Features a chapter on a research paper about the GI/GL: **International Trial**

THE END OF DIETING

FIRST EDITION

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Teaching the World, LLC.

The End of Dieting

CONTENTS

Chapter 1: Never Skip Breakfast

The many reasons you should never skip OR rush through breakfast

BREAKFAST
The Rule: NEVER SKIP BREAKFAST or RUSH THROUGH BREAKFAST.

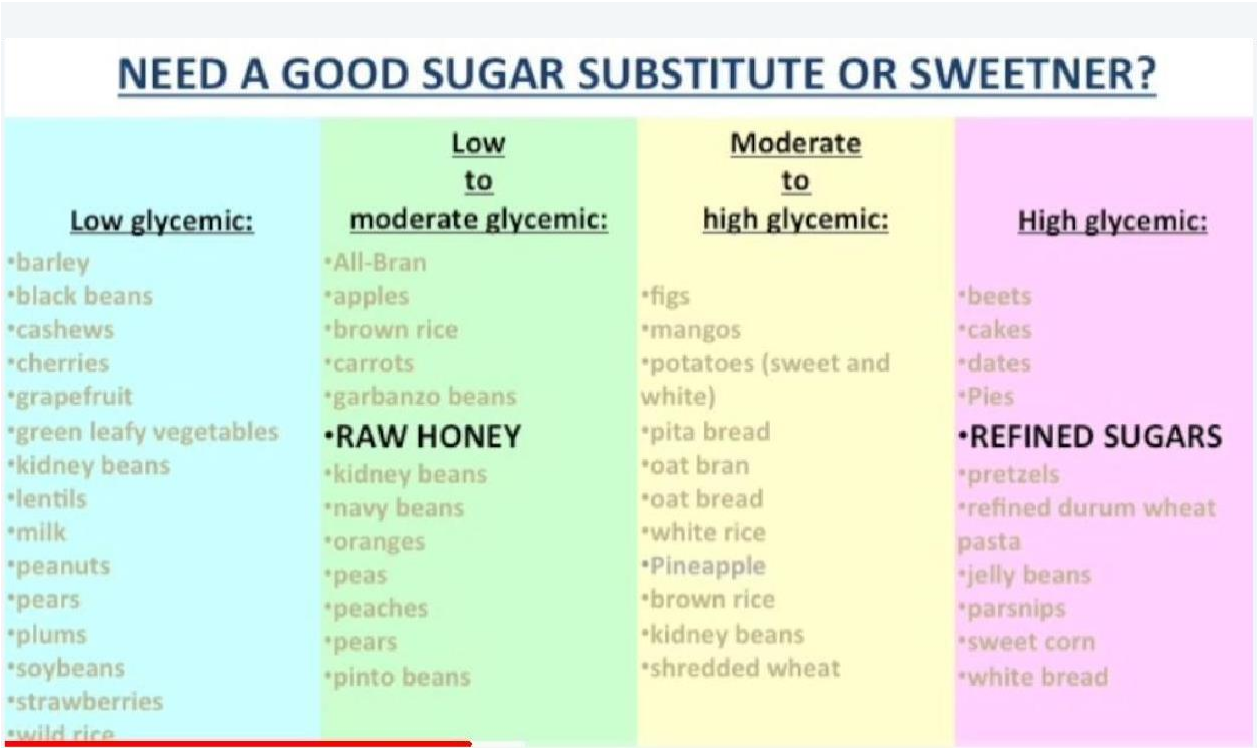
Why: 1) Your metabolism starts to slow down when you customarily "skip" breakfast. 2) You will start the day off with indigestion when you eat breakfast too FAST. It should take you 30-45mins to eat your breakfast

DRINKS
The Rule: Drink 4 ounces of any drink you crave in the morning. Anything you drink afterbreakfast can only be WATER.

Why: 1) You will consume 1,200 fewer calories a day. 2) Your brain gets the "FIX" it needs in the morning until you can transition in to just drinking something healthy in the A.M 3) Your metabolism is "Fast" in the morning so most of the bad calories are consumed without having toexercise and burn them off.

SWEETNER
The Rule: Use natural BEES HONEY as your "SUGAR SUBSTITUTE" for all drinks and foodsyou wish to sweeten. www.lower6app.com

Why: NATURAL BEES HONEY is the only natural sweetener that contains fiber, is a low glycemic index food, (lower your risk of developing Diabetes), and adding just a few drops to your drink(s) or food(s) provide a lot of flavors. If you hate the taste of water, then adding a fewdrops or a teaspoon of Natural Bees Honey will add some flavor to the water.



