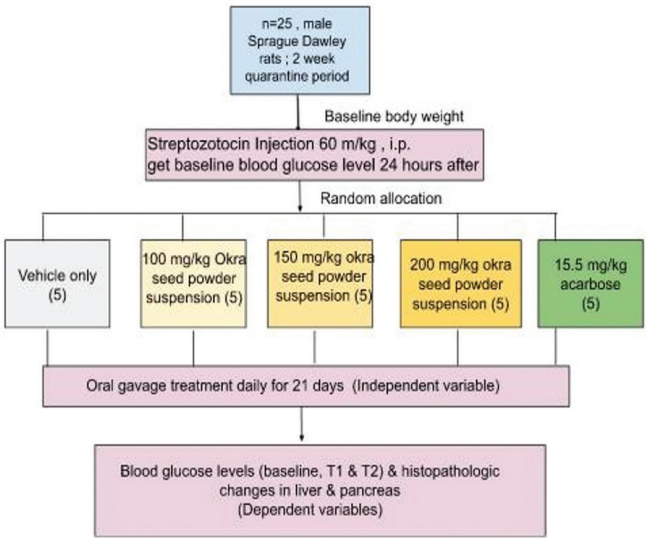

Figure 1. Research protocol

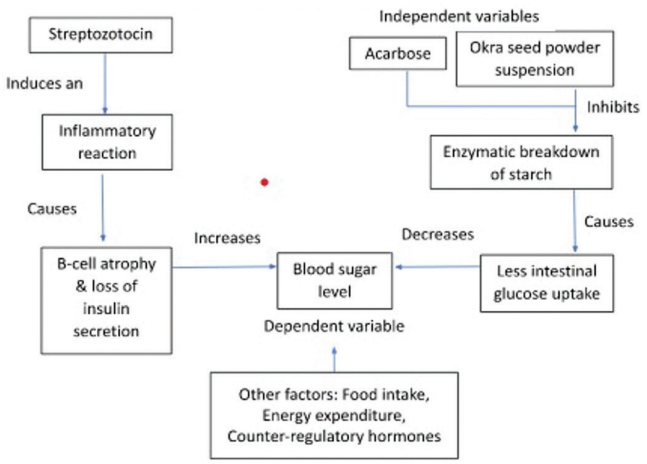

Figure 2. Factors which affect blood glucose

The STZ-diabetic rats were allocated to one of five treatment groups by simple randomization: okra seed powder at three different concentrations (100 mg/kg; 150 mg/kg and 200 mg/kg), negative control (vehicle only), and positive control with acarbose 15.5 mg/kg.[23,24] Each rat was given an oral gavage (maximum volume of 1.5 mL) of the assigned treatment daily for 21 days by a lab technician who was blinded to the treatment group of each rat. The gavage procedure followed the technique described in the Johns Hopkins Animal Care Committee for procedures specific for the rat.[25] The technician who prepared these suspensions was also blinded to the composition of these treatments. Blood glucose was measured using a BTS 350 semi-automatic analyzer (BioSystems SA) with 1 mL of glucose reagent added to 10 uL of serum sample obtained from blood drawn either by tail vein venipuncture at baseline (day 0) and at Day 12 of treatment (T1); and obtained by cardiac puncture on the day of sacrifice, Day 22 (1 day after the 21-day treatment period, T2). Histologic changes in the liver and pancreas at necropsy on Day 22 were assessed qualitatively by a veterinarian pathologist who was blinded to the treatments used on the rats. The research protocol is illustrated in Figure 1.

The rats were housed under standard conditions. Food was standard rat chow, and food and water were available ad libitum. Cages and water bottles were checked daily; food was replenished daily; distilled water was given through water bottles that were also changed daily, and replenished as needed. As per protocol, room temperature was regulated at 20-26ºC; with appropriate ventilation (exhaust fan provided to allow one way flow of air and ensure adequate air exchange and humidity control); light was turned on 12 hours during the day and turned off at night.

All treatment protocols used in this experiment conformed with published and accepted protocols and were accordingly approved by the IACUC. STZ was dissolved in a cold citrate buffer and given intraperitoneally at a dose of 60 mg/kg on Day 0.[22] Okra fruits were purchased from a single online market based in Quezon City, and identified by the Bureau of Plant Industry. The fruits were processed by the Industrial Technology Development Institute of the Department of Science and Technology as follows: fresh seeds were separated from the okra fruit, then oven dried for 16 hours at 60ºC until brittle, then pulverized using a Wiley mill. This process yielded 135 g of seed powder from 10 kg of okra fruit. The following stock solutions were prepared fresh daily by dispersing okra seed powder in 0.2% carboxymethylcellulose: 32.25 mg/mL for the 100 mg/kg group, 48.375 mg/mL for the 150 mg/kg group, and 64.5 mg/mL for the 200 mg/mL group. An appropriate amount (not exceeding 1.5 mL) was withdrawn from the stock solutions daily and gavaged to the rats in the okra treatment groups. The acarbose tablets were ground to a fine powder and were weighed out and dispersed in 0.2% carboxymethylcellulose solution in order to yield a solution containing 5 mg/mL of acarbose. A dose of 15.5 mg/kg, computed to be equivalent to the standard adult human dose, was

given by oral gavage to the acarbose treatment group. The gavage vehicle was a 0.2% carboxymethylcellulose solution used to suspend the okra powder or acarbose powder to be given as an oral gavage. It served as the negative control.

The body weights were determined using an electronic balance. Each rat was weighed at baseline prior to the start of the treatments and every other day during the treatment period; and on the day of euthanasia. Body weights were taken because the oral gavage treatments were based on body weight. Blood samples were obtained to check for blood glucose values at baseline and at T1 of treatment, using the tail vein. Using an immobilization chamber, the tail was exposed and warmed in order to make the lateral tail veins more visible. Under aseptic technique, a sterile scalpel was used to nick the lateral tail vein, and an appropriate volume of blood, not more than 0.5% of the rat's body weight in grams, was collected.[28] The blood was centrifuged to separate the serum. Collection of blood at the day of euthanasia was through cardiac puncture.[29] Blood glucose levels were measured using a BTS 350 semi-automatic analyzer (BioSystems SA).

The rats were sacrificed by CO_2 gas administration in a CO_2 chamber following the NIH Guidelines for euthanasia of rats using carbon dioxide on Day 22 or 1 day after the completion of the treatment period under study.[29] The rats were placed in a CO_2 chamber with flow rate of 7 L/min until the rat stopped breathing and the pupils were dilated. The rat was removed from the chamber after waiting 1-3 minutes following cessation of respiration. Immediately after the rat was euthanized, the blood was collected by cardiac puncture as per NIH guidelines and the liver and pancreas were dissected out, weighed and placed in neutral buffered 10% formalin solution and were subsequently prepared for hematoxylin and eosin staining.[29] Carcass disposal was done in accordance with the approved IACUC protocol of the laboratory. Data was analyzed using SPSS version 23 software. Significant differences in blood glucose were determined between treatment groups in terms of relative change from baseline, using one-way ANOVA with Dunnett's method with acarbose as the referent group. Repeated measures ANOVA was used to analyze the blood glucose levels across the time point collections (baseline, T1 and T2) and $p < 0.05$ was used to indicate statistical significance. Histopathologic changes on the liver and pancreas were described using counts and proportions.

Results

Five rats in each of the five treatment groups completed the experiment. As shown in Table 1, the baseline weights ($p = 0.822$) and blood glucose of the five treatment groups were comparable. The differences in mean blood glucose values between time periods were statistically significant in all treatment groups as shown in Table 2. There was an increasing trend observed in the mean blood glucose values from baseline to Time 2 in the vehicle-only, acarbose, and 100 mg/kg okra seed powder groups. Conversely, this increasing trend was observed up to Time 1 only in the 150 mg/kg and 200 mg/kg okra seed groups, with decreasing levels thereafter. The relative change in the mean glucose values was largest for the acarbose group (46.4% ± 20.5) and least for the 200 mg/kg okra seed group (12.7% ± 9.4) but the differences in this relative change among treatment groups was not significant ($p = 0.087$), as shown in Table 2. The smaller relative change in the 150 and 200 mg/kg okra seed powder suspension groups were reflective of the observed decrease in mean blood glucose values at Time 2. Hence, a potential lowering effect in blood glucose values can be noted in these two doses of okra seed powder suspension. In contrast, the large relative change was reflective of the observed increase in the mean blood glucose values at Time 2 for the acarbose and 100 mg/kg okra seed groups. This was because blood glucose values remained elevated up to the end of the observation period even with treatment (Table 2). However, as shown in the last column of Table 3, using acarbose as the referent group for comparing the relative change from baseline for each of the treatment groups, there was a significant difference was found between acarbose and the 200 mg/kg okra seed powder suspension ($p = 0.040$). This may imply a potential lowering effect of blood glucose values at 200 mg/kg dose of okra seed powder suspension.

There were no significant differences in mean body weights between treatment groups at baseline ($p = 0.822$), Time 1 ($p = 0.215$), and Time 2 ($p = 0.253$). Through time there was a decreasing trend in the mean body weights in all treatment groups except between baseline and Time 1 in the

Table 1. Comparison of baseline weights and blood glucose of the five treatment groups (mean ± SD).

	Vehicle only	Acarbose 15.5 mg/kg	Okra 100 mg/kg	Okra 150 mg/kg	Okra 200 mg/kg
Body weight (g)	274.6 ± 62.0	299.2 ± 76.8	308.3 ± 30.3	290.0 ± 34.2	311.2 ± 42.2
Blood glucose (mg/dL)	352.2 ± 69.5	350.2 ± 71.3	343.4 ± 73.1	368.2 ± 24.9	405.0 ± 45.9

Table 2. Comparison of mean blood glucose values from baseline to end of study period.

	Baseline	Time 1	Time 2	p-value[1]
Vehicle only	352.2 ± 69.5	428.0 ± 118.1	471.6 ± 107.5	0.025
Acarbose	350.2 ± 71.3	438.8 ± 89.4	502.8 ± 64.4	0.002
Okra seed powder suspension				
100 mg/kg	343.4 ± 73.1	384.4 ± 129.3	473.0 ± 68.0	0.018
150 mg/kg	368.2 ± 24.9	514.4 ± 51.7	464.0 ± 34.5	0.001
200 mg/kg	405.0 ± 45.9	490.8 ± 37.3	455.3 ± 53.1	0.015

[1]Repeated measures ANOVA

Table 3. Comparison of relative change from baseline in mean blood glucose between treatment groups.

Treatment groups	Relative change from baseline (mean % ± SD)	Relative change from baseline between treatment groups and acarbose§
Vehicle only	33.9 ± 15.1	0.657
Acarbose 15.5 mg/kg	46.4 ± 20.5	--
Okra seed powder suspension		
100 mg/kg	41.7 ± 28.2	0.978
150 mg/kg	26.2 ± 8.6	0.263
200 mg/kg	12.7 ± 9.4	0.040
p-value*	0.087	

*One-Way ANOVA; §Dunnett's test

vehicle-only (negative control) group and between Time 1 and Time 2 in the 100 mg/kg group where an increase was noted. The differences through time were significant in the 150 mg/kg (p = 0.030) and 200 mg/kg (p = 0.012) okra seed groups as shown in Table 4.

There were no significant differences in the means of the percent to body weights ratios of the liver and pancreas across the treatment groups (Table 5). Histopathological examination of the liver specimens revealed absence of hemorrhage, inflammation, and necrosis in all groups. Mild to moderate cell swelling with few to diffuse granular degeneration was noted in 80% of the animals in the negative control group, 40% in the positive control group, and 75%, 20%, and 0% in the 100, 150, and 200 mg/kg okra seed groups, respectively. Mild fatty change was observed in one animal in the negative control group and moderate fatty change was observed in one animal in the positive control group. No fatty changes were observed in any of the okra treatment groups as seen in Table 6.

Figure 3 shows a representative photomicrograph of severe atrophy of the Islet of Langerhans observed in 40% of the rats in the acarbose group. The rest of the 60% in this group showed very slight to slight

Table 4. Comparison of mean body weights between treatment groups (mean ± SD).

Treatment groups	Baseline Mean ± SD	Time 1 Mean ± SD	Time 2 Mean ± SD	p-value±
Vehicle (negative control)	274.6 ± 62.0	307.3 ± 24.8	306.0 ± 28.8	0.428
Acarbose (positive control)	299.2 ± 76.8	290.0 ± 64.4	278.1 ± 49.9	0.169
okra seed powder suspension				
100 mg/kg	308.3 ± 30.3	259.8 ± 48.1	262.9 ± 51.9	0.428
150 mg/kg	290.0 ± 34.2	251.3 ± 17.6	248.1 ± 13.2	0.030
200 mg/kg	311.2 ± 42.2	277.5 ± 27.6	263.8, 50.1	0.012
p-value*	0.822	0.215	0.253	

*One-Way ANOVA
±Repeated measures ANOVA

Table 5. Average body weight (BW), liver and pancreas gross weights.

Treatment Group	Body weight (g)	Liver		Pancreas	
		Gross weight (g)	% to BW ratio	Gross weight (g)	% to BW ratio
Vehicle (Negative control)	306.0	10.52	3.45	0.97	0.32
Acarbose (Positive control)	272.8	9.92	3.63	0.62	0.23
100 mg/kg	283.4	9.87	3.50	0.69	0.24
150 mg/kg	248.1	9.36	3.78	0.78	0.31
200 mg/kg	275.6	9.91	3.59	0.70	0.24
p-value *			0.265		0.659

*One-Way ANOVA

Table 6. Histopathologic findings in the liver of all treatment groups.

Liver No. (%)	Acarbose	Vehicle only	100 mg/kg	150 mg/kg	200 mg/kg	Overall
Hemorrhage						
none	5	5	4	5	4	23 (100)
Cell swelling/granular degeneration						
none	3	1	1	4	3	12 (52)
mild to mild, diffuse	2	2	2	1	1	8 (35)
moderate, diffuse		2	1			3 (13)
Fatty change						
none	3	4	4	5	4	20 (87)
mild, few		1				1 (4)
moderate, diffuse	1					1 (4)
Hepatic necrosis						
none	5	5	4	5	4	23 (100)
Inflammation						
none	5	5	4	5	3	22 (96)

atrophy. Very slight to slight atrophy was also observed in 60%, 75%, 80% and 75% of the negative control, 100 mg/kg, 150 mg/kg, and 200 mg/kg okra seed groups, respectively. The presence of atrophy in the islets of Langerhans is characteristic of the effect of streptozotocin.[30] No degeneration, necrosis and beta cell vacuolization were observed across all specimens in all groups as seen in Table 7.

Discussion

The mean blood glucose values from baseline to Time 2 increased in all treatment groups. However, the increasing trend was observed only up to 12 days of treatment for the 150 mg/kg and the 200 mg/kg treatment groups. Comparing okra treatment groups to acarbose, the percentage increase of mean blood glucose from baseline to T2 was significantly lowest in the 200 mg/kg okra suspension group ($p = 0.040$). There was absence of fatty change and reduced cell swelling and granular degeneration in the liver of rats treated with okra suspension in this study as compared to positive and negative control groups indicating a possible hepatoprotective effect of okra. Compared to positive and negative control groups, okra-treated rats had lesser cellular swelling and degeneration in the hepatocytes, and this was observed to be a dose dependent effect as no liver cellular swelling and degeneration was observed in the histological sections of the livers of the rats treated with 200 mg/kg.