Rice, Pasta and Bread

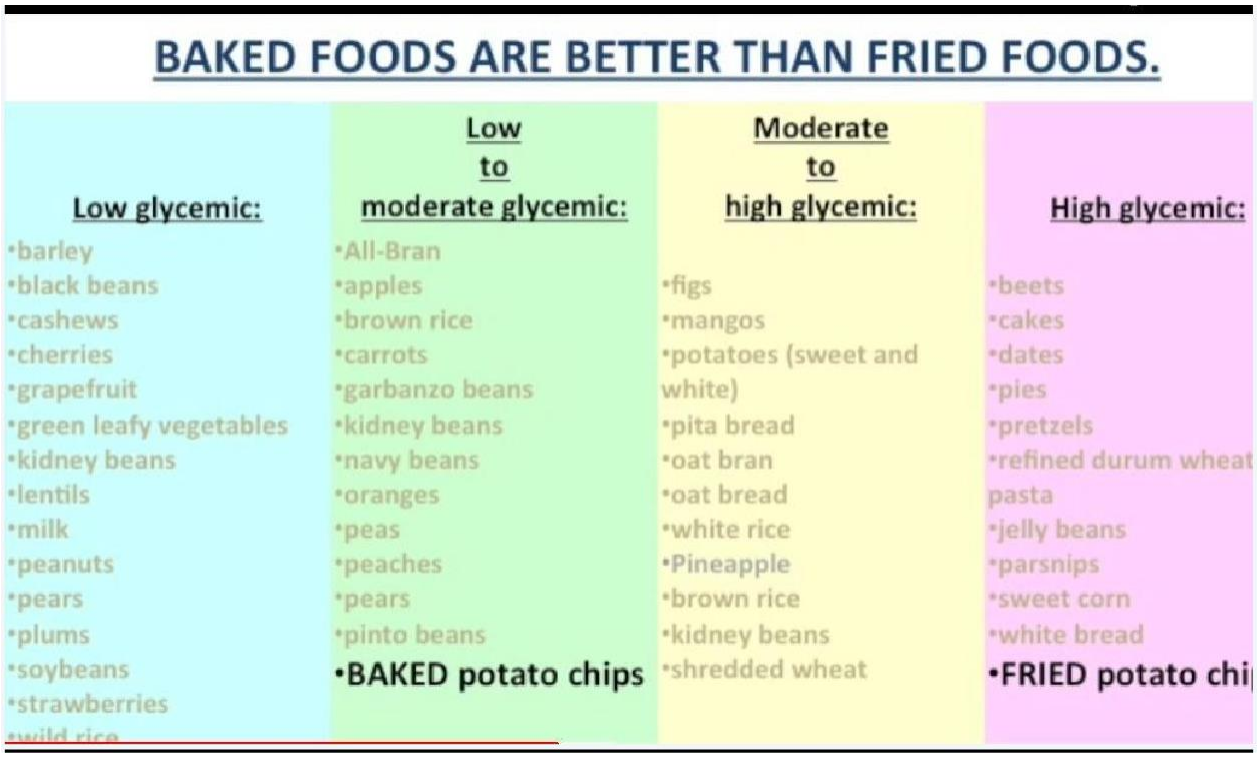
The Rule: Do not eat Rice, Pasta or Bread on the same day. Pick your days when you will eat bread, but not rice and/or pasta. For example, eat bread on Mondays, Rice on Tuesdays and Pastaon Fridays.

Why: 1) Use the lower 6 app to find the best breads, rice or pastas available. 2) Never overloadyour metabolism with carbohydrates in a 24-hour time period. 3) You would have to jog one hour every day to burn off all the Carbs consumed and stored when rice, bread and pasta are consumed on the same day. www.lower6app.com

Food Preparation

The Rule: Foods, even the same food, are best prepared either BOILED, BAKED but avoideating FRIED FOODS.

Why: 1) Frying the same food, increases the glycemic index of that food. 2) Fried food is moreof a challenge for your body to digest.



BAKED FOODS ARE BETTER THAN FRIED FOODS.

Low glycemic:	Low to moderate glycemic:	Moderate to high glycemic:	High glycemic:
•barley	•All-Bran		
•black beans	•apples	•figs	•beets
•cashews	•brown rice	•mangos	•cakes
•cherries	•carrots	•potatoes (sweet and	•dates
•grapefruit	•garbanzo beans	white)	•pies
•green leafy vegetables	•kidney beans	•pita bread	•pretzels
•kidney beans	•navy beans	•oat bran	•refined durum wheat
•lentils	•oranges	•oat bread	pasta
•milk	•peas	•white rice	•jelly beans
•peanuts	•peaches	•Pineapple	•parsnips
•pears	•pears	•brown rice	•sweet corn
•plums	•pinto beans	•kidney beans	•white bread
•soybeans	•BAKED potato chips	•shredded wheat	•FRIED potato chi
•strawberries			
•wild rice			

2 Snacks a day. 1 healthy snack at 10am and another healthy snack at 3pm

Rule: Eat a green salad or fruit salad as one, (10 am or 3 pm), or both, (10am and 3 pm), of yoursnacks. The second snack, if not another salad, should be only a handful of a healthy food. (Peanuts, kale, yogurt etc...).

Why: 1) Decrease your lunch time and dinner time cravings with small healthy snacks. 2) Enjoy the social interactions of Breakfast, Lunch and Dinner without thinking about healthy eating. 3) Bring back the joy of eating and stop punishing yourself by stating "I can only eat salad". 4) You are eating "healthy snacks" outside the social hours of Breakfast, Lunch and Dinner.

FLAVORS

Use the Lower 6 App to find flavors or foods which you enjoy eating but that are either 1-2flames, (Low to medium), (Glycemic Index/Glycemic Load). www.lower6app.com

Here are just a few examples of flavors, (Strawberry, Chocolate, Vanilla), or foods, (Rice, Bread,Pasta, drink, pizza, pancake), with which the phone app can help you make better food choices.

3 SONGS

Pick three songs you absolutely LOVE. Start walking at a normal pace to the first song. When the first song ends then walk at a slightly faster pace, but not a jog to the second song. When thesecond song ends then walk at a normal pace to the third song.