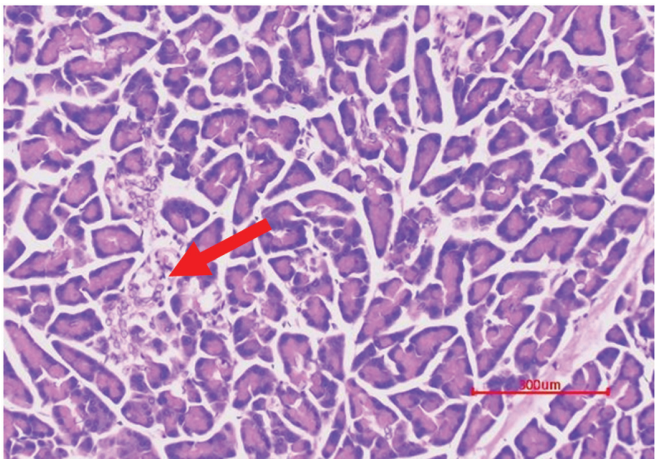

Figure 3. Severe atrophy of the Islet of Langerhans.

Continuous rise in the mean blood glucose levels over the treatment period is evidence that the STZ-treated rats had little ability to lower their blood glucose. This is correlated with the histologic data where low quantity of the islets of Langerhans was observed in 96% (20% had none to almost none and 76% had very few to few Islets), and 64% of the rats had very slight to minimal atrophy while 12% had moderate to severe atrophy. The observed atrophy of islets cells as shown in Figure 3, particularly of the beta cells is a consequence of the STZ treatment.[30] Junod showed a dose-dependent decline in insulin secretion resulting from STZ injection over a period of time, and that 65 mg/kg STZ injection resulted in a significant decline of insulin secretion and resultant

Table 7. Histopathologic findings in the pancreas of all treatment groups.

Pancreas No.(%)	Acarbose	Vehicle only	100 mg/kg	150 mg/kg	200 mg/kg	Overall
Islets of Langerhans						
Atrophy						
none		2	1	1	1	5 (22)
very slight to slight/minimal	3	3	2	4	3	15 (65)
moderate			1			1 (4)
severe	2					2 (9)
Degeneration						
none	5	5	4	5	4	23 (100)
Necrosis						
none	5	5	4	5	4	23 (100)
Beta cell vacuolization						
none	5	5	4	5	4	23 (100)

hyperglycemia in 24 hours.[31] The blood glucose values of all the rats at baseline in this study were consistent with the report of Junod and other researchers who have used STZ to eliminate beta cell function in the study animal.[22,31] The mean blood glucose levels of all groups at baseline were greater than 150 mg/dL and was therefore considered diabetic.[32]

In this study, the histologic examination documented atrophy of the pancreatic islets in the majority of the rats (76%), consistent with the report of Honjo.[30] Given this finding, it is therefore expected that blood glucose in the negative control would have increased from baseline to T1 and T2.

An increasing trend in the mean blood glucose was seen in all the treatment groups, including those that were given an oral hypoglycemic agent acarbose and the okra treatment groups in the three different concentrations. However, the increment in the mean blood glucose values was not as high for the 150 mg/kg and 200 mg/kg okra seed powder groups in contrast to the 100 mg/kg okra seed powder, the negative control and acarbose groups. Therefore, this result shows a potential blood glucose-lowering effect in these two doses of okra seed powder suspension. Post hoc analysis showed that the lower rise in blood glucose at Time 2 for the group treated with 200 mg/kg okra seed powder is statistically significant. The results of the current study further strengthen the findings of local and foreign studies that okra had a glucose lowering effect in human subjects.[13-16,18,19]

Despite the similarity in the findings of the current study with those of Sabitha, there were also differences.[14] In contrast to the study of Sabitha where the effect of 100 mg/kg and 200 mg/kg okra seed powder was evident in the first week of treatment, in the current study, the effect was only evident and statistically significant after three weeks of treatment.[14] This was seen in the percentage change (elevation in glucose) in Time 2 was also statistically significantly lesser compared to the positive and negative control groups. Although the protocol of Sabitha was very similar to the current study, there were slight differences: 1) the study animals were male Wistar rats in the Sabitha study, and Sprague Dawley rats in the current study, and 2) the okra used could be a different variety and possibly could have been planted in different types of soil, such that the active ingredient in the okra seed powder may actually have a different concentration even if the solutions were similar in concentration (200 mg/kg).[14] Gemede reported that okra contains many flavonoids and antioxidants while Thanakosai and Phuwapraisirisan, in a separate study, reported that the okra seed and peel contain – among the many flavonoids – two flavonol glycosides that have the ability to inhibit glucosidases in the rat intestinal epithelium and thus prevent the absorption of simple sugars.[15,17] Based on the analysis of the okra seed powder done by the Industrial Technology Institute, the okra seed powder used in the current study contained flavonoids. However, the amount was not quantified and chemical composition of these flavonoids was not also identified.

In addition, Sabitha reported that the effect of okra seed powder at 100 mg/kg and 200 mg/kg were similar to the effect of glibenclamide at 5 mg/kg.[14] Glibenclamide is a second-generation sulfonylurea oral hypoglycemic agent used to treat Type II diabetes (non-insulin dependent) because its mechanism of action is to increase insulin secretion by acting on the ATP-sensitive potassium channel receptors.[33] In the current study, as evidenced by the histopathologic examination, absence of islet cells and atrophy of remaining islet cells would have meant a limited capacity to secrete insulin in the study animal that was treated with STZ. Elimination of the insulin secretion capacity as a factor in the experiment would be crucial as insulin secretion is known to lower the blood glucose as it is the main glucose lowering hormone in the body. Thus, the logical comparator to the okra seed powder suspension would be acarbose, an alpha glucosidase inhibitor used as an oral hypoglycemic agent.[26] It is also appropriate to test the effects on an animal model where the insulin secretion capacity of the beta cells is greatly impaired by STZ.[22,30,31] The dose that was used in this experiment resulted in a high degree of islet cell atrophy for almost all of the study rats. Since the results of the current study show that okra seed powder at 200 mg/kg, after three weeks of treatment was able to prevent the high increment of the blood glucose at T2 this is evidence that at this concentration, the absorption of simple sugars was likely to have been limited by the action of the active ingredient in the okra seed powder. Thus, the blood glucose did not increase as much as it did from baseline to T1, in an animal model that had none to very little insulin secretion due to the Islet cell atrophy. This effect was not demonstrated in the acarbose solution given at a dose computed based on the human dose of the drug.[24,26] Therefore, the result points to the possible potential usefulness of okra seed powder suspension at

the 200 mg/kg dose for patients with Type I diabetes as a complementary herbal treatment.

Okra is reported to have hepatoprotective effects, however very few studies have described the mechanism. The absence of fatty change and reduced incidence of cell swelling and granular degeneration in the okra treatment groups compared to the acarbose and vehicle only groups may be attributed to this hepatoprotective effect. In a study by Alqasoumi where liver toxicity was induced in rats through administration of carbon tetrachloride (CCl_4). He demonstrated that rats treated with CCl_4 and okra (250 mg and 500 mg/kg) had minimal inflammation while those treated only with CCl_4 had severe necrosis and inflammation.[34] He further discussed that the possible mechanisms of okra extract to protect liver toxicity produced by CCl_4 in rats might be due to following effects: 1) prevention of lipid peroxidation; 2) hepatocyte membrane stabilization; 3) abolition or inhibition of the cytochrome P450-dependent oxygenase activity and 4) enhancement of non-protein sulfhydryls (NP-SH) and total proteins (TP) concentration in liver tissue possibly due to its antioxidative potential.[34] Wahyuningsih reported that a methanolic extract of okra seed pods at doses of 50 to 100 mg/kg BW given to mice for 19 days following treatment with sodium nitrite by gavage showed hepatoprotective effects of okra demonstrated as a reduced proportion of swollen cells, necrotic cells, number of inflammatory cells, and also reduced levels of ALT and AST in the serum.[35] Although the analysis in the current study was somewhat different, the histologic findings of the liver sections of the rats treated with okra showed no significant cell swelling/granular degeneration in a greater proportion of the rats in the 150 mg/kg and 200 mg/kg groups compared to the acarbose and the vehicle only groups. This may be interpreted also as the presence of hepatoprotective effect. However, the current study did not measure liver function (ALT and AST levels).

The results indicate that the 150 mg/kg and 200 mg/kg okra powder solutions resulted in a lower elevation of glucose after three weeks of treatment as compared to acarbose or vehicle only. In addition, the same concentrations of okra also did not produce any adverse histological changes in the liver. The histological changes seen in the pancreas were expected changes due to the effect of STZ causing eventual death and atrophy of islet cells, especially beta cells as these changes were also seen in the negative control that did not receive any treatment other than the STZ.[36] And because similar atrophy of islet cells was seen in the okra treatment and in the acarbose treatment groups, it can also be inferred that the action of okra or acarbose did not change the effect of STZ on the pancreas.

At the end of a 21-day treatment period, the mean blood glucose levels were significantly higher for all treatment groups. However, there was a lower increase in mean blood glucose levels in the 150 and 200 mg/kg okra seed treatment groups that was significantly much less compared to acarbose and vehicle only groups and was statistically significant in the 200 mg/kg group. There was no histologic evidence of hepatocellular damage for all okra treatment groups and a dose-dependent decrease in cellular degeneration most evident in the 200 mg/kg group indicating a hepatoprotective effect of okra seed powder. Thus, 200 mg/kg okra suspension has a potential blood glucose lowering effect and a hepatoprotective effect.

It is recommended that an analysis of the specific concentration of known flavonoids found in okra seed powder be made using different sources of the okra fruit from different parts of the country in order to identify which areas yield the okra seed powder with highest concentration of these compounds. Moreover, the period of observation be lengthened to see if 200 mg/kg okra suspension can produce a lowering of blood glucose, but using a lower dose of STZ to prevent early demise of the STZ diabetic rats. In addition, since higher doses of okra had a hepatoprotective effect, it is recommended to study the effect of higher doses of okra suspension to see if higher doses may produce a glucose lowering effect that may be seen at an earlier time point. Lastly, studies of the efficacy of okra seed powder at least at 200 mg/kg concentration or higher, may be used in an animal model of Type II diabetes mellitus. It may also be used for initial clinical trials for Type I diabetic patients, as it was shown to produce an effect on glucose absorption at the 200 mg/kg concentration of okra seed powder, without any adverse effects on the liver.

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Lived experiences of Filipino Red Cross volunteer nursing students in COVID-19 vaccination programs

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Abstract

Introduction Student volunteers in COVID-19 vaccination activities help augment the health care workforce. However, there is a lack of literature that explores student volunteerism in the Philippines. This paper analyses the shared meanings of the lived experiences of volunteer nursing students during a pandemic.

Methods Student nurses who had joined Red Cross vaccination activities were recruited by purposive sampling and interviewed online using a pilot-tested interview guide with open-ended questions. Participants were recruited until data saturation. The data collected was analyzed using Colaizzi's Seven-Step Method.

Results The study has identified two main themes that describe the phenomenon of student- nurse volunteerism during COVID-19 vaccination programs: 1) *personal motivation* and 2) *perceived benefits and outcomes*. There were four sub-themes under *personal motivation* - desire for personal growth, intrinsic altruism, past experiences and involvement in volunteer work, and opportunity for advocating against vaccine hesitancy. *Perceived benefits and outcomes* had two sub-themes - sense of fulfillment in the act of volunteering and opportunity for actual nurse-patient interaction.

Conclusion: The findings from the study suggest that, despite the lack of experience of working as frontliners during the COVID-19 vaccination programs, nursing students volunteered due to personal motivations and perceived benefits and outcomes.

Key words: Volunteers, students, nursing, COVID-19, vaccination

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People volunteer on a long-term basis as a function of various selfish and selfless motives and specific dispositional variables.[1] The Philippines' volunteer service sector has seen a major consolidation of non-governmental voluntary organizations in the last two decades, with organizations like the Philippine Association for Volunteer Efforts (PAVE) in 1994 and the Voluntary Organizations' Information,

Coordination, and Exchange (VOICE) in 2002. In the light of the COVID-19 pandemic, Filipino volunteers have become increasingly organized and empowered. Student nurses may possess a unique collection of knowledge, skills, and abilities that make them a particularly helpful resource during a health emergency.[2] Although nursing students may lack the precise training and certification required to offer clinical care, they can perform other tasks that could relieve the burden of patient care on professional registered nurses. In the Bachelor of Science of Nursing curriculum in the Philippines, professional courses are threaded from the first year through the fourth year, emphasizing the concepts with corresponding related learning experience (RLE). The BSN curriculum includes an intensive nursing practicum designed to improve nursing skills further and ensure that the BSN program results expected of an entry-level nurse are met (CHED, 2017).[3] Service learning, which is any experiential learning opportunity that combines clear educational goals with service to the community, is an integral part in many health courses because it engages students in patient advocacy and active learning while providing needed health services to underserved populations.[4] A study found that volunteering gives students the "nurse" identity among the student volunteers and non-volunteers.[5] Among volunteer nursing students in Nigeria, 87.8% were ready to care for COVID-19 infected patients only if trained, 85.8% were willing to volunteer if there was protective equipment, and 56.7% were willing to volunteer if paid.[6] Another study noted several motivations to volunteer – interest in a disease (68%), desire to interact with patients (61%) and a general interest in volunteering (57%).[4] On the other hand, despite that 50% of nursing student volunteers reported a desire to use nursing knowledge and skills in relief operations after the 2016 Kumamoto earthquakes, many nursing volunteers engaged in activities that required no nursing knowledge or skills. Because they were nursing students without nursing certification, it is possible that they were viewed as unable to independently perform professional tasks done by the more experienced members of the team.[7]

Healthcare students are perceived to have the moral and professional obligation to volunteer during pandemics. However, existing literature on nursing student volunteerism in the Philippine context is very limited. This study wishes to address the lack of existing literature that supports Filipino nursing student volunteers during the COVID-19 pandemic as these students are seen as untapped resources that can help address the scarcity of healthcare workers, a highly sought workforce in the event of a pandemic. This study was formulated to provide support to volunteer nursing students and to understand how nursing student volunteers as manpower resources can be utilized to assist in the vaccine rollout and distribution as COVID-19 cases remain high, and to aid in the serious decline in the nursing workforce so crucial in fighting COVID-19. This study hopes to provide valuable knowledge to nursing students, nursing education, community health nursing, non-government organizations, and policy-making bodies to support and empower student volunteers.

Methods

The study assumed a philosophical worldview of the social constructivism paradigm to enable participants to construct and share their own meanings of their own experiences. A descriptive phenomenological approach was used to describe and explore the meanings of the lived experiences of volunteer student nurses during Red Cross vaccination programs. Students aged 18 to 23 years currently enrolled in the BS Nursing program in any school in the Philippines who had volunteered in any Red Cross Youth COVID-19 vaccination program at least once were recruited by purposive sampling through posters uploaded on each researcher's Facebook account and through school mates. Those who joined vaccination programs not managed by the Red Cross Youth were excluded. Students who agreed to join the study were scheduled at the interviewee's most convenient time. A 15-minute meeting prior to actual interview was conducted for each participant to explain the study, obtain informed consent, and schedule an interview date. The interview was conducted through online conferencing applications and lasted for about 30-45 minutes. The interviewer followed a pilot-tested interview guide which included open-ended questions. The researchers interviewed in groups of three, with one member being the interviewer, and the two others documenting the proceedings. The researchers continued to gather participants until data saturation was achieved.

The researchers ensured data saturation by conducting a data analysis after every interview. After several interviews, themes were repeating and no more

new themes emerged, indicating that data saturation had been reached. One of the validity and reliability methods the researchers used was bracketing, which was done prior to data collection and analysis - each researcher wrote down his or her own assumptions about the study and what themes he or she thought would emerge, to ensure that there was no bias during data analysis. Another method was part of Colaizzi's Seven-Step Method, seeking verification of the fundamental structure wherein participants were asked to review the themes and to check for any inconsistencies in findings compared to their personal experience of the phenomena.[8]

The researchers followed Colaizzi's Seven-Step Method for data analysis: familiarization which involved reviewing and transcribing recordings; identifying significant themes or statements that answered or were related to the research questions; formulating meanings or interpreting the identified significant statements; clustering themes or clustering of statements that were similar or had the same root into sub-themes; developing an exhaustive description or describing the experience from the participant's view, or how the participant defined a certain experience; producing fundamental structure or the chaining together of themes to describe the phenomenon and to chronicle the shared meanings of the lived experiences of Filipino nursing student volunteers; and verifying the fundamental structure by returning the summarized data to all participants to confirm if the structure made by the researchers was really the participants' experience/s.[8] Significant themes and formulated meanings were organized into tables. Another table was created for the clustered themes.

Results

The researchers interviewed eight student nurses until data saturation was reached. Five of the respondents were females; six were in the fourth year and the two others were in second and third year, respectively. The study identified two main themes that describe the phenomenon of student-nurse volunteerism during Red Cross COVID-19 vaccination programs: personal motivation and perceived benefits and outcomes. There were four sub-themes under personal motivation - desire for personal growth, intrinsic altruism, past experiences and involvement in volunteer work, and opportunity for advocating against vaccine hesitancy. Perceived benefits and outcomes had two sub-themes - sense of fulfillment in the act of volunteering and opportunity for actual nurse-patient interaction. The interrelationship of the themes and sub-themes is shown in Figure 1.

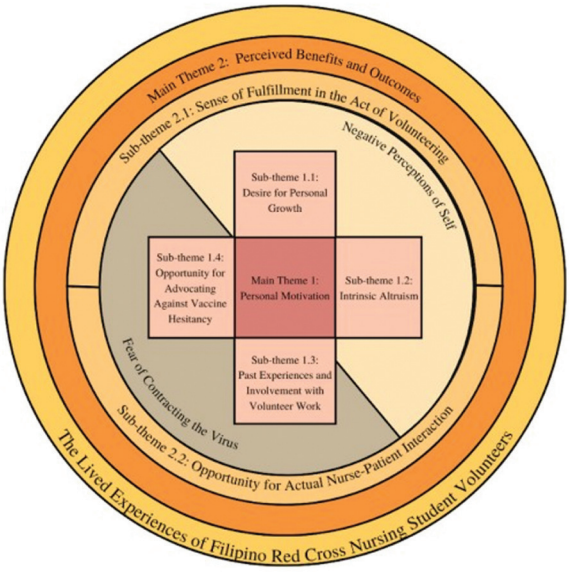

Figure 1. The lived experiences of Filipino Red Cross Nursing student volunteers.

Main Theme 1: Personal Motivation

The lived experiences of student nurses had a recurring theme of *personal motivation* which explained the reasons behind why they volunteered. The respondents talked more about intrinsic motives rather than the external factors that prompted them to volunteer. Although the participants were driven mostly by positive personal motivations, a few participants discussed their negative perceptions of themselves as volunteers because of their inadequate experience as students.

Sub-theme 1.1: Desire for personal growth

All the respondents mentioned being able to practice their nursing skills as one of the main motivators for volunteering. One participant said, "help me gain uh new experience and improve my skills so I um that opportunity, isa yung malaking opportunity for me to enhance nga my skills." Not only were nursing skills developed, most mentioned other crucial assets for nurses that could be learned and practiced, including communicating with patients

and health education, as well as important values that they deemed necessary for a nurse. This was seen in one participant saying, "mas nagiging open minded ka, tapos parang nagkakaroon ka ng additional insights dahil sa pakikisalamuha sa mga uhm tao," and another said, "to be more grounded or become more empathetic kasi parang lahat maraming tao kasi dun sa vaccination sites, may mayaman, may di gaanong mayaman… mas namulat ako na hindi talaga lahat makaka afford or nakukuha ang mga bagay na kailangan nila. Mas na-appreciate ko na dapat maging ano mas maging thankful." Aside from that, some of them volunteered with the belief that having the experience would not only add to their credentials but also help them improve themselves as future professional nurses; as one participant said, "it is good for our CV… Yah, you'll get certificates for it".

Sub-theme 1.2: Intrinsic altruism

The respondents expressed intrinsic altruism as their personal motivation in volunteering. They basically want to care for other people; they perceived participation as a chance to help and serve others. Participants verbalized: "as a student nurse parang andun na sa aking - nasa, nasa puso ko na [to help]" and "gusto ko ma-try kase parang yun nga, yung feeling na (pauses) na satis- na satisfied ka to help other people." Volunteering also meant expecting nothing in return for services offered, according to one respondent, "[volunteerism is] willingness to help without any hesitation and asking for something in return." Moreover, the healthcare worker-patient ratio during vaccination programs was observed by the nursing student volunteers as inadequate to meet patient demands such that it prompted them to extend help to the nurses and other healthcare workers. They saw their volunteering as a means to increase manpower during the pandemic. This was seen as participants verbalized "kulang daw yung healthcare workers sa kesa sa ratio ng patient or ng mga iva-vaccine kaya nag - kailangan nila ng help sa student nurses para matulungan sila or madagdag" and "konti lang po talaga yung uh yung nagiging volunteers natin most especially during the pandemic pero yung konting yon parang super laki sa help sa healthcare workers natin, considering na gamit na gamit na yung health care providers natin during the pandemic tapos medyo kulang pa nga actually.. as volunteers, tayo na yung parang tumutulong."

Sub-theme 1.3: Past experiences and involvement in volunteer work

One respondent said that his parent's invitation to previous volunteer activities during childhood influenced his decision to volunteer. "Actually, I think my volunteering time started nung elementary pa, kasi nung sa previous school ko yung mom ko kasi teacher tapos usually may mga school events na nag cacater sa mga adopted barangay ng school namin, so usually inaaya ako ng mom ko na parang [sali tayo sa ganito]." It was also seen among volunteers that previous exposure to activities outside the Red Cross encouraged one respondent to volunteer. One participant mentioned, "iniinvite lang ako ng outside sources, like out of the blue like "hey do you wanna join?... ininvite lang talaga ko… minsan Pasay, minsan Rizal, uh minsan Quezon City, kaya na-expose din ako at nag volunteer sa vaccination."

Sub-theme 1.4: Opportunity for advocating against vaccine hesitancy

Some respondents shared their experiences discussing the importance of receiving the vaccine. One participant expressed, "So ayun parang na-kwento nila na uh ayaw daw nila, na ayun hesitant pa din sila magpa vaccinate tapos ni-rerequire daw ng office nila kaya lang daw sila nandun, para magpa-vaccine so most of the time sinasabi ko, ah ito na yung chance para ma-educate mo sila for vaccination na hindi lang sila napipilitan for the purpose of their work to like help themselves para maka-cope din sa pandemic." They saw volunteering as an opportunity to educate individuals about vaccine hesitancy. Some volunteers even stated that they were volunteering because they wanted to fight vaccination reluctance. For student nurse volunteers who deliver health education to vaccinees who only got the jab because it was required, the problem of vaccine reluctance was addressed not just before, but also during, and after vaccination. Volunteers were aware of their purpose as nurse advocates. One participant said, "At tsaka ano kasi no'n diba nakakainis 'yong mga taong ayaw maniwala sa vaccine no'n 'yong mga time na bago pa lang 'yong vaccine kasi no'n eh noong nag-volunteer kami."

Main Theme 2: Perceived Benefits and Outcomes

The study also noted another recurring theme which is the perceived benefits and outcomes. Volunteering is thought of as an act of generosity which one does not for the benefit it bestows but for the betterment of the community. However, volunteering does not mean that a volunteer could not earn any benefit. The respondents were aware of the benefits of volunteering and understood what it could do for them in the future in terms of career opportunities. Some understood that volunteering could further improve their knowledge for their profession in the future while some saw it as an opportunity to further improve their resume. Volunteering for them was seen as a way to enhance their skills and credentials.

Sub-theme 2.1: Sense of fulfillment in the act of volunteering

A participant said, "although malayo parang pursigido pa din kami na pumunta dun kasi sobrang exciting din kasi nakalimutan ko na feeling pero ayun exciting at the same time sobrang ano ang ganda, ang satisfying sa feeling, ang fulfilling." The respondents felt that volunteering was fulfilling because they were able to use their nursing skills again since they did not have any face-to-face interaction with patients during the pandemic. Participants verbalized "during vaccination nag take kami ng vital signs siguro mga around 500 yung inassess namin… pagkatapos nun sobrang sakit ng kamay namin pero ayun mas iniisip namin na ano na fulfilling siya kasi naka help kami." and "masaya siya yon fulfilling yung feeling ko non." It was observed that they felt a sense of accomplishment for doing good and assisting others. Despite the tedious and tiring workload, they said volunteering was fulfilling.

Sub-theme 2.2: Opportunity for actual nurse-patient interaction

Several participants expressed their longing for experiential learning since the pandemic had prevented face-to-face classes. The student volunteers perceived the COVID-19 vaccination program as an avenue for actual nurse-patient interaction which they missed because of the health protocols and lockdowns. For the nursing student volunteers, performing tasks like data collection was already a part of their experience in handling a patient, with one participant saying, "miss ko na din kasi mag-handle ng patient kahit na nagsusulat lang kami ng data ganyan." They were actively engaged in the process during the vaccination programs and took the opportunity to communicate with people. They demonstrated their enthusiasm for educating people who were only getting vaccinated because of job requirements in a face-to-face setting.

Discussion

It is a shared characteristic among volunteers, including Filipino student volunteers, to be pushed by personal motivation to do volunteer work. Volunteers are people who have high intrinsic motivations to improve themselves. Student nurses volunteer because they see that this activity fuels an intrinsic motivation for them to grow into competent nurses. They seek these opportunities to improve competencies needed as a student nurse. This mirrors a study in Japan, wherein the topmost motives of many participants for volunteering were also centered on intrinsic values, their 1) willingness to support the victims, 2) engage in reconstruction support activities in affected areas, and 3) utilize the knowledge and skills they had gained as nursing students.[9]

The prevalence of online classes during the pandemic produced a lack of skill practice or experience and was recognized by the student volunteers as a weakness and something to improve on. Similarly, student volunteers from Spain reported feelings of stress due to the novelty of the virus and lack of knowledge about pandemic and disaster management.[10] Volunteering provided the following educational benefits: learning soft skills such as social skills, organizational skills, and stress management by communicating under stress. Volunteer programs enabled them to engage in authentic nurse-patient communication, which was scarce in regular university education.[11] Although the pandemic caused serious disruption in health professions education, student volunteerism is a viable solution for such disruptions, as it also provides patient contact opportunities that may complement remote learning.[11] This showed the participants' desire for personal growth, as there was an intention to improve as a student nurse. Moreover, many participants verbalized their negative perceptions of themselves after volunteering because they were able to recognize the gap between online

demonstrations and real-life skills and recognized some areas they had hoped to improve on.

Altruism is seen as another driving force behind the interest in volunteering in the present study. According to Llenares and Deocaris, the primary reason for volunteering, grounded on the theory of selflessness and altruism, is to help others.[12] The authors added the motivation to volunteer can either be intrinsic or extrinsic.[12] Volunteers driven by intrinsic factors extend themselves out of personal enjoyment, interest, or pleasure. The definition of one respondent is shared by the same authors who cited volunteerism as a phenomenon where an individual or a group act to share resources (time, money, skills, etc.) in response to the need of others without expecting any material reward or incentive.[12] Student volunteerism is recognized as an educational motivation as it assists the overburdened health system and is recognized as a solution to staff shortage during the pandemic.[11] Key factors such as previous volunteer experiences are positively associated with volunteering, confirming that it is an important determinant in predicting likelihood to participate in voluntary work.[13] Moreover, volunteering in schools is also linked to a greater possibility of students engaging in future community service and service-oriented professions.

According to Seah, "pre-registered healthcare students, when equipped with the right skills and knowledge, can render great support to the formal healthcare workforce."[5] Nursing students grabbed the chance to volunteer as they believed that this experience could hone and nurture their nursing skills even make them stand out. A study by the Center for Economic Policy Research found that "volunteering is in fact associated with a significant improvement in job prospects." Student volunteers identified volunteering as a great opportunity to apply nursing knowledge and skills in "real-life scenarios". They looked forward to seeking "new, interesting, and meaningful learning experiences".[5] Volunteer work can highlight one's abilities, skills, and sense of altruism especially if he/she is a novice nurse. Volunteering is seen as an act of compassion since it is done for the greater good of the community rather than for personal gain. Most of the respondents were also aware of the advantages of volunteering and what it could mean for their career prospects. They also saw volunteering as an opportunity to gain more knowledge and improve their skill and expertise in nursing. Volunteering for them was considered a chance for them to simultaneously strengthen their abilities and credentials for their future.

Volunteering gave students the feeling of taking part in the fight against the pandemic, which provided them with self-satisfaction and a career-related experience.[14] Through volunteering, student nurses lent their time and skills to help in vaccination programs. The participants felt joy since they had the opportunity to help and use their nursing skills and gain new experiences. They felt a sense of satisfaction and fulfilment through these volunteer programs. Despite the venues being far from their homes, the student nurses still felt motivated to join the volunteer programs. The tasks of these volunteers ranged from doing paperwork, monitoring patients to vaccinating. Participants expressed that they felt that volunteering was fulfilling despite the workload being tedious and exhausting. Although nursing students expressed how difficult the situation had been, they saw their experiences as a source of personal and professional growth, which led to the sense of fulfillment.

The findings from the study suggest that despite the lack of experience of working as frontliners during the COVID-19 vaccination programs, nursing students volunteered for personal motivations and perceived benefits and outcomes. Personal motivations included improving their skills as a nurse, having the desire to help others driven by innate altruism, past volunteering experiences that led to the desire to volunteer again, and the opportunity to advocate against vaccine hesitancy. In addition, respondents also expressed their own perceived benefits and outcomes such as the feeling of satisfaction and fulfillment from doing volunteer work, having the opportunity to interact with patients, and viewing their experience in volunteering as something that could be helpful in their future careers.

The study findings also show similarities between the motivation of Filipino nursing students to volunteer, as well as with the motivation of student nurses in other countries such as Japan, Spain, and Singapore, specifically their altruism and dedication to provide assistance. The interviews were carried out online which resulted in internet connectivity-related issues in certain interviews. This also restricted the group from fully understanding the nonverbal cues observed during the interview.

Acknowledgements

To the Dean of the UERMMMCI - College of Nursing, Dean Betty F. Merrit, MN, RN, the authors would like to express their deepest gratitude and appreciation. To their Nursing Research faculty, Prof. Wilhelmina Atos, MAN, RN and Prof. Paulo Carl Mejia, DNS, DNM, RN for sharing their skills and knowledge which helped them conduct and write this research. To the research defense panelists, Prof. Flory May G. Agustin, MAN, RN; Prof. Melissa E. Alarzar, MAN, RN; Prof. Mildred G. Glinoga, PhD, RN; Prof. Carmelita C. Salvador, MAED, AS; and Prof. Razel Custodio, MAN, RN for their critique and for sharing their valuable knowledge and insights to help them write a better thesis. They cannot express their most profound gratitude through these words. To their participants who helped in their research without second thoughts, they appreciate their help and their valuable time that they gave them despite their busy schedules.

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Prevalence of burnout and its perceived contributing factors among Level III physical therapy students

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Abstract

Introduction Physical therapy students, who train on how to handle patients, also experience burnout due to social, academic, and personal factors. The study aimed to determine the prevalence of burnout among third year physical therapy students of UERM and the factors that contribute to it.