Why: Exercising in slow to fast and slow to fast INTERVALS, burns twice the amount of bodyfat in ½ the amount of time you exercise. As your endurance with walking to the three songs improve then add 4, 5 or as many songs as your endurance level permits. Also try different activities such as biking, hiking, weight training, dancing etc....but with the same routine of training in slow to fast, slow to fast intervals.

Food Groups

Finally remember that consuming plant-based foods in their Natural Form is your best chance ofEATING your way to HEALTH. Eat more natural and less processed foods. www.lower6app.com

PLANT BASED FOODS ARE BEST FOR OUR OVERALL HEALTH IF WE WANT TO "LOWER" OUR RISK OF DISEASE

Low glycemic:	Low to moderate glycemic:	Moderate to high glycemic:	High glycemic:
•barley •black beans •cashews •cherries •grapefruit •green leafy vegetables •kidney beans •lentils •peanuts •pears •plums •soybeans •strawberries •wild rice	•All-Bran •apples •carrots •garbanzo beans •kidney beans •navy beans •oranges •peas •peaches •pears •pinto beans	•Figs •potatoes (sweet and white) •pita bread •oat bran •oat bread •white rice •kidney beans •shredded wheat	•Beets •Sweet breads •dates •pies •pretzels •refined durum wheat pasta •jelly beans •parsnips •sweet corn •white bread

FOODS ARE BEST CONSUMED IN THEIR NATURAL FORM.

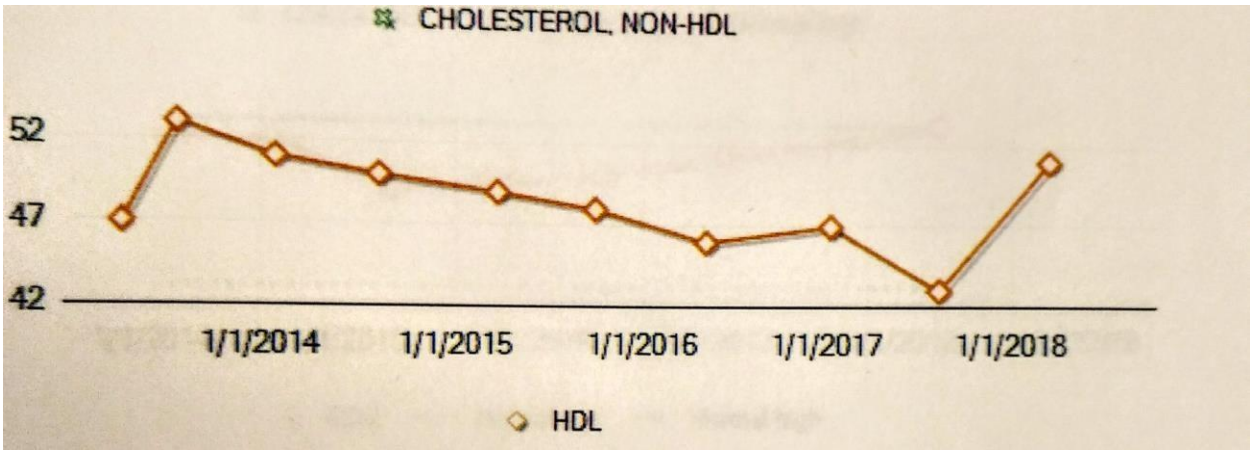
Low glycemic:	Low to moderate glycemic:	Moderate to high glycemic:	High glycemic:
•barley	•All-Bran		
•black beans	•apples	•figs	•beets
•cashews	•brown rice	•mangos	•cakes
•cherries	•carrots	•potatoes (sweet and white)	•dates
•grapefruit	•garbanzo beans		•pies
•green leafy vegetables	•grapes	•Raisins	•pretzels
•kidney beans	•kidney beans	•pita bread	•refined durum wheat pasta
•lentils	•navy beans	•oat bran	•jelly beans
•milk	•oranges	•oat bread	•parsnips
•peanuts	•peas	•white rice	•sweet corn
•pears	•peaches	•Pineapple	•white bread
•plums	•pears	•brown rice	
•soybeans	•pinto beans	•kidney beans	
•strawberries		•shredded wheat	
•wild rice			