Methods A descriptive cross-sectional research design was used to determine the prevalence of burnout and its perceived contributing factors. Eligible students answered the Maslach Burnout Inventory General Survey for Students (MBI-GS(S)) and a self-developed questionnaire regarding academic, social, and personal factors of burnout. Microsoft Excel was used to compute the standard (*z*) values and prevalence rate.

Results None of the 26 respondents fit the criteria to be classified as "burnout", however 42.3% were "overextended", 34.6% were "ineffective" and 23.1% were "engaged". The top factors reported by the participants were too much workload to handle, being left behind academically compared to peers, and pushing oneself too hard for the academic, social, and personal categories, respectively

Conclusion None of the limited number of respondents met the criteria for "burnout". The most perceived academic reason contributing to their burnout is the volume of workload. The feeling of being left behind academically compared to their peers was shown to be the most perceived social factor. The tendency to push themselves too hard to accomplish their task perfectly/completely was seen as the most perceived personal factor in this study.

Key words: Burnout, physical therapy, students, college students, contributors, factors

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As the prevalence of burnout rises globally amidst the pandemic, it is noteworthy to look at how many of our students experience burnout. Physical therapy students, who train on how to handle patients, may also experience burnout due to social, academic, and personal factors. These factors were noted to be recurring in the literature on students in the medical field due to high physical and academic demands.[1-6] The study looks at how prevalent burnout is among

third year physical therapy students of UERM and determines what factors contribute to it. Third-year physical therapy students were chosen as the participants of the study as they are taking major subjects which are more difficult than their other subjects. The results could then provide additional information regarding burnout among students and could therefore be used as reference to create an intervention on how to best handle burnout among students. Knowing the presence of academic, personal, and social contributing factors and determining what students feel as the most contributing factor would help future researchers and the staff to address the issue.

Methods

A descriptive cross-sectional research design was used to determine the relationship between the variables burnout and its perceived contributing factors. The population of interest were third year physical therapy students in UERMMMCI enrolled in SY of 2021-2022 with a 25-unit load; those who had a part-time job were excluded. Google Forms was utilized as a means of data collection. The researchers started collecting data by posting recruitment posters on Canvas Homeroom, the school's learning management system, with the link to the consent form and questions regarding the demographics provided. Participants answered the Maslach Burnout Inventory General Survey for Students (MBI-GS(S)) and the self-developed questionnaire regarding factors of burnout.[7]

The MBI-GS(S), designed to assess burnout in college and university students, consists of 16 items and takes 10 to 15 minutes to answer. It consists of the subscales emotional exhaustion, cynicism, and professional efficacy.[7] Emotional exhaustion is a feeling of being overextended and exhausted by one's studies.[7] Cynicism is defined as indifference or a distant attitude towards one's studies while professional efficacy is satisfaction with past and present accomplishments, and it explicitly assesses the student's expectations of continued effectiveness in school.[7] A respondent is classified as having a "burnout profile" by attaining high scores in emotional exhaustion and cynicism that are beyond the computed critical boundaries and a low score in professional efficacy.[7] The reliability of the three MBI scales in the various versions exceeds the recommended levels for research instruments and the validity of the MBI in its multiple versions has been demonstrated by numerous studies and meta-analytic reviews that confirm hypotheses about the relationships between job attributes and experienced burnout.[7] The self-developed questionnaire is designed to measure the perceived factors of burnout among students with high levels of burnout. It is a ranking type of questionnaire of possible factors collated from the literature. Items are under three subcategories: academic, social, and personal. Factors in each subcategory are ranked from 1 (most perceived reason) to 7 (less perceived reason).

Microsoft Excel was used to compute the standard (z) values and prevalence rate. The MBI-GS(S) scores were analyzed using the scoring key provided by the MBI Manual to determine if the respondent's score in each sub-category indicates the presence of burnout. The Perceived Contributing Factors questionnaire was analyzed by obtaining the weighted average scores for each factor and ranking them from highest to lowest.

The study was approved by the Ethics Review Committee of the Medical Center RIHS (ERC Code 0933/C/2021/014; approved June 28, 2021).

Results

Twenty-six out of 85 third year physical therapy students studying at the University of the East Ramon Magsaysay Memorial Medical Center participated in the study. Their mean age was 20.4 years; 61.5% were female. None of the 26 respondents fit the criteria to be classified as "burnout", however 42.3% were "overextended", 34.6% were "ineffective" and 23.1% were "engaged" as shown in Figure 1. Table 1 shows that many of the respondents had high averages in emotional exhaustion and professional efficacy, and low levels of cynicism, resulting in 4 out of 10 respondents being "overextended" (Figure 1). Nine respondents scored low in professional efficacy, putting them in the "ineffective" group (Figure 1). The top factors reported by the participants were too much workload to handle, being left behind academically compared to peers, and pushing oneself too hard for the academic, social, and personal categories, respectively, as shown in Table 2.

Discussion

Maslach defined burnout as having scores in emotional exhaustion and cynicism that are beyond the computed critical boundaries.[8] Since none of the participants

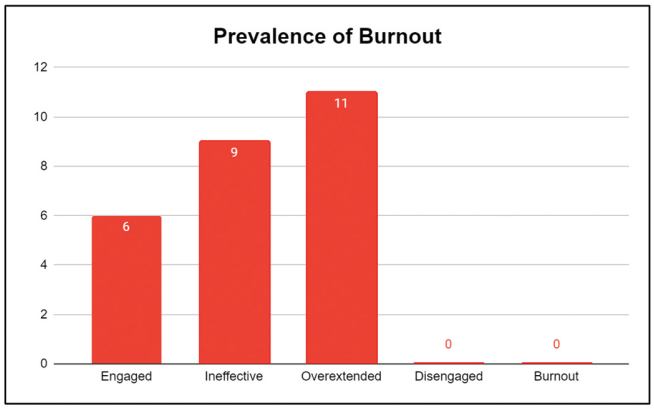

Figure 1. Prevalence of burnout among 26 respondents.

Table 1. Summary of results of subscales of the Maslach Burnout Inventory General Survey for Students (MBI-GS(S))

Subscales	Mean score ± SE	Frequency (%) exceeding critical boundary
Emotional exhaustion	4.72 ± 1.48	11 (42.3)
Cynicism	3.65 ± 1.73	0
Professional efficacy	3.91 ± 1.48	15 (57.7)

Table 2. Top three academic, social and personal factors among 26 respondents.

Academic
Too much workload to handle Rushed with meeting deadlines Inability to keep up with fast-paced lectures
Social
Left behind academically compared to peers Exhausted studying alone Stress of peers performing better
Personal
Pushing oneself too hard Inability to get enough sleep Withdrawn in the online setup

had an average score above the critical boundary in the cynicism subscale, the participants could not be classified as having a "burnout" profile. However, almost half (11/26) of the participants were found to be overextended meaning that they experienced work overload in their studies. According to Maslach, an "overextended" profile was defined as individuals who attained high scores on the emotional exhaustion subscale of the MBI-GSS beyond the computed critical boundary.[8]

In contrast to a study in 2022 on pharmacists using the MBI–General Services and MBI–Health Services in assessing the presence of burnout, it was seen that the average scores on the emotional exhaustion and cynicism subscales were lower, indicating less degree of burnout, although the study's population was exclusively pharmacists. There is still limited literature when it comes to assessing burnout using the Maslach Burnout Inventory exclusively on physical therapy students.[1]

Overall, the most perceived academic, social, and personal factors were all consistent with current available studies. The "feeling of too much workload" was ranked as one of their most perceived factors as to why physical therapy students likely experience burnout. This is consistent with the study of Yang that course load is the biggest factor of stress in students.[9] In this study, the most perceived personal factor that most likely contributed to burnout is that students push themselves too hard to be able to do their task perfectly/completely (Table 2). Literature indicates that perfection, being competitive, and being self-driven were also noted to trigger burnout.[2-4,10] However, this study showed that the least perceived personal factor was having too many responsibilities outside school which was in contrast with studies stating that personal-life or family-related events greatly affect the possibility of developing burnout.[5,6] None of the limited number of respondent physical therapy students had burnout defined as having high levels of emotional exhaustion, high levels of cynicism and low levels of professional efficacy. The most perceived academic reason contributing to their burnout was the volume of workload. The feeling of being left behind academically compared to their peers was shown to be the most perceived social factor. Finally, the tendency to push themselves too hard to accomplish their task perfectly/completely was seen as the most perceived personal factor in this study.

Acknowledgements

The authors extend their deepest gratitude to Ms. Jeshanah M. Villones, PTRP; Ms. Anna Margarita

A. Lugue, CPO; Ms. Jaira Mari A. Paat, PTRP; and Ms. Ma. Louise Katrina M. Gonzales, PTRP for the continuous support and assistance in their study. They also would like to acknowledge the valuable feedback and assistance from Ms. Michelle Bautista, the authors' psychometrician, in creating the self-developed questionnaire. Finally, they would like to thank all the 3rd year physical therapy students who contributed to the study.

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Effectiveness of chia (*Salvia hispanica L.*) as an adjuvant therapy for Type 2 diabetes mellitus: A systematic review and meta-analysis

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Abstract

Introduction Salba-chia (Salvia hispanica L.) is a popular functional food containing high levels of protein, total dietary fiber, and is an excellent source of α-linolenic acid. Chia seeds significantly decreases weight, suppresses appetite, and has a potential benefit in the management of Type 2 diabetes mellitus (T2DM). This study aimed to determine the effectiveness of chia seeds as an adjuvant treatment for T2DM.
Methods Randomized controlled trials from 1990 onwards involving Type 2 diabetic patients given chia seed were included. PubMed, Cochrane, ClinicalKey, Google Scholar, and Hinari were searched systematically using MeSH terms "chia", "*Salvia hispanica*", "dietary supplement", and "diabetes". The quality of trials was assessed using the Cochrane Collaboration tool. Data on the study design, blinding status, characteristics of participants, medications taken by participants, chia seed intervention, comparator, duration of intake, and interval of assessment were extracted. The percent change of outcome from baseline was compared between the chia and control groups.
Results Four randomized trials with a total of 213 diabetic patients were enrolled in the treatment group using ground salba-chia or the control group using bran. The supplementation of chia resulted in a statistically significant decrease in fasting glucose (-2.90 mmol/L; 95% CI, -3.08, -2.72; $p < 0.001$), waist circumference (-2.49 cm; 95% CI -2.81, -2.17; $p < 0.001$), total cholesterol (-2.72 mmol/L; 95% CI -3.68, -1.74; $p < 0.001$), HDL (-3.69 mmol/L; 95% CI -3.95, -3.42; $p < 0.001$), LDL (-3.22 mmol/L; 95% CI -4.08, -2.36; $p < 0.001$); and an increase adiponectin levels (6.50 mg/L; 95% CI 6.25, 6.25; $p < 0.001$).
Conclusion Intake of chia seeds resulted in a statistically significant decrease in fasting blood glucose, waist circumference, total cholesterol levels, HDL and LDL cholesterol levels, and increased adiponectin. Chia seeds are generally safer and have lesser side effects compared to the placebo. Chia is effective as adjunctive treatment for Type 2 diabetic patients.

Key words: Chia, Type 2 diabetes, glycemic control, appetite suppression, dietary supplement, adjunct, adjuvant

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There is an increasing popularity of chia seeds in the Philippine market as a possible therapeutic option for a variety of common diseases such as diabetes, obesity, and cardiovascular problems. Chia seeds contain high levels of protein (16-26%) and total dietary fiber (23-41%). It is an excellent source of polyunsaturated fatty acids such as α-linolenic (60%) and linoleic (20%) acids.[1,2] Studies have shown that these nutrients have a significant effect in weight

control and in some cases, in improving cardiovascular disease risk factors.

A literature search showed one meta-analysis on dietary supplementation with chia seed covering all health conditions.[3] Two previous reviews summarized the evidence on the effects of chia seed but used very broad inclusion criteria (i.e., non-human studies and non-clinical trials) and evaluated the cardiovascular risk factors only.[4,5] The objective of this study is to determine the effectiveness of chia seeds as an adjuvant treatment for Type 2 diabetes mellitus in terms of reduction or improvement of glycemic control, waist circumference, and its effect on the lipid profile, and safety through a systematic review of available clinical evidence in humans.

Methods

This meta-analysis was performed in accordance with the principles outlined in the Cochrane Handbook for Systematic Reviews of Interventions and is reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.[6,7] The studies for inclusion were randomized clinical trials from 1990 onwards in English involving patients with Type 2 diabetes mellitus - not limited by age, sex, and race - whose interventions used chia seeds (in any functional form) as an adjuvant therapy directly compared with another drug or supplement or placebo, and whose outcome of treatment success included but was not limited to reduction or improvement of glycemic control, weight loss, and reduction of waist circumference.

The literature search was conducted from September 9 to 20, 2020 on MEDLINE (PubMed), Cochrane Library (CENTRAL), Clinical Key (Elsevier), Google Scholar, and Hinari. Search strategies for each of these databases were developed using Medical Subject Headings (MeSH) terms, including keywords: "chia", "chia seeds", "salvia", "Salvia hispanica", "salvia and chemistry", "seeds and chemistry", "alpha-linolenic acid and blood", "dietary supplements", "chia supplementation", "supplementation", "adjuvant therapy or adjuvant", "overweight", "obesity and blood", "metabolic", "metabolomics and methods", "hyperlipidemia", "lipid profile and lipid", "LDL", "HDL", "triglyceride, "blood glucose", "lipoproteins and blood", "dietary fats and blood", "effect", "diabetes", "glycemic", "Hba1c", "weight loss", "satiety", "insulin", "chia and adjuvant therapy", "chia and diabetes", and "chia and dietary supplementation". Five pairs of review authors independently screened the titles and abstracts obtained in the search against the inclusion criteria. These were then assessed by the primary investigator and another main author for eligibility. The full reports were then obtained for all titles that met the inclusion criteria or when there was uncertainty. All review authors then screened the full text reports, decided whether these met the inclusion criteria, and then recorded the reasons for exclusion. Disagreements were resolved through discussion. No review authors were blinded to the journal titles or to the study authors or institutions.

Five teams of review authors extracted data independently and in pairs from each eligible study using REVMAN. All review authors utilized a standardized data extraction sheet (i.e., web-based Google Docs Office Suite) to extract the characteristics and results of the clinical trials. Data extracted were the demographic and clinical characteristics of the subjects (mean age, gender, baseline diabetes profile, and medications), trial design, trial size, frequency and duration of treatment, composition and form of chia seed and its comparator used, medications given, daily quantity intake, diet control, duration of intake and duration of follow-up. Whenever possible, results from an intention to treat analysis were used.

Critical appraisal of each article was done using the Center for Evidence-Based Medicine (CEBM) Critical Appraisal Tool to assess the risk of bias. To facilitate the assessment of risk of bias for each study, the researchers collected information using the Cochrane Collaboration tool for assessing the risk of bias which covered sequence generation, allocation concealment, blinding, incomplete outcome data (e.g., dropouts and withdrawals) and selective outcome reporting. All data were encoded using RevMan 5.4.1.

Outcomes of interest included the following: glycemic control based on glycosylated hemoglobin (HbA1c) and fasting blood glucose; effect on waist circumference, lipid profile, and on adiponectin. The percent change of outcome from the baseline was compared between the chia and control groups. The results were expressed as mean differences with 95% confidence intervals. A statistical significance level of $p < 0.05$ was used together with 95% confidence intervals. Relative risk was used to determine the risk of an outcome or side effect in both chia and control groups. A relative risk < 1.00 was deemed to

have a decreased risk of experiencing the side effect. Statistical heterogeneity was evaluated by chi square and I-test. The authors used an I2 > 75% and a $p < 0.01$ for chi-square as indicative of statistical heterogeneity.[8]

Results

The electronic search yielded a total of 166 articles of which 63 were screened. Thirty of the screened articles were deemed relevant and their full texts were retrieved for review. Twenty-six articles were excluded because they included non-diabetic participants (n = 6), did not use chia as adjunct therapy (n = 6), or had inadequate data (n = 14). Thus, only four trials involving 213 participants were included in this review. The flow diagram of study selection is shown in Figure 1.