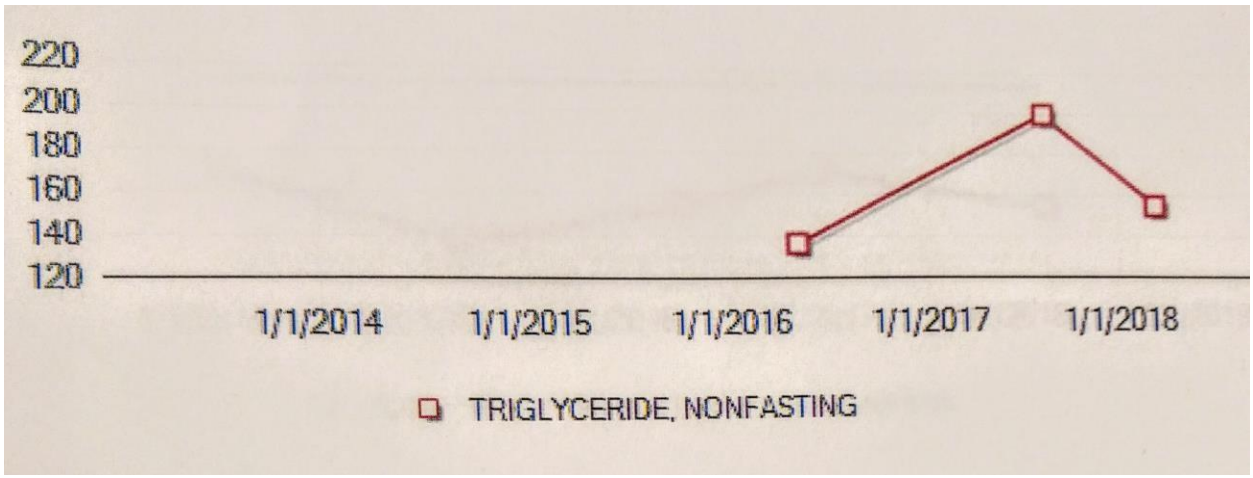
Chapter 2: Lower 6 Application

Clinical trial utilizes the Lower 6 phone application to measure the effects of the App.

From January 2017 to March 2018 a group of 100 people who live between Barranquilla, Colombia and Cali, Colombia were enrolled in a T-Dependent clinical trial utilizing the Lower 6phone application to measure how use of the App would affect the following health conditions;
1) HDL levels (Good cholesterol) 2) Triglyceride levels (Foods that are TRIED and FRIED) 3) Men with BPH or Prostatic carcinoma stage 1 or 2 4) Persons diagnosed with early onset DBM type 2 or Pre-Diabetes. A summary of the results and proposed physiological mechanism precedeeach graph. Too many people are dying from "Preventable illnesses" because patients are always non-compliant with taking their medications but human beings are always compliant with eating food. Eternal thanks to Dr. Vincente Jimenez from Cali, Colombia (R.I.P y Q.E.P.D) who passed away at a ripe old age 2 days before our meeting to advance the cause of preventive medicine. Colin Ross MD PhD MPH.

Estrogen production in pre-menopausal women, Omega 3-6-9 (Fish Oil) use and three to four 45min sessions of rigorous aerobic activity a week are three collective factors known to elevate cardio-protective HDL. High and functioning HDL levels are known to help prevent heart attacks, stroke and even the development of Alzheimer's disease. Excessive triglyceride consumption or production, a condition known as Type 4 hyperlipidemia, will suppress HDL levels hence increasing the risk of heart attack, strokes and even the development of Alzheimer's dease. None of the research subjects suffered from Type 4 hyperlipidemia. The triglyceride level chart and HDL chart demonstrated that as subjects included more LOW Glycemic indexed and LOW Glycemic load foods in their diet the level of triglycerides DECREASED as their levels of HDL INCREASED. This was for both men and women. BOTTOM LINE of this factor is LOWER RISK of heart disease, LOWER RISK of stroke and LOWER RISK of developing Alzheimer's Disease. (LOWER 6)





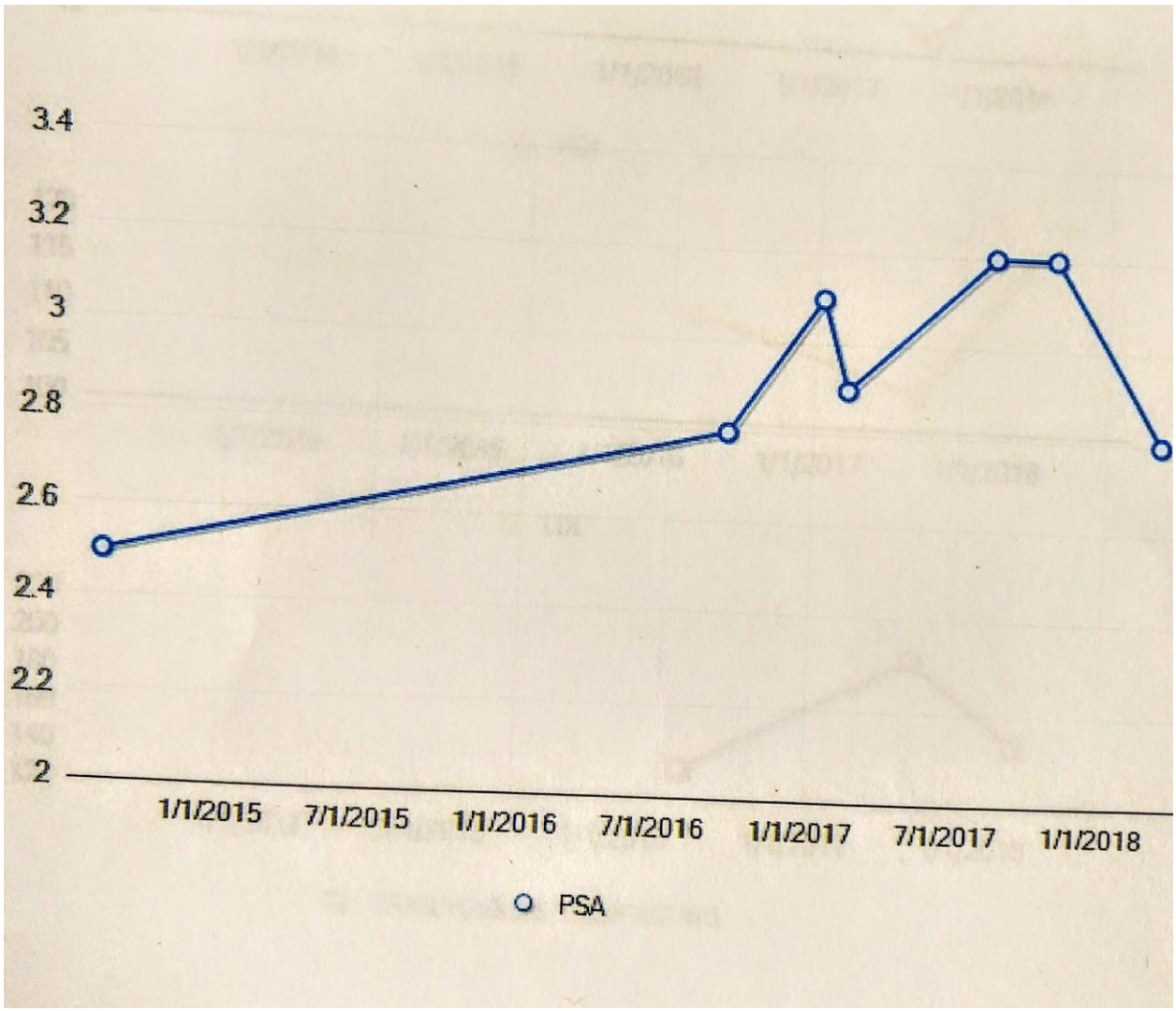
The link between GI and GL in terms of carcinogenesis, grade/staging, appear to have their link in Tyrosine Kinase activity. My conclusion at this point of the study points to a consistent and strong enough "GROW" signal linked to tyrosine kinase activity which causes the cancer cells, (not close in age to apoptosis), mixed in with normal cells, (closer to Apoptosis), to "GROW". Ifthis is true the I foresee three possible strategies in combating "genetically based cancers";