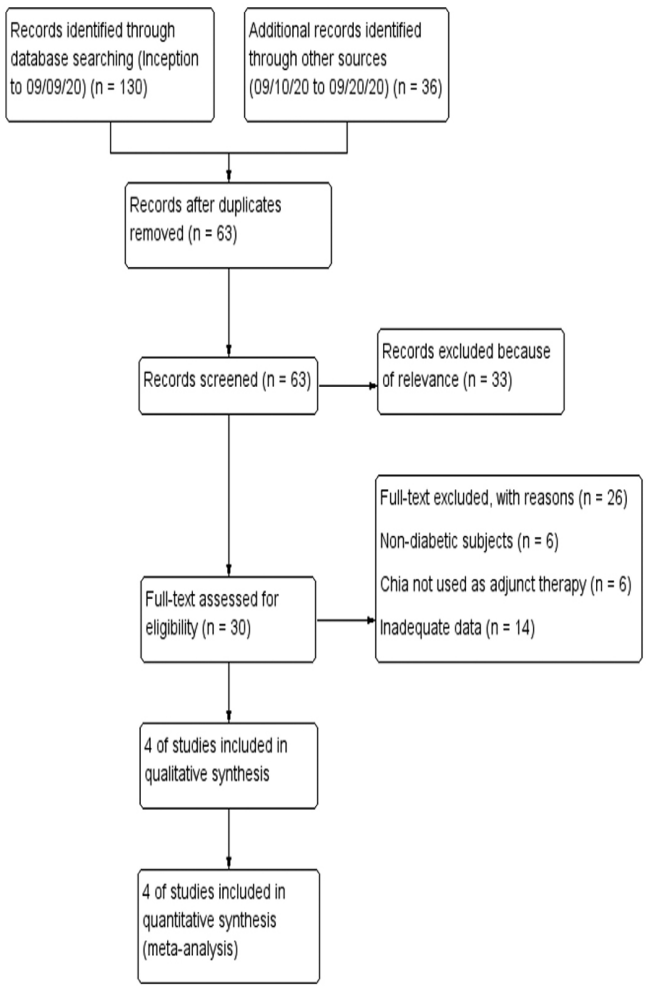

Figure 1. Flow diagram of the article screening and selection process.

The characteristics of the four included studies are summarized in Table 1. All trials were conducted in Canada. Three studies utilized a double-blind parallel design and their primary inclusion criteria consisted of those with Type 2 diabetes mellitus of one year with baseline HbA1c levels between 6.5 and 8.0%.[9,10,11] One study used a single-blind cross-over design and included those who had Type 2 diabetes mellitus of at least six months duration.[12] All studies required that the participants be treated with diet and/or oral hypoglycemic medications. Medications received concomitantly by the participants were either single or combined oral hypoglycemic agents such as insulin secretagogues, metformin, pioglitazone, HMG-CoA reductase inhibitors, atorvastatin, and simvastatin. Ground salba-chia was the main form of treatment for all studies. The control in three studies was oat-bran while one study used wheat-bran.

Most studies had a low overall low risk of bias as shown in Figure 2. The risk was low except for attrition bias as all four studies had attrition rates of 25%, 26%, 32%, and 26%, making them high risk, as shown in Figure 3. Vuksan's 2007 study did not do an intention-to-treat analysis (Figure 3).

There was a statistically significant decrease in the fasting glucose level of 2.90 mmol/L (95% CI -3.08%, -2.72%; $p < 0.001$; $I^2 = 0\%$, $x^2 = 0.81$) in the studies of Brisette and Vuksan (2007) as shown in Figure 4. Two out of three studies showed an increase in HbA1c levels; however, the overall effect was not statistically significant (1.03%; 95% CI -1.43, 3.50; $p = 0.41$; $I^2 = 100\%$, $x^2 < 0.001$) as shown in Figure 5. Two studies showed a significant mean decrease in body weight and two showed an increase. The result was an overall 0.64 kg (95% CI (-1.85, 0.57; $p = 0.30$) decrease which was not statistically significant. Three studies showed a significant mean decrease in the waist circumference ranging from 2.40 to 3.10 cm. The overall decrease of -2.49cm (95% CI (-2.81, -2.17; $p < 0.00$; $I^2 = 0\%$, $x^2 = 0.42$) was statistically significant, as shown in Figure 6. Brisette and Vulcan (2007) showed a statistically significant decrease in the total cholesterol of 2.72 mmol/L (95% CI -3.69, -1.74; $p < 0.001$; $I^2 = 0\%$, $x^2 = 0.67$), as shown in Figure 7. The summary data of both studies showed a statistically significant decrease in the HDL (-3.69 mmol/L (95% CI -3.95, -3.42; $p < 0.001$; $I^2 = 65\%$, $x^2 = 0.09$) and LDL-C levels (-3.22 mmol/L; 95% CI (-4.08, -2.36; $p < 0.001$; $I^2 = 0\%$, $x^2 = 0.80$), as shown in Figures 8 and 9. Brisette and Vuksan (2016) demonstrated a statistically significant

Table 1. Characteristics of included studies (n = 4).

Reference	RCT design; blinding status (stated by the author)	Total no. of participants (ITT; completed trial)	Characteristics, mean age (years) and age range of participants	Medications taken by participants	Form of CS and comparator used	Comparator; Test conducted to check similarity between CS and comparator	Daily quantity of CS; Diet control	Duration of intake
Vuksan, et al (2016) Canada	Randomized, double-blind, parallel design, Intention-to-treat analysis	77: 54	Presence of type 2 diabetes mellitus of 1 year (HbA1c between 6.5 and 8.0%) 55 (35 – 75)	Metformin (MET), MET + Sulfonylurea (SU), Metformin + Thiazolidinedione (TZD), Metformin + dipeptidyl peptidase 4 (DPP4), MET + SU +TZD, SU + DPP-4, SU + DPP4 Meglitinides (MIG) + TZD	Ground salba-chia	Oat-bran based control; no	30g/1000kcal/ day Yes	6 months
Vuksan, et al (2007) Canada	Randomized, placebo-controlled, single-blind, cross-over	27: 20	Stable type 2 diabetes (HbA1C,6.0% to 8.5%; fasting plasma glucose, 6.4-8.5mmol/L) of at least 6 months duration 64 (18 – 75)	Insulin secretagogues, Metformin, Pioglitazone	Ground form added to bread for both groups	Wheat bran; no	37 +/- 4g Yes	12 weeks (84 days)
Brisette (2013) Canada	Randomized, double-blind, parallel study Intention-to-treat analysis	78:58	Stable type 2 diabetes (HbA1C,6.0% to 8.5%; fasting plasma glucose, 6.4-8.5mmol/L) at least 1 year 55 (35 – 75)	Antihyperglycemic agents biguanides (Metformin), sulphonylureas (Glyburide, Glipizide) thiazolidinediones (Pioglitazone), dipeptidyl peptidase-4 inhibitors (Sitagliptin) and combinations of these (Janumet)	Ground salba	Oat bran, inulin, maltodextrin; no	7.5g Yes	24 weeks or 168 days
Choleva (2011) Canada	Randomized, double-blind, placebo-controlled, parallel design Intention-to-treat analysis	41: 20	T2DM for at least 1 year (treated with diet and/or oral hypoglycemic medications) (HbA1c between 6.5% and 8.0%) 55y (35 - 75)	Anti-hyperglycemic medications included biguanides (Metformin), sulphonylureas (Glyburide, Glipizide) thiazolidinediones (Pioglitazone), dipeptidyl peptidase-4 inhibitors (Sitagliptin) and combinations of these (Janumet).	Ground Salba and Salba enriched bread	Oat bran, inulin, maltodextrin; no	30g of Salba/1000kcal intake Yes	24 weeks or 168 days

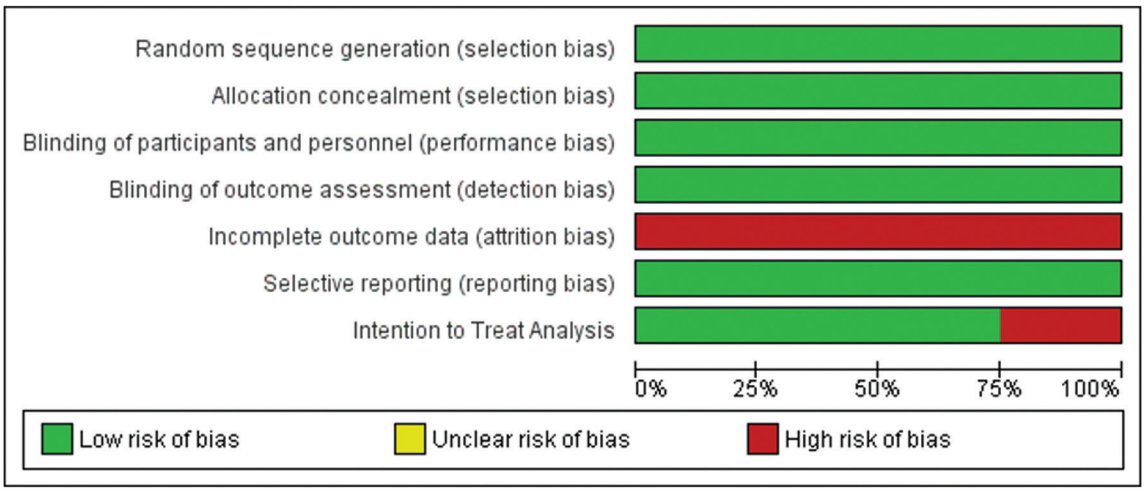

Figure 2. Risk of bias graph for all studies.

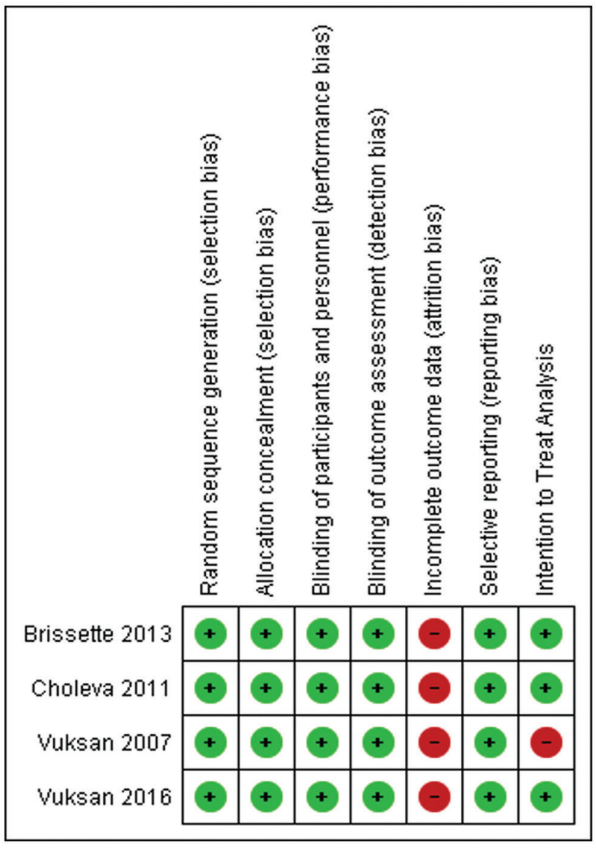

Figure 3. Risk of bias summary for individual studies.

6.50 mg/L increase in the adiponectin levels (95% CI 6.25, 6.75; $p < 0.001$; $I^2 = 0\%$, $x^2 = 1.00$) as shown in Figure 10.

Bristte, Choleva and Vuksan (2007), but not Vuksan (2016) found a decreased risk of gastrointestinal symptoms; the overall effect was a statistically significant lower risk of experiencing bloating, belching, diarrhea, flatulence, constipation, nausea, and abdominal pain (RR = 0.37, 95% CI 0.25, 0.55; $I^2 = 0\%$, $x^2 = 0.45$) as shown in Figure 11. Brisette and Choleva showed a decrease in the risk of renal symptoms that was not statistically significant (RR = 0.38, 95% CI 0.06, 2.34; p = 0.30). The same studies also showed a decrease in the risk of neurologic symptoms that was not statistically significant (RR = 0.60, 95% CI 0.32, 1.13; p = 0.11).

Discussion

Four studies with 213 participants were included in this systematic review and meta-analysis. The parameters investigated in this study included glycemic control, waist circumference, lipid profile, and satiety hormones. In summary, chia seeds as adjuvant treatment led to statistically significant decreases in fasting blood glucose, waist circumference, total cholesterol, HDL and LDL and a statistically significant increase in adiponectin. Except for the decrease in HDL, all these outcome parameters favor the use of chia seeds as an adjuvant treatment for diabetes. Side effects noted in this study included symptoms referrable to the gastrointestinal tract, kidneys, and central nervous system. There was a statistically significant reduced risk of experiencing gastrointestinal symptoms (i.e., bloating, belching, diarrhea, flatulence, constipation,

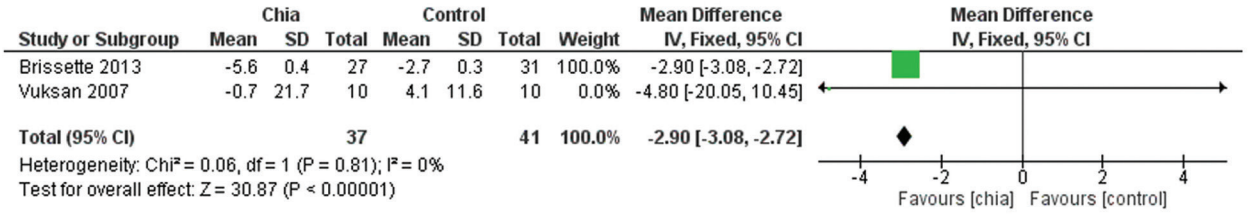

Figure 4. Forest plot of the effect of chia seeds on fasting blood glucose.

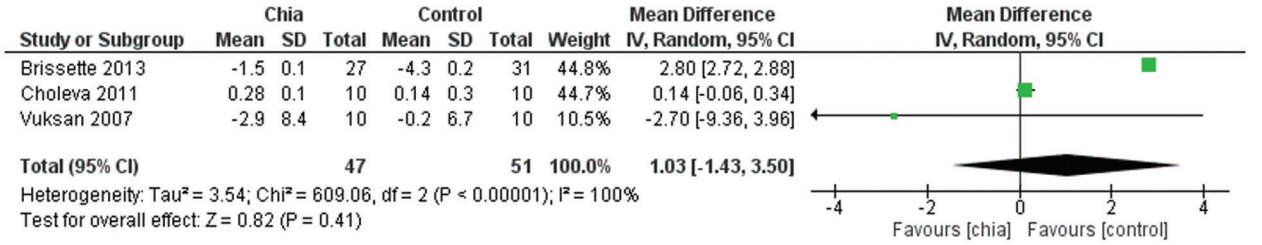

Figure 5. Forest plot of the effect of chia seeds on HbA1c.

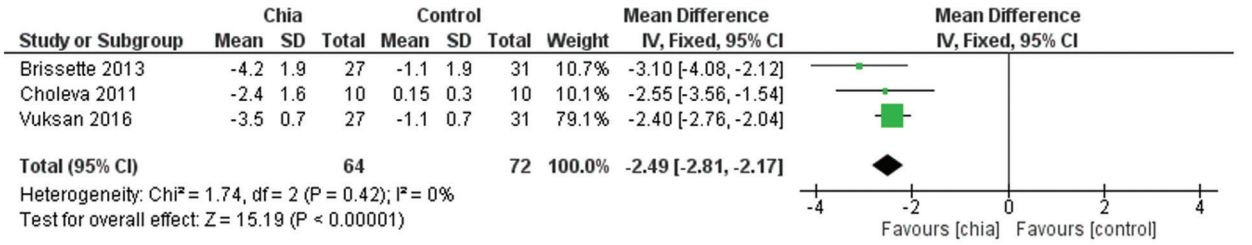

Figure 6. Forest plot of the effect of chia seeds on waist circumference.