1) Creating a list of High GI and GL foods such as processed sugars being potentially carcinogenic for persons with high carcinogenic risk to avoid. (Food industry and Lower6 phoneapp)

2) Potentially blocking Tyrosine Kinase activity in persons discovered to have a stage 2-4cancer. (Pharmacological agent)

3) Toxicology study which identifies other potential chemicals shown to mimic Tyrosine Kinaseactivity in the body if this exists.

An Additional phase of this project which I haven't tweaked yet would be the incorporation of Vitamin E intake, (Antioxidant in the blood), Vitamin C intake, (Antioxidant in the G.I), at levelssufficient to minimize any potential free radical effect on the cancer cells, (not close in age to apoptosis), mixed in with normal cells, (closer to Apoptosis), to "GROW"



Use of the Lower6 app helped participants improve their A1C profile. For participants already on diabetic therapy we followed this "physiology" based guideline when selecting medications to help treat DBM type 2;

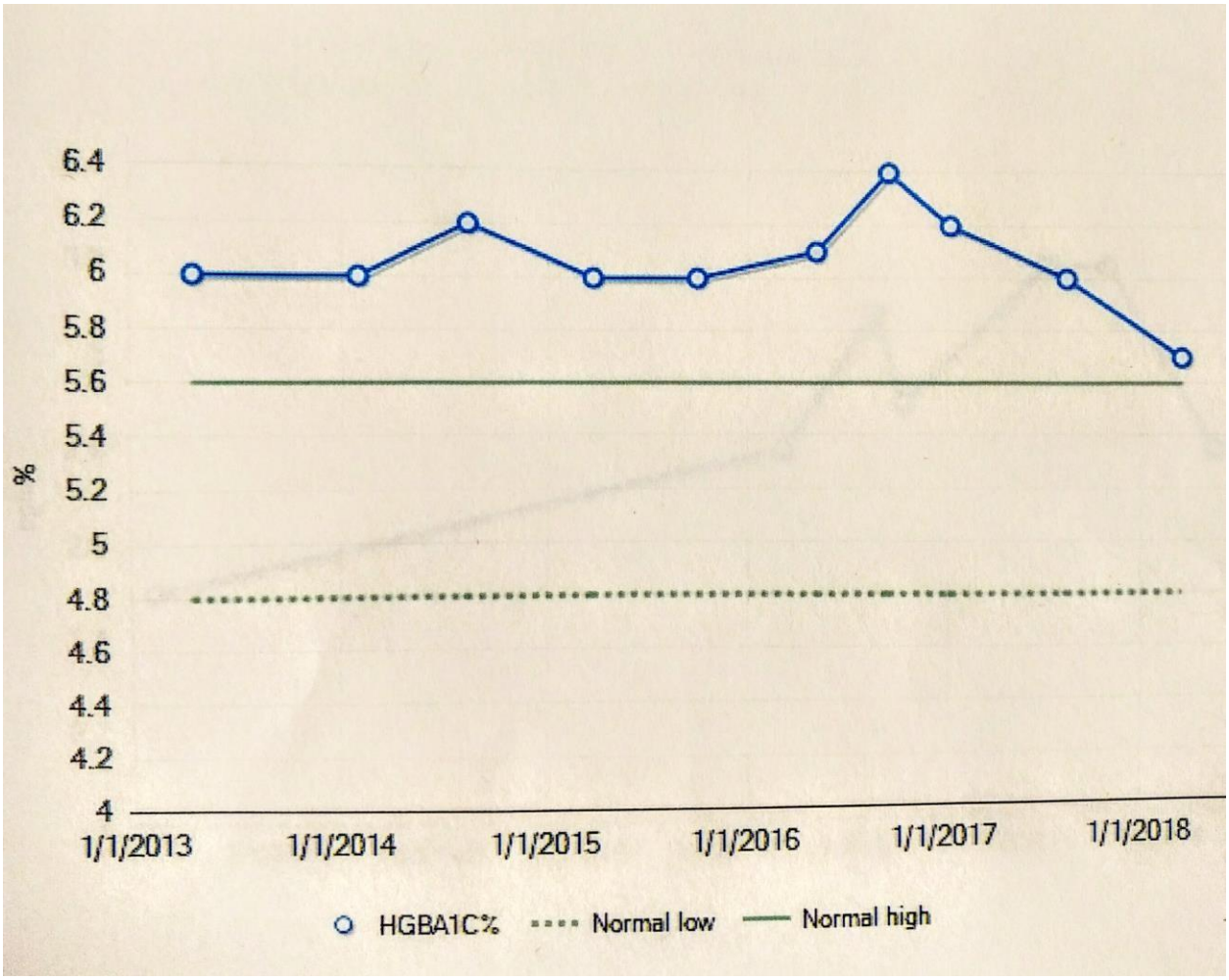
1) Basal insulin, Bolus Insulin and meal transmission time are crucial for DBM2 management.
2) Metformin/Rapid acting insulin, help control Bolus sugar spikes.
3) Sulfonylureas/Long-acting insulin, help control Basal sugar levels.

3) Use Metformin (First) = Bolus sugar control. When this starts to fail then #4

4) Metformin/Sulfonylureas = Bolus/Basal sugar control. When this starts to fail then #5

5) Metformin/Long-acting insulin = Bolus/Basal sugar control. When this starts to fail then #6
6) Rapid acting insulin/Long-acting insulin = Bolus/Basal sugar control.

My research demonstrated dark colored beans slow gastric emptying similar to the DBM2 medication Byetta. Slow gastric emptying helps a person feel full faster which stops them fromover eating. Stay tuned.



Chapter 3: Telemedicine

Improved A1C Readings for Diabetic Patients through Telemedicine

Improved A1C Readings for Diabetic Patients through Telemedicine

Colin Ross, M.D. Ph.D.
M.P.H.

Abstract

Background: Telemedicine has greatly affected healthcare service delivery in terms of reducing pharmaceutical errors, decreasing medical malpractice rates, and improving patient wait times during clinical visits. Telemedicine technologies are defined as electronic interfaces and information technologies that provide or support clinical healthcare at a distance. This study examined the influence of personalized mobile phone text messaging containing specific feedback based on patients' blood glucose levels and dietary choices on hemoglobin A1C levels for patients with type 1 diabetes living in rural areas.

Method: This study involved a quasi-experimental design. The dependent variables were the receipt of dietary instructions via text messaging and the subsequent lowering of hemoglobin A1C levels over a 3-month period of time. The sample consisted of 40 patients who were 18 years or older, suffering from type 1 diabetes, receiving bolus insulin therapy 3 times daily with suboptimal or poor glycemic control and having an HbA1C level ranging from 8.0% to 11.0%. **Results:** The results illustrated that a majority of study participants experienced statistically-significant changes in their hemoglobin A1C levels over the 3-month period of the study in response to patient-provider text message intervention.

Conclusions: These results indicated that personalized distance-care attended by chronic disease experts can facilitate general care and treatment of patients with diabetes and their needs that require timely intervention.

Introduction

Glycemic control is a focal matter for management of patients with diabetes. Erratic blood glucose fluctuations can occur in patients whose blood glucose level falls below 70 mg/dl or above 150 mg/dl, often due to the consumption of either high or low glycemic indexed or glycemic loaded foods [1]. A patient with diabetes who experiences continued erratic blood glucose fluctuations for time periods greater than 2 months could suffer from increased morbidity, disease burden, disease outcomes, or mortality [2].

Controlling carbohydrate intake (e.g. consumption of low glycemic foods) independent of body mass index (BMI) is crucial for diabetes management [3]. A 0.5 reduction of hemoglobin A1C (A1C) levels decreases the burden of disease for patients with diabetes in terms of days lost from work or school, as well as the physical strains associated with the disease such as feeling weak or tired [4]. Each

0.5 decrease in A1C also reduces the risk of developing chronic complications in patients with diabetes [4]. The most common strategy for diabetes management is pharmacological, wherein the patient administers insulin [5]; however, although the effect of insulin on erratic blood glucose levels is important, this effect is temporary and secondary to that of improved dietary sugar intake [6].

Mobile phone applications for diabetes can record and save a patient's food intake and blood glucose levels [7]. In cases of erratic blood sugar fluctuation, the patient can use the application and send a text message to the healthcare provider from any location. The healthcare provider can then send detailed instructions for dietary adjustments based on glycemic index or glycemic

loading through text message. Such telemedicine interventions involving exchanges of messages through mobile phone applications are approved by the Health Insurance Portability and Accountability Act (HIPPA) [7].

With rapid feedback provided via text messaging, there may be reduced occurrences of patients seeking treatment at medical facilities or missing school or work because of erratic blood glucose levels. Additionally, mobile applications for diabetes self-management have become popular, with features such as healthy eating and self-monitoring [8]. As the increasing number of patients with diabetes poses significant challenges for health providers, telemedicine may serve as an effective way to alleviate these challenges and reduce treatment costs [9].