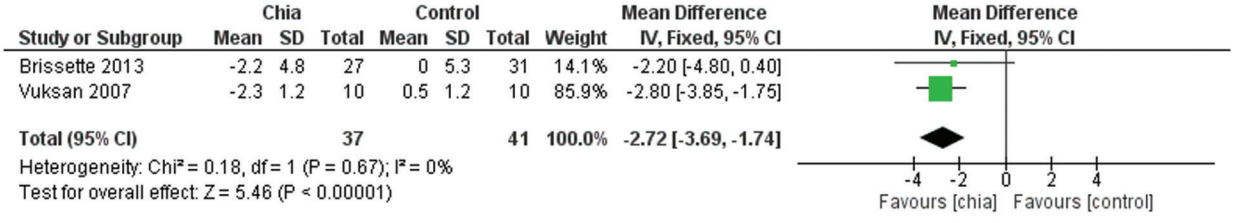

Figure 7. Forest plot of the effect of chia seeds on total cholesterol.

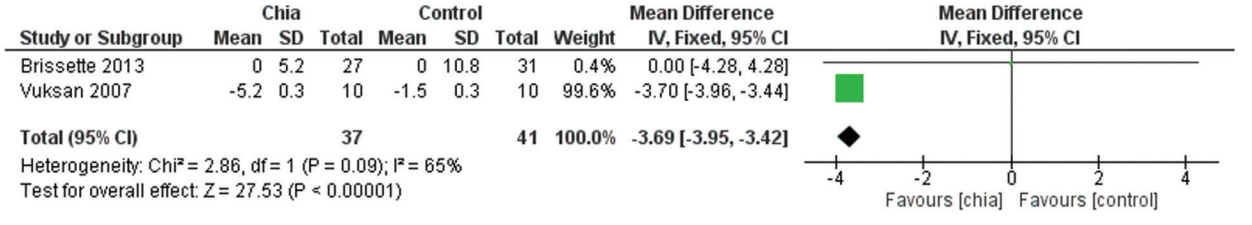

Figure 8. Forest plot of the effect of chia seeds on HDL.

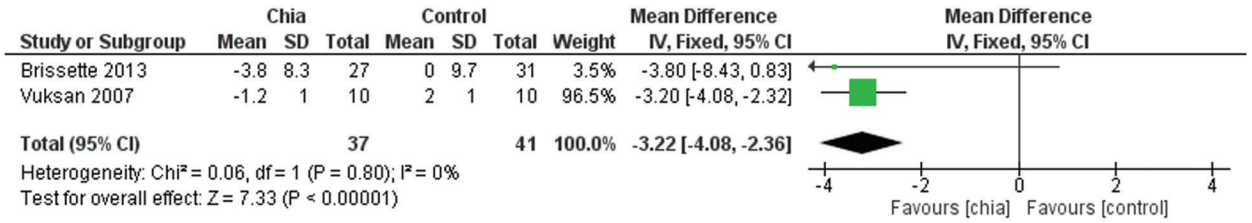

Figure 9. Forest plot of the effect of chia seeds on LDL.

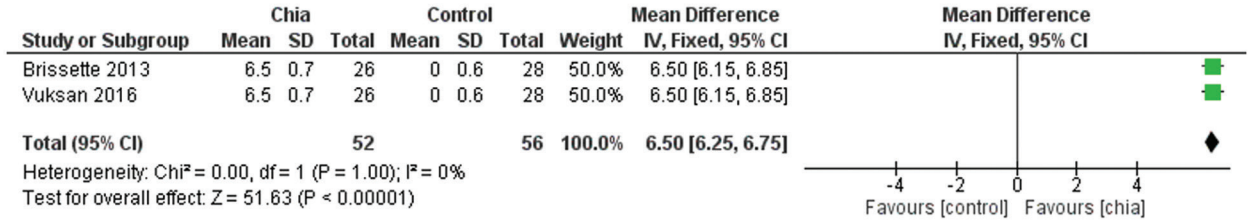

Figure 10. Forest plot of the effect of chia seeds on adiponectin.

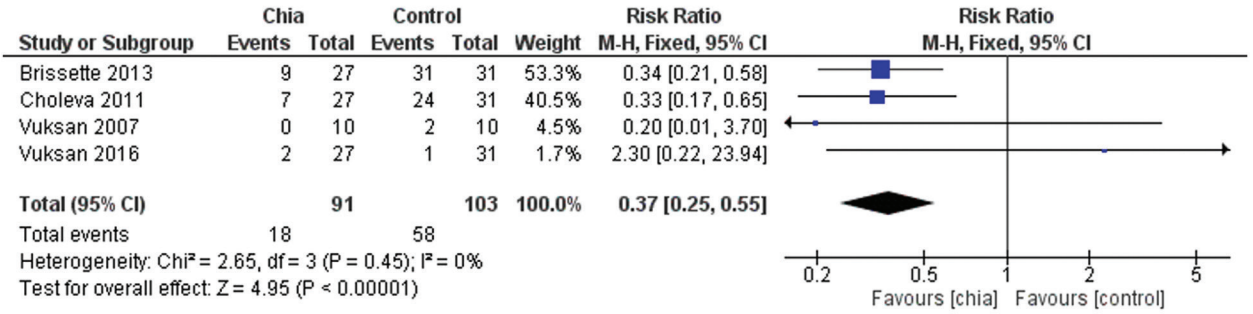

Figure 11. Forest plot of the gastrointestinal side effects of chia seeds.

nausea, and abdominal pain) for those who used chia seeds as adjuvant therapy compared to the control group. There was also a reduced risk of developing renal symptoms (i.e., excessive urination), and CNS symptoms (i.e., headache, dizziness) but the results were not statistically significant.

Although this meta-analysis has shown that chia seeds had a significant effect on fasting blood glucose, waist circumference, total cholesterol, HDL, LDL, and adiponectin, previous meta-analyses did not share the same result. However, the subgroup analysis done by Teoh showed significant effects on postprandial glucose, HDL cholesterol, and diastolic blood pressure when a higher dose of chia seeds was used.[3]

It is postulated that the high fiber content of chia seeds leads to its effect. Chia seeds contain about 23% to 41% dietary fiber, making it a high fiber containing food.[1,2] Fibers are known to induce satiety, causing lower food intake and greater weight changes. The lack of statistical significance for weight loss obtained in this meta-analysis may be attributed to the lack of dietary restrictions noted in the methodology of the studies.[10] In a study where the participants were put in a 500 kcal reduced diet based on the estimated energy requirement using the Harris-Benedict Equation, reduction in weight led to a 58% reduction in the occurrence of T2DM if there was a sustained weight loss of $\geq$ 3.5 kg.[12] Chia seeds with an addition of dietary restriction caused a significant reduction in weight.[9]

In addition to satiety, dietary fiber causes delays in digestion, gastric emptying time and absorption

of carbohydrates that controls hyperglycemia in T2DM patients.[13] Lipid lowering effects by fibers were attributed to the binding of soluble fibers to bile acids and cholesterols during micelle formation. This results in decreased cholesterol levels in the liver causing upregulation of the LDL receptor that enables the clearance of LDL cholesterol.[14] Addition of 4 to 19 grams of fiber supplements in the daily diet improves glycemic control and lowers the risk for cardiovascular events.[15]

Based on the β Cell-Centric Model: Egregious Eleven, there are eleven known pathways that lead to the development of hyperglycemia in diabetes mellitus. These involve the β-cells, incretin, β-cells, brain, liver, muscle, adipose tissue, colon, stomach, small intestine, kidney and the inflammatory response.[16] Chia seeds acts on the gastrointestinal tract, mainly the stomach and small intestine, leading to a decrease in the overall rate of absorption of carbohydrates.[13] Chia seeds' effect on adiponectin, a satiety-regulating hormone often noted to be low among patients with T2DM, is directly correlated to its ability to decrease plasma glucose levels.[17,18] Studies have shown that increasing fiber intake causes an elevation in the plasma adiponectin levels among both diabetic men and women.[18,19] Adiponectin not only increases insulin sensitivity but also decreases risk for atherosclerotic disease.[20] Another study has indicated fiber can increase post-meal insulin and GLP-1 within 15 minutes as compared to a diet without fiber. However, the exact mechanism of action is currently unknown.[21]

A systematic review and meta-analysis of four randomized clinical trials involving 213 participants demonstrated a statistically significant decrease in fasting blood glucose, waist circumference, total cholesterol levels, HDL and LDL cholesterol levels, and an increase in adiponectin. There was lower risk of side effects of those taking chia seeds. Chia is effective as adjunctive treatment for type 2 diabetic patients.

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A cross-sectional study on the risk factors and prevalence of common warts

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Abstract

Introduction Common warts are frequent benign cutaneous and mucosal infections. However, recommendations from previous studies have focused on personal and public factors to prevent warts and reduce its transmission. This study aimed to determine the prevalence of common warts and its relation to individual, family, school, public, and occupational factors.

Methods This is a cross-sectional study wherein the cutaneous surfaces (except the mucosa and genitalia) of residents of Barangay Doña Imelda, Quezon City were examined for the presence of warts. Information on individual, family, school, public, and occupational risk factors was obtained from the respondents themselves, parents or guardian using a data extraction sheet. A PRR of > 1.0 was interpreted as a positive association. Chi-square and Fisher's exact tests were used to test for significance. A p-value of < 0.05 was considered significant.

Results The prevalence of common warts among 315 residents was 7.6 %. The presence of family (PRR = 6.41, 1.91), school (PRR = 1.68), and occupational (PRR = 1.50) factors increased the risk of developing warts. In contrast, a personal history of warts and public factors were not associated with the development of warts.

Conclusion The prevalence of common warts is 7.6%, compatible with the results of previous studies. Having a family member with warts, large family size (more than five family members), having at least one closest school friend with warts, and occupation (fish or meat or poultry vendor) increase the risk of developing warts.

Key words: Common warts, verruca vulgaris, risk factors, prevalence, cross-sectional study

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E-Poster, and oral presentation in the Free Paper Presentation during the joint 13th Asia Pacific Environmental and Occupational Dermatology Symposium and 38th Philippine Dermatological Society Annual Convention held in Edsa Shangri-La Hotel, Manila on November 4-6, 2015

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Verrucae or warts is a benign infection of the cutaneous and mucosal surfaces caused by the human papillomavirus (HPV), a small DNA virus.[1] A high prevalence of warts exists in the general population - 3.28% in adults and 4% to 33% in children with an overall prevalence of 5.3%.[2,3,4] There are 100 HPV types causing varied clinical manifestations.[5] Common and plantar warts are caused by HPV Types 1 to 4; plane warts by Types 3, 28, 29; with poultry and fish vendors affected by Type 7.[6]

Common warts or verruca vulgaris appear as hyperkeratotic scaly dome-shaped papules and nodules appearing singly or in groups commonly on the digits and hands.[1,7] They can be filiform, flat with minimal scales or appear as "cutaneous horns". Plantar warts

appear as hyperkeratotic papules with punctate black dots representing thrombosed capillaries with pain occurring on pressure.[1] The diagnosis is often made clinically and can be confirmed histologically.[1] Transmission occurs through direct contact with individuals having clinical or subclinical infection or through fomites.[2] Development takes several months indicating a long sub-clinical infection.[1]

Previous studies recommended decreasing development and transmission by minimizing exposure within a person or in public and include avoiding touching, picking or scratching warts, avoiding using slippers in pools or public showers and keeping the feet dry.[2,8] Spontaneous clearance occurs in 40% of affected children, however, social stigma and pain warrant treatment.[4] An individual's immune status plays an important role in the spontaneous regression of the wart which may take several years. Susceptibility to infection and recalcitrant treatment is therefore seen in immunocompromised individuals.[5] Increased HPV exposure is said to have a consequent increased wart development.[2] However, studies on the epidemiology and transmission of warts are limited and are centered mostly on school children and occupational meat workers. Also, most studies are focused on warts located only on the hands and feet discounting warts on other cutaneous surfaces. Transmission of warts occur in areas prone to microtrauma with subsequent inoculation into the basal layer of the epidermis.[5] Autoinoculation occurs frequently on adjacent sites such as digits of hands.[1] Several factors such as the number of virions, quality of contact, location and immunity of the patient contribute to disease spread.[1]

According to Kilkenny a large household of more than five inhabitants increases the chance of spread while those with only one offspring decreases infectivity, similar to the findings of Kasim.[6,9] Van Haalen showed no association between environmental risk factors and wart development.[10] This is in contrast to the presence of warts in the family and class which increased the development of warts. Bruggink confirmed the previous results that the presence of warts in the family and in class were associated with wart development in contrast to a personal history of warts and the use of public pools which had no independent association.[2] Occupational factors also affect the prevalence of warts. Poultry, fish and meat handlers have an increased prevalence of warts on their hands due to trauma and maceration of the skin.[6] Keefe concluded that HPV Type 7 can be attributed to contact with meat which may be a means of transmission from one person to another.[11]

The general objective of the study was to determine the prevalence of common warts and its relation to individual, family, school, public, and occupational factors. The specific objectives are to determine the association of the following characteristics with the development of common warts: personal history of warts; presence of family member with warts and large family size; presence of warts in at least one close school friends; use of public swimming pools and/or public shower; and being a fish/meat/poultry vendor. The researchers included other cutaneous surfaces such as the face, trunk, and extremities aside from the hands and the feet in this study unlike that of Van Haalen who examined only the hands and the feet.[10] This study did not include examination of the genitalia and the mucosa.

Methods

This was a cross-sectional study done in Barangay Doña Imelda, Quezon City in September 7-22, 2014, using simple random sampling. Approval from the UERMMMCI Research Institute for Health Sciences Ethics Review Committee (ERC 0119/e/h/14/26; approved September 4, 2014) was obtained prior to conducting the study proper. Data on individual, family, school, public, and occupational factors were obtained by the principal investigator through one-on-one interviews using a data extraction sheet.

Included in the study were residents of Barangay Doña Imelda, with or without common warts, both male and female, of any age. Those who had warts located on the genitalia or mucosa and those with serious concurrent medical conditions (such as uncontrolled diabetes mellitus, immunocompromised state, positive for human immunodeficiency virus, cancer, chronic kidney disease) were excluded from the study as these groups of individuals are susceptible to the infection. Assuming a 95% confidence interval, level of significance at $p < 0.05$, the sample size was computed at 308 based on an estimated prevalence of 5.3% in the population using Kelsey/Fleiss method.[4] A simple random sampling was done. Household numbers were secured from the Doña Imelda Barangay Hall. The barangay was divided into 12

blocks. Based on the sample size of 308 and assuming that there were five members per household, five to six households per block were picked using a fishbowl technique. The respondents were then picked from each household. A respondent was included in the study if he/she met all the inclusion criteria and had none of the exclusion criteria.

Informed consent and assent, when applicable, were obtained from all eligible participants. Each respondent underwent a one-on-one interview and examination by the principal investigator with a barangay health worker present. Those who were found to have common warts had the lesions were measured in centimeters using a 15-centimeter stainless steel straight ruler. Clinical photographs were obtained for documentation as exemplified by Figures 1 and 2. Electronic pictures of warts were shown to the respondents to help them identify and recall a previous history of warts and the presence of such among household members and closest school friends to minimize information bias.