Despite the benefits of telemedicine in managing diabetes, there is scant published research supporting its effectiveness [10]. [11] indicated that, because telemedicine leads to increased patient empowerment, it can help reduce A1C; however, [11] provided no specific strategies to achieve this goal. Existing systematic review data have shown little to no improvement of A1C in patients with type 1 diabetes who use mobile phone text or e-mail messages [12]. The missing component of such interventions has been the behavioral component, which could produce changes in dietary behaviors of patients with diabetes. When patients with diabetes have no expert guidance on nutritional choices, they may not adhere to dietary routines, resulting in harmful erratic blood glucose fluctuations [13].

The purpose of the present study was to test the efficacy of a mobile phone feedback mechanism to achieve tight glycemic control (i.e. maintaining blood

glucose levels between 70 to 150 mg/dl). The goals of the present study were to test the impact of telemedicine via text messaging and the ability of patients with diabetes to positively follow instructions to maintain healthy blood glucose levels through dietary adjustments. Based on the purpose and goals, the research question that was used to guide this study was: To what extent will the receipt of personalized instructions via text messaging reduce A1C levels over a three- month time period?

Methods

Study Design

The present study involved a within-subject pre-post quasi-experimental design, with supplementary evidence from another study conducted by the researcher. A dependent *t* test was used to compare random blood glucose levels of participants before and after telemedicine intervention. By having a single group of patients and taking repeated samples from them throughout the study, the researcher was able to eliminate between-subject variability and enhance the likelihood that changes seen were due to the intervention rather than other uncontrollable variables [14].

Population/Sample

The population for this study included patients diagnosed with type 1 diabetes. The sample included 40 participants who met the following inclusion criteria: (a) aged 18 and above; (b) had a diagnosis of type 1 diabetes; (c) was a patient undergoing daily bolus insulin therapy three times daily, with suboptimal or poor glycemic control based upon their A1C level; (d) had an A1C level

between 8.0% and 11.0%; (e) had missed time from school or work within a 3- month period because of erratic blood sugar fluctuation; and (f) lived in rural California, the designated area for this study.

Instruments/Measures

Participants were used the Glucose Buddy free mobile phone application by Azumio to record blood glucose levels and foods consumed, and their own glucometers to measure blood glucose levels. Participants also recorded their insulin dose, food intake, and activity levels in the electronic patient diary within the application. Random blood sugar levels were identified as readings less than 70 mg/dl or greater than 150 mg/dl. The A1C levels of participants were taken at the beginning of the study and 3 months after the study.

Data Collection

The researcher organized the raw data composed of random blood glucose readings and text messages exchanged between the healthcare provider and patient using the Glucose Buddy application. At the end of 3 months, the researcher calculated the hemoglobin A1C using the following formulas:

1. Three daily random blood glucose/3 = average daily random blood glucose.
2. The addition of average daily random blood glucose for 90 days/90 = three-month average daily random blood glucose.
3. Three-month average random blood glucose + 86/35 = calculated A1C over the 3-month period [15].

Data Analysis

Based on the results of the a priori power analysis conducted, the research required a minimum sample size of 35 patients. The power analysis was conducted based on several considerations, namely, the type of statistical analysis to be conducted (dependent samples *to* test) and a confidence interval of 95%. The

following formula was used [16]:

$$N = \frac{Z^2 S^2}{D \text{ x } 2}$$

Where:

N is the size of sample;

Z is the *z*-statistics for the desired level of confidence (1.96 for 95% confidence level);

S is the population standard deviation; and

D is the half width of the desired interval.

The precision of sample estimates was denoted by *D* [16], and based on the narrow A1C interval of 8.0 to 11, *D* was selected as 10. Based on the estimates, 30 was determined to be the appropriate *S* for the present study. For a 95% confidence level, the *Z* value was set at 1.96. A narrow A1C interval of 8.00 to 11 with a mean of 9.5, is more precise than a wider one. In this study, the researcher chose *D* = 10, or the A1C of 9.5 rounded up. As such, the required sample size was:

$$\text{N} = \frac{1.96(2) \text{ x } 30(2)}{10 \text{ x } 2} = 34.6$$

Rounding the number of 34.6, the researcher needed a sample size of 35 patients to be 95% confident that the true mean of the study was reflective of the

majority of patients with type 1 diabetes in the general population [16]. To test the hypotheses, dependent (paired sample) *t* tests of the preintervention and postintervention A1C levels were conducted. The *t* tests were conducted using IBM SPSS 22. The goal of the intensive feedback was to reduce the A1C calculation by 0.5 over 3 months, which is considered significant for the reduction of morbidity and mortality [17].

Ethical Considerations

Participants were examined by nursing staff to verify that they met the inclusion criteria for this study. The nurse informed patients of their rights as study participants including the voluntary nature of participation, their right to leave the trial at any time, what to do in case of emergencies, and how to download the Glucose Buddy application. Patients then signed an informed consent form while in the vitals processing room before meeting with the healthcare provider.

Patients who qualified for the study were assigned a random number that identified where they were placed on the data collection list. No value was associated with these hidden nominal variables, which served only to keep the

pre-post measurements together during the statistical data analysis. The researcher is a clinical staff member certified by the federal government to abide by HIPPA regulations to keep patient information private. Informed consent and release of information forms were reviewed by the researcher for each of the participants.