The study used a data extraction sheet that was developed from a review of related literature. This contained the name, age, sex, marital status, contact number, address, occupation, and level of education of the respondent. Questions regarding personal history of warts, presence of warts in the family, number of family members, presence of warts in at least one of closest school friends, a history of use of public swimming pools and/or public shower, and whether he/she was a fish/meat/poultry vendor, were answerable by yes or no. The questionnaire was in both English and Tagalog to facilitate communication between the principal investigator and the respondent.

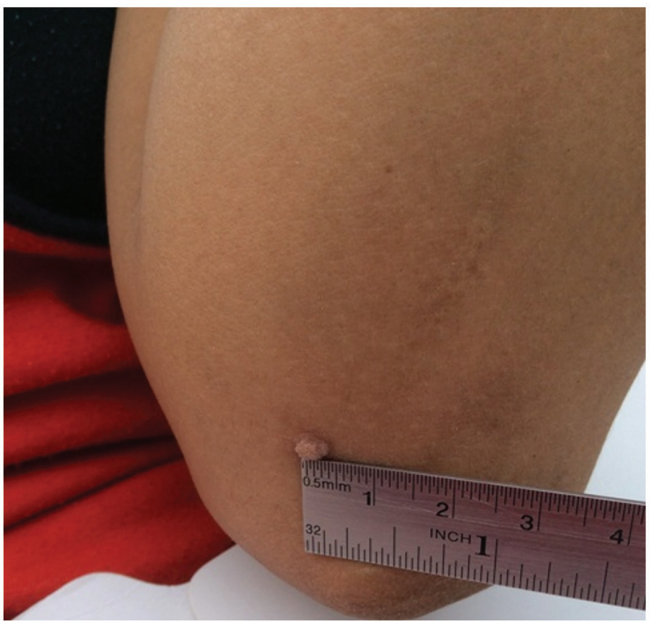

Figure 1. A 0.3 cm hyperkeratotic papule on the left forearm, of four years duration, in a 13-year-old, female.

Figure 2. A 0.2 cm hyperkeratotic papule on the right hand, of one year duration, in a 45-year-old, male.

The dependent variable in this study was the number of patients with common warts seen in Barangay Doña Imelda. Microsoft Excel© was used encode the data and to plot the graphs. Data analyses were done using GraphPad Prism version 5© statistical software. Percentage, mean, standard deviations and range were reported to describe the population characteristics. The prevalence rate ratio (PRR) was used to determine association. A PRR of > 1.0 was interpreted as a positive association. Chi-square and Fisher's exact tests were used to test for significance. A p-value of < 0.05 was considered significant.

Results

There were 315 respondents seen and assessed, with a mean age of 27.4 years; there were more women (203 vs 112). There was no statistically significant difference in terms of baseline demographics between those with common warts and those without as shown in Table

1. The overall prevalence was 7.6% and was highest in the 10-14-year age group (16%) compared with the other age brackets (5.13%, 4%, 9.09%, respectively). The sex specific prevalence rate was twice as high in females (9.36% vs 4.46%). Among those with common warts, the mean duration of the lesions was 2.5 years, the average number of lesions was 1.5, and the mean diameter was 0.4 cm. Around 95% of common warts were noted in the hand, trunk/extremities, and foot (45.8% 29.2%, and 20.8%, respectively) as shown in Table 2.

Having a family member with warts was associated with a six-fold increase in the risk of developing warts (PRR = 6.4; 95% CI 2.94, 13.99; $p < 0.001$). Having more than five family members with warts (PRR = 1.9, 95% CI 0.84, 4.34), a close friend in school with warts (PRR = 1.7, 95% CI 0.08, 33.5), and being a fish, meat or poultry vendor (PRR = 1.5, 95% CI 0.54, 4.16) increased the risk for developing warts but were not statistically significant. A previous history of warts may decrease the risk by 36% (PRR = 0.64, 95% CI 0.23, 1.81; $p = 0.465$). The use of public swimming pools and/or shower had minimal effect on the risk of developing warts (PRR = 0.92; 95% CI 0.43, 1.99; $p = 0.84$). These results are shown in Table 3.

Discussion

The results of this cross-sectional study reveal that the prevalence of common warts in Barangay Doña Imelda, Quezon City is 7.6 %, with 2.2% occurring in children and 5.4% in adults. This was almost similar to a previous study with an overall prevalence of 5.3%,

Table 2. Characteristics of warts.

Characteristic	n (%)
Disease duration (year)	
< 1	8 (33.3)
1	7 (29.2)
2	5 (20.8)
10	4 (16.7)
Mean	2.49
Number of lesions	
1	14 (58.3)
2	8 (33.3)
3	2 (8.33)
Mean ± SD	1.5 ± 0.66
Location	
Hand	11 (45.8)
Foot	5 (20.8)
Hand and foot	1 (4.2)
Trunk or extremities	7 (29.2)
Size (cm)	
Mean ± SD	0.40 ± 0.20

Table 1. Patient demographics and characteristics of warts.

	With warts (n = 24)	Without warts (n = 291)	All patients (n = 315)	Prevalence rate (%)	p-value
AGE (years; mean ± SD)	35.5 ± 20.7	26.7 ± 19.3	27.37 ± 19.60	Age specific prevalence rate (%)	
0 – 11 months	0	6	6	0.00	
12 – 23 months	0	6	6	0.00	
2 – 4 years	0	27	27	0.00	
5 – 9 years	2	37	39	5.13	
10 – 14 years	4	21	25	16.00	
15 – 19 years	1	24	25	4.00	
20 years and over	17	170	187	9.09	
GENDER, n (%)				Sex specific prevalence rate (%)	
Male	5 (19%)	107 (37%)	112 (36%)	4.46%	
Female	19 (81%)	184 (63%)	203 (64%)	9.36 %	0.127+

+Fisher's Exact Test

Table 3. Factors in developing common warts.

Factor	With warts (n = 24)	Without warts (n = 291)	PRR (95% CI)	p-value
Personal history of warts	4/20	71/220	0.64 (0.23, 1.81)	0.466+
Family history	15/9	50/241	6.41 (2.94, 13.99)	< 0.001*
> 5 family members with warts	16/8	145/146	1.9 (0.84, 4.34)	0.113*
Close school friend with warts	0/24	3/288	1.68 (0.08, 33.51)	1.00+
Use of public swimming pool and/or shower	13/11	164/127	0.92 (0.43, 1.99)	0.84*
Fish/ meat/ poultry vendor	4/20	33/258	1.50 (0.54, 4.16)	0.504+

+ Fisher's Exact Test *Chi-square test

having 3.28% in adults and 4% to 33% in children.[2-4] Common warts was found to be most prevalent among the 10-14-years age group which was consistent with the studies of Kilkenny, Pragya, Kasim, and Van Haalen.[6,7,9,10] Moreover, it was more prevalent in females unlike the findings of Bruggink, Kilkenny, and Kasim.[2,6,9] However, a similar female preponderance was noted by Pragya owing to the increased awareness of unpleasant lesions on their face.[7] The hand was the most commonly involved site (45.83 %) which was consistent with the results of Pragya owing to its direct skin-to-skin contact transmission and trauma-prone location.[8]

Though the result of this study is not statistically significant, it supported the findings of Bruggink that there is no association between personal history of warts and development of warts. This could be because HPV exposure, host susceptibility, immunogenicity, and host immune status are important factors to consider in the development of warts.[2] That having a family member with common warts and having more than five family members with common warts increased the risk six- and two-fold, respectively, are consistent with previous studies.[2,6,9,10] This could be explained by a higher degree of exposure and crowding.[8] The higher risk of developing common warts among those with at least one close school friend correlates with the findings of Bruggink.[2] The findings regarding the use of public swimming pools and showers are consistent with previous studies.[2,10] Being a fish, meat or poultry vendor was associated with a higher risk of developing warts, consistent with a previous study which explained it on the basis of the meat, fish or poultry being a means of transmission of the virus.[6] The respondents' or parent or guardian's assessment and recall of a personal history of warts, presence of warts in at least one closest school friend, and environmental risk factors may have influenced the outcome of the study leading to information bias.

A high prevalence of common warts was found in Barangay Doña Imelda, Quezon City wherein the highest age specific prevalence rate was seen among children 10-14 years, with females having the highest sex-specific prevalence rate. The results of the study correlate well with previous studies done in other countries or communities. A personal history of warts and use of public swimming pools and/or public shower were not associated with the development of warts. On the other hand, having a family member with warts, large family size (more than five family members), having at least one closest school friend with warts, and occupation (fish or meat or poultry vendor) increased the risk of developing warts. Based on the findings, the researcher recommends that measures to limit the spread of warts be directed to the family, school and specific occupations.

Acknowledgement

The authors would like to express their deepest gratitude to Dr. Jose Ronilo G. Juangco for helping them with the sampling and statistics.

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Persistent trophoblastic neoplasia in the broad ligament, a case report

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Abstract

Gestational trophoblastic neoplasia (GTN), a malignancy arising from trophoblastic tissue of pregnancy, is an aggressive disease process with a high probability of metastasis if left untreated. This is a case report on metastatic invasive mole arising from a molar pregnancy. Four months after suction curettage, a mass was noted in the left broad ligament on exploratory laparotomy with intact uterine serosa. Clinical presentation, biochemical, and radiological parameters led to a diagnosis of persistent trophoblastic disease. Histopathological findings also confirmed the diagnosis. Prompt chemotherapy was given after removal of the left intraligamentary mass, and subsequent response to treatment was documented. We report a case demonstrating a different clinical presentation of invasive mole and its potential to metastasize to the broad ligament without uterine perforation or direct extension.

Key words: Gestational trophoblastic neoplasia, hydatidiform mole invasive, methotrexate chemotherapy, postmolar gestational trophoblastic disease

Gestational trophoblastic neoplasia (GTN), the malignant end of gestational trophoblastic diseases (GTD), may arise either from premalignant conditions such as complete and partial hydatidiform or from non-molar pregnancies. Development of GTN is mostly from postmolar gestations (50%) compared to history of abortion or ectopic gestation (25%) or history of normal deliveries (25%).[1] Complete molar pregnancy compared to partial hydatidiform has a higher incidence of malignant complications (post-molar GTN, local proliferation and metastasis)

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GTN encompasses four histopathologic disease types of which invasive mole is the most common localized GTN.[2] It is characterized as invasion beyond the normal placental site into the myometrium and often including the venous system. Its metastatic potential may lead to complications such as massive intraperitoneal hemorrhage or pulmonary symptoms. Invasive mole without myometrial invasion and a pulmonary component is rare.[3]

This case highlights the variable presentations of GTN, which might easily cause misdiagnosis and delayed treatment. Low risk GTN is chemosensitive and responds well to treatment. Therefore, early diagnosis and prompt initiation of management is essential for a successful course and preservation of fertility.

The Case

A 22-year-old, G1P0 (0010), came in because of intermittent vaginal spotting with hypogastric pain associated with nausea and vomiting of four days. With a positive a pregnancy test, she had an ultrasound prior

to consult showing a normal sized empty uterus with a thin endometrium (0.57 cm). A left adnexal mass measuring 1.94cm x 1.47cm x 1.65cm (Figure 1) was noted with a consideration of an ectopic pregnancy.

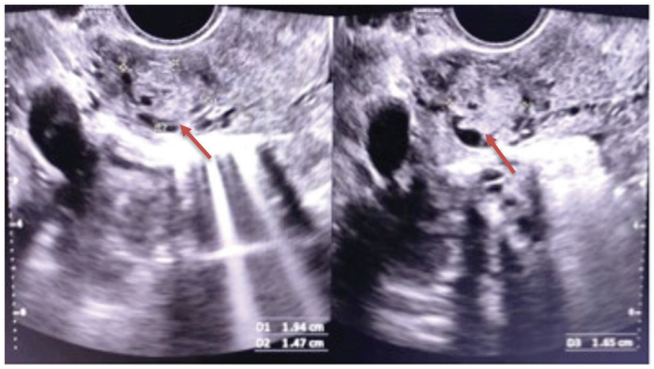

Figure 1. Initial transvaginal ultrasound, sagittal view showing a 1.94cm x 1.47cm x 1.65cm left adnexal mass (red arrow) probably ectopic pregnancy

Her previous pregnancy was a complete hydatidiform molar pregnancy where she underwent suction curettage four months prior to consult. Her baseline β-hCG was elevated at 816,276 mIU/mL. Pertinent diagnostics at that time revealed elevated liver enzymes and thyroid function tests. Imaging also showed a normal chest radiograph and hepatobiliary ultrasound showing no evidence of metastasis. She was discharged on the third postoperative day and was advised to monitor β-hCG, liver enzymes and thyroid function tests after one week. Despite counseling the patient was unable to comply with surveillance of β-hCG and contraceptive use. In the interim, the patient was allegedly asymptomatic but reported irregular vaginal bleeding episodes attributed to resumption of her menstrual cycle.

On examination, the patient was ambulatory and hemodynamically stable. Systemic findings were all within normal. Her abdomen was soft but with direct tenderness on the hypogastric area on deep palpation. On pelvic examination, the cervix was violaceous, smooth, with minimal clear non-foul-smelling discharge. Internal examination documented a closed cervix with cervical motion tenderness, a small uterus with left adnexal tenderness but no mass palpated. Rectovaginal exam revealed no further tenderness. Given the clinical presentation together with ultrasound finding of an adnexal mass, impression at this time was an ectopic pregnancy to rule out persistent trophoblastic disease (PTD). This was supported by an elevated β-HCG of 73,000 mIU/mL. Transvaginal ultrasonography showed an increased size of the previously identified left adnexal mass measuring 4.18cm x 3.82cm x 3.09cm posteromedial to the left ovary with minimal color flow (Figure 2). No fluid was detected in the abdomen and pelvis, however, a possible cornual ectopic pregnancy was also considered. Emergency exploratory laparotomy was contemplated.

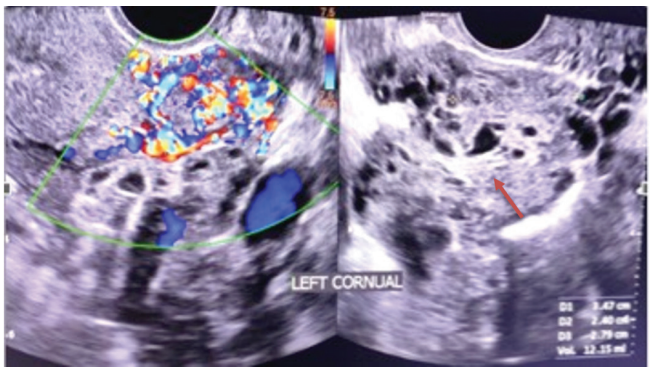

Figure 2. Follow up transvaginal ultrasound, sagittal showing a 4.18cm x 3.82cm x 3.09cm left adnexal mass posteromedial to the left ovary with minimal color flow.

The patient was placed in dorsal lithotomy position under regional anesthesia. The abdomen was entered through a vertical midline incision. Upon exploration, no hemoperitoneum appreciated. The uterus was grossly normal. A soft, irregularly shaped hyperemic mass measuring approximately 4cm x 4cm x 2cm was noted in the left broad ligament (Figure 3). The mass was isolated and had no distinct connection with the fallopian tube and uterus. The left fallopian tube was grossly normal and the absence of cornual pregnancy was confirmed. PTD was considered, thus an intraoperative referral to a gynecologic oncologist was done for further evaluation. Isolation and excision of mass was contemplated however active bleeding was noted while attempting to cut from the fimbriated end of the fallopian tube. In the background of a trophoblastic disease, excision of the mass and left salpingectomy was done to avoid profuse bleeding (Figure 4). The final histopathologic diagnosis was a complete hydatidiform mole with moderate trophoblastic proliferation, with paratubal chronic inflammation and fibrosis of the left fallopian tube (Figures 5A & 5B).

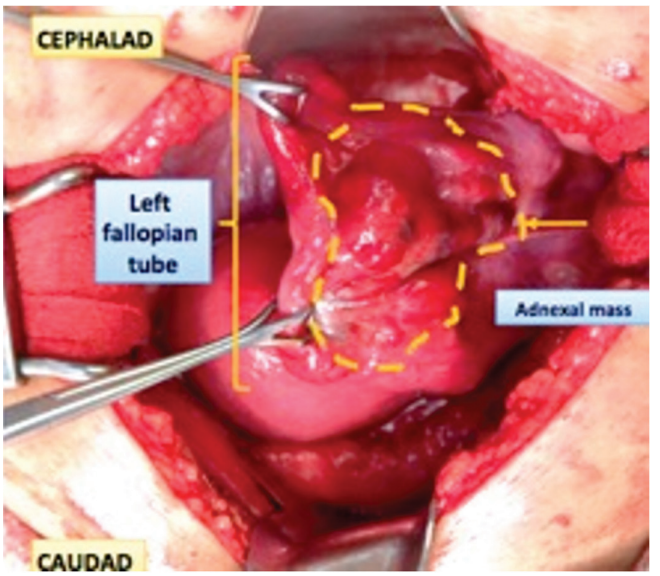

Figure 3. Intraligamentary 4cm x 4cm x 2cm soft, irregularly shaped, hyperemic mass in the left mesosalpinx of the broad ligament.

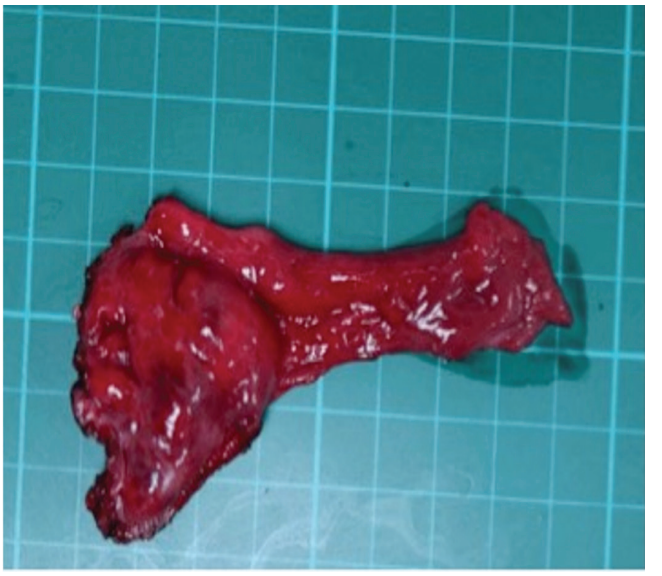

Figure 4. Left fallopian tube (5.5cm x 1.2cm x 1.0cm) with left adnexal mass.

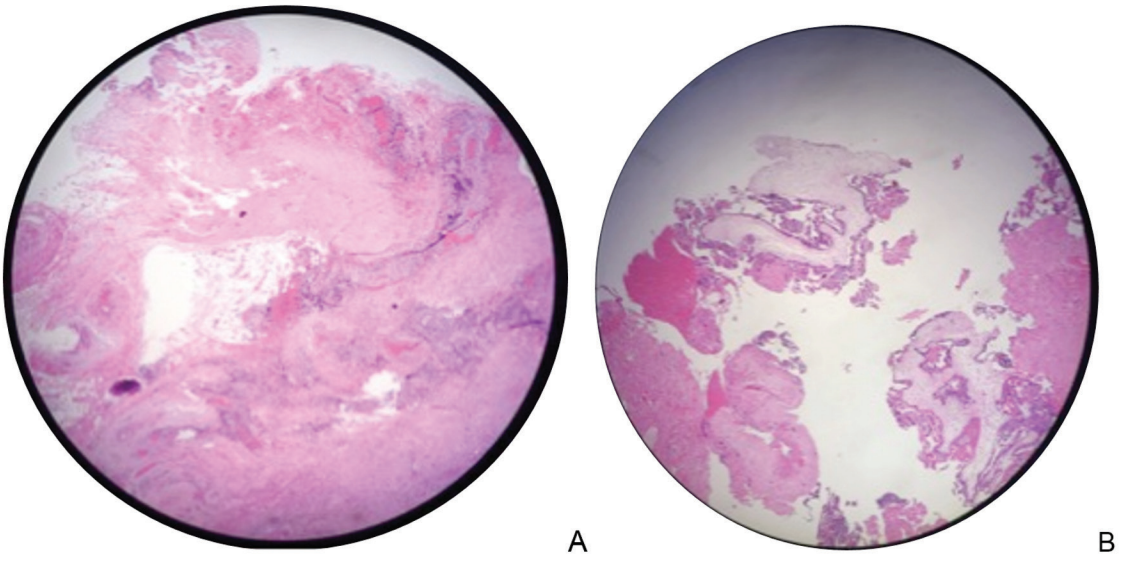

Figure 5. Microscopic examination of the (A) fallopian tube showing Intact luminal mucosal plicae with a surrounding intact fibromuscular layer and note of inflammatory infiltrates; (B) paratubal soft tissue showing hydropic chorionic villi with trophoblastic proliferation on the villous surface and the presence of inflammatory infiltrates (lymphocytes and plasma cells).

Combining the patient's symptoms, history of a complete molar pregnancy with previous suction curettage, and persistent elevated β-HCG, she was assessed as a case of GTN. Using the FIGO anatomical staging and WHO prognostic scoring system, the patient was classified as low-risk GTN and chemotherapy with methotrexate was started. Strict follow up with β-HCG monitoring and serial blood work up was done. Trends of β-HCG showed exponential decrease over the subsequent months with six cycles of chemotherapy as shown in Figure 6.

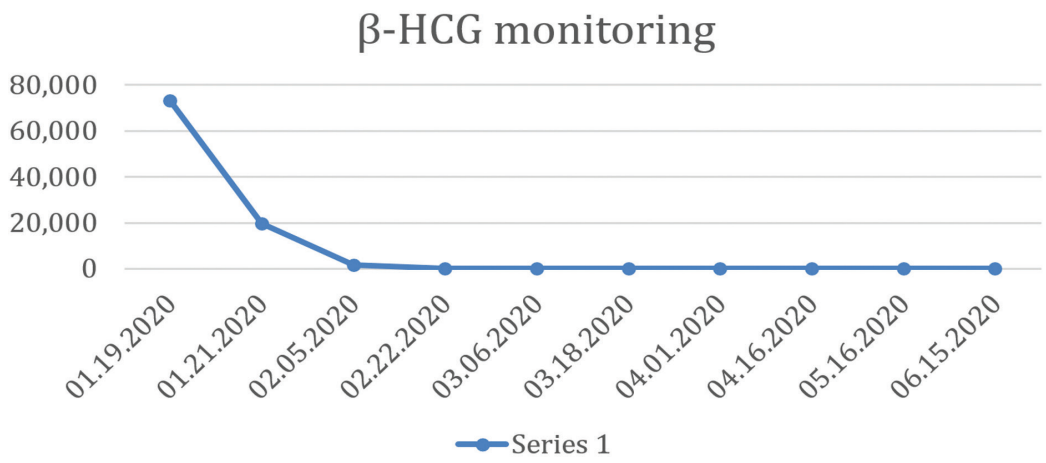

Figure 6. Serial monitoring of β–HCG showing a decrease in the levels.

Regular monthly monitoring and consultations were followed for the first six months since her procedure. On these consults, a thorough history and physical examination were done. On the patient's 6th postoperative month, the patient was hemodynamically and psychologically stable with normal systemic physical findings. Future pregnancies and family planning counseling, including strict compliance to contraceptive use for one year were discussed with the patient and her partner. In addition, early preconception consultation was emphasized. The long-term prognosis of disease as well as possible complications for future pregnancies (fetal abnormalities) were explained thoroughly.

Discussion

Gestational trophoblastic neoplasia (GTN), also referred to as postmolar trophoblastic neoplasia or persistent trophoblastic disease (PTD), is diagnosed based on FIGO 2000 criteria (β-hCG level remains elevated for 6 months or more).4 GTN results from a disruption of normal regulatory mechanisms controlling trophoblastic function such as myometrial implantation and production of β-hCG. It can aggressively proliferate and perforate the uterine wall, metastasize systemically and lead to maternal death if untreated.[1] Therefore, early detection of progression to GTN from a molar pregnancy (15-20% in complete H. mole and 0.5-5% in partial H. mole) is essential.[4] A history of previous molar pregnancy and extremes of reproductive age (< 15 and > 35 years) are two of the most important identifiable risk factors for GTN.[5] Although the patient is only 22 years old, GTD in general occurs within the reproductive age. This is evident in a study by Chhabra and Qureshi revealing a J-shaped age-specific incidence curve in GTN cases.[6] Other risk factors pertinent in this case for postmolar GTN include pretreatment hCG > 100,000 mIU/mL, enlarged uterus from date of gestation, uterus size > 16 weeks, and the presence of any medical complications associated with increased trophoblastic proliferation. The patient had a hydatidiform mole on the 14th week of her first pregnancy with uterine size of 18 weeks AOG. On her previous pregnancy, the patient was managed with molar-induced hyperthyroidism.

The clinical diagnosis of postmolar GTN relies on a complete and thorough medical history, clinical symptoms, and diagnostics (hormonal assay and imaging). Histopathology results although not necessary, aid in confirmation of disease.[2] The patient showed a typical course of disease and presentation of symptoms such as amenorrhea and vaginal bleeding. However, despite the patient's clinical background of previous molar pregnancy, a differential diagnosis of ectopic pregnancy was considered with an ultrasound finding of an adnexal mass and an empty uterus. At 6 1/7 weeks AOG by amenorrhea, she presented at the OPD with vaginal spotting and a positive pregnancy test, which is typical for both ectopic pregnancy and GTN. On physical examination, the patient had a small uterine size, which is not a typical presentation of a molar pregnancy. In contrast to GTD, the diagnosis of GTN is based on patient's clinical presentation.

More so, the pathological diagnosis of invasive mole is rarely reported due to conservative fertility sparing management. With only 2% of ectopic pregnancies located in the cornual area and a background of previous complete molar pregnancy in less than six months, with neither β-hCG, nor chemoprophylaxis, a persistent gestational trophoblastic disease cannot be totally ruled out.

Pathologic features of complete H-mole with direct invasion into the myometrium and beyond the placentation site defines invasive mole, a locally invasive trophoblastic neoplasia. Its aggressive trophoblastic growth characteristics lead to destruction, penetration, and invasion of myometrial wall and eventually parametrium and uterine vasculature. It is usually confined within the uterus and extra uterine involvement occurs in 5% of complete hydatidiform mole, and rarely in partial hydatidiform mole.[1] Its potential for metastasis to distant sites such as the lungs, liver, and brain can occur from hematogenous or lymphatic spread. However nearby metastasis to the vagina or adjacent pelvic area are mostly through direct extension.[7]

In a study by Shen, a metastatic invasive mole was diagnosed secondary to an iatrogenic uterine perforation despite having no myometrial invasion histologically. Molar lesions found at the pelvic peritoneum, posterior uterine serosa, and omentum metastasized by direct spread through the perforated site.[8] This patient had an atypical invasive mole with metastasis to the broad ligament with no evidence of myometrial invasion more and no uterine rupture. Due to the lack of reports of metastasis to the broad ligament, the exact pathophysiology for this atypical disease presentation remains unclear. Possible explanations were considered to rationalize and clarify etiology of disease.

In a study by Moser, trophoblast invasion happens in all luminal structures in the placental bed such as arteries, veins, lymphatics and glands. Prior to endoarterial invasion, trophoblasts were observed to have invaded large caliber veins and lymphatics as early as five weeks of pregnancy. Endovenous and endolymphatic trophoblastic invasion function to connect vessels to the intervillous space for removal of waste products and fluid balance.[9]

Wong hypothesized that distant metastasis occurred by intravasation to blood vessels or lymphatic routes. The trophoblastic cells may prefer the lymphatic route due to its permeability from lack of tight interendothelial junctions and reduced shear fluid flow. In his study, morphological differences and accessibility of a vascular pathway contribute to this route of metastatic spread.[10] In support of the former theory, Kleppe studied lymphatic drainage pathways of the ovaries and Hironori also confirmed lymphatic routes in the broad ligament.[11,12] The broad ligament contains lymph vessels accompanied by the uterine ovarian anastomosis alongside the whole corpus. Presumably there is an element of stasis in this region as it is a site of predilection for secondary deposits from the uterus region. This theory of the pathophysiology of an independent invasive mole without uterine rupture has not been verified by any studies. This anatomical relationship most likely explains the spread of metastasis and is compatible with patient's case presentation and disease pattern.

GTN is typically sensitive to chemotherapy as well as continued β-HCG monitoring. Treatment success is about 80-90%. The cure rate may increase to 100% with appropriate initial classification and proper treatment. The patient belongs to the low-risk group based on FIGO prognostic score; hence methotrexate alone was given. Chemotherapy was continued until response to treatment was noted via documentation of three consecutive normal serum β-HCG levels (< 5 mIU/mL).[2] Thorough surveillance for evidence of drug resistance (plateau or increase in β-HCG) was done since 30-50% of patients develop resistance to first line-chemotherapy agents and 5-15% may require multi-agent chemotherapy and/or other modalities. The patient has been on close follow up since surgery and has shown good response evidenced by an exponential decline in β-HCG. After six cycles of single agent methotrexate, the patient had three consecutive normal β-HCG levels.

Patient was reassured of a high overall survival rate for GTN which is attributed its high sensitivity to chemotherapy and effective surveillance of β-HCG. With this, the patient was started on oral contraceptives and was informed of possible complications (spontaneous miscarriage, stillbirths, repeat molar pregnancy) if pregnancy occurs within one year. The patient and her partner are both desirous of pregnancy. Garcia reviewed 18 articles and reported that chemotherapy did not show a decrease in fertility, however, those who conceived within six months of treatment had increased abortion rates.[13]

Family counseling and psychosocial counseling was done. It was emphasized that first trimester ultrasound and serum β-HCG testing are indicated for the first pregnancy after treatment of GTN to establish a normal intrauterine pregnancy. Moreover, a repeat quantitative β-HCG should also be requested postpartum to assure that there is no recurrence of GTN.

Summary

This case highlights the different clinical presentations of GTN. Possible etiologies were examined and correlated with the clinical presentation. The high invasive ability of trophoblastic disease should always be considered and help broaden the perspective of the disease process. GTN accounts for less than 1% of cancers among women and is highly treatable with cure rates of 80 to 90% with intensive therapy.

Invasive mole with metastasis is a rare occurrence. Its early detection is important because it is responsive to chemotherapy with high remission rates. A complete and thorough history and physical examination cannot be overemphasized. A history of a prior molar pregnancy and other risk factors should immediately prompt a high index of suspicion for a possible GTN. Determination of serum β-HCG levels, with subsequent monitoring is recommended. Management of such patients is individualized with consideration of fertility preservation. The patient should be counseled postoperatively regarding future pregnancies.

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Krugman S, Overby LR, Mushahwar IK, et al. Viral hepatitis type B: studies on the natural history and prevention reexamined. N Engl J Med 1979; 300: 101-6.

Nyland LJ, Grimmer KA. Is undergraduate physiotherapy study a risk factor for low back pain? A prevalence study of LBP in physiotherapy students. Retrieved from: http://www.Biomed-central.com/1471-2474/4/22. 2003. [Accessed August 27, 2011].

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Books and other monographs

Personal authors

Adams RD, Victor M. Principles of Neurology. New York: McGraw-Hill; 1981.

Chapter in a book

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