Participants' clinical records were not needed, so these records were not obtained. Transparency characterized every level of this research in such a way that the

participants' information did not end up in the databases of third-party organizations. The nurse in charge of quality assurance authorized the site and the participant group in this study.

Results

Assumption Testing

Prior to conducting inferential statistics to address the research questions, the researcher conducted assumption tests required for a paired or dependent samples *t* test. For this study, the sample was derived from patients living in a rural, California area, which comprised the population. Thus, the assumption that a random sample must be collected from a defined population was met [18]. The dependent variable was the difference in A1C level scale from baseline to posttreatment measurement. This variable was operationalized as a continuous variable, which satisfied the second assumption of having a continuous dependent variable. The results of the outliers test for the third assumption are shown in Figure 1 and Table 1.

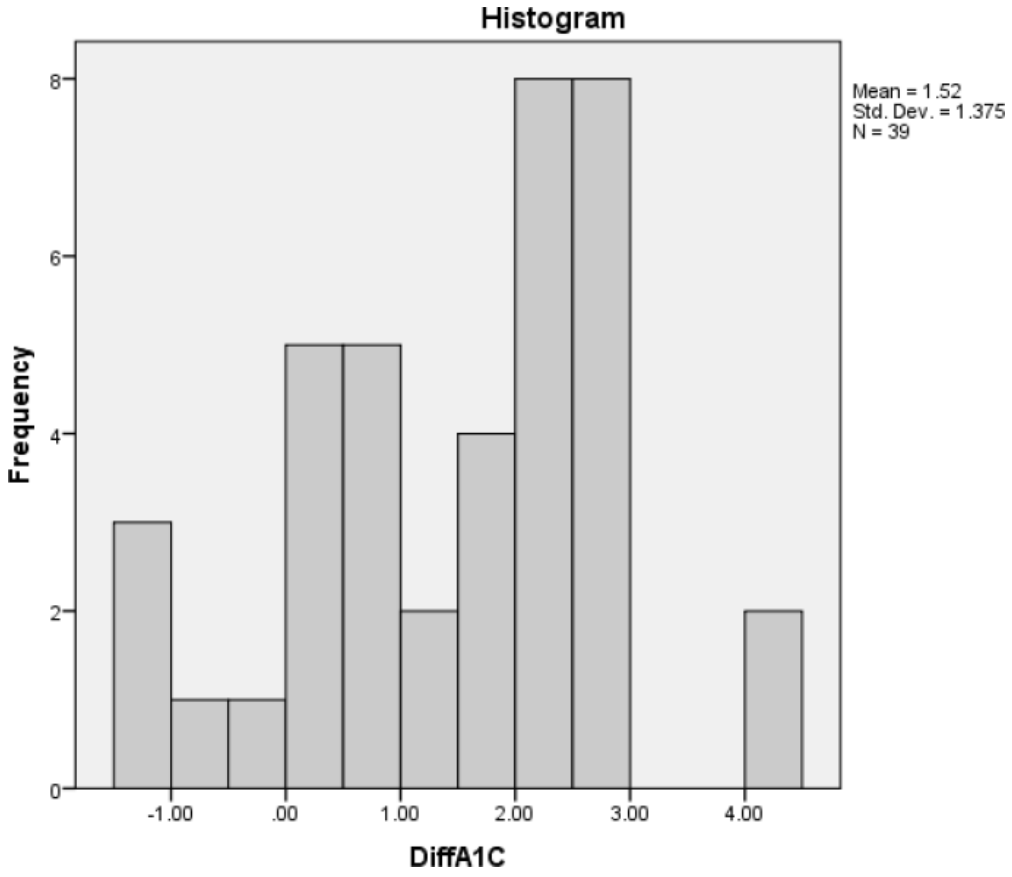


Figure 1. Histogram of DiffA1C

Table 1

Results of Outliers Test

		Case number	Value
Diff A1C	Highest	13	4.10
		25	4.10
		10	2.90
		11	2.90
		22	2.90
	Lowest	29	-1.10
		17	-1.10
		3	-1.10
		7	-.80
		37	-.10

Mean differences of the dependent variable must be normally distributed within the sample. In the present study's case, the dependent variable was the difference between the post- and preintervention scores, calculated by subtracting the post- from the preintervention scores. To determine whether the assumption of normality was met, a Shapiro-Wilk test was run in SPSS, using the reduced sample set of 35 participants. The results of the Shapiro-Wilk test are shown below in Table 2; with a *p*-value of .058, the sample is normally distributed.

Table 2

Results of Normality Testing

	Kolmogorov-Smirnov[a] Statistic	*df*	Sig.	Shapiro-Wilk Statistic	*df*	Sig.
Pre-post A1C	.175	38	.004	.946	39	.058

[a]Lilliefors significance correction.

Description of Blood Glucose Changes

The data was also tested for visual analysis of changes in A1C levels from pre- to postintervention. Figure 2 shows changes in the A1C levels of each

participant while Figure 3 shows changes in A1C levels for the entire sample. Table 3 shows the groupings of the participants with regard to the degree of changes in their A1C levels. The degree of change was determined based on the following ranges: minimal (< 1), moderate (1.1 - 2.5), and maximal (2.5 and above).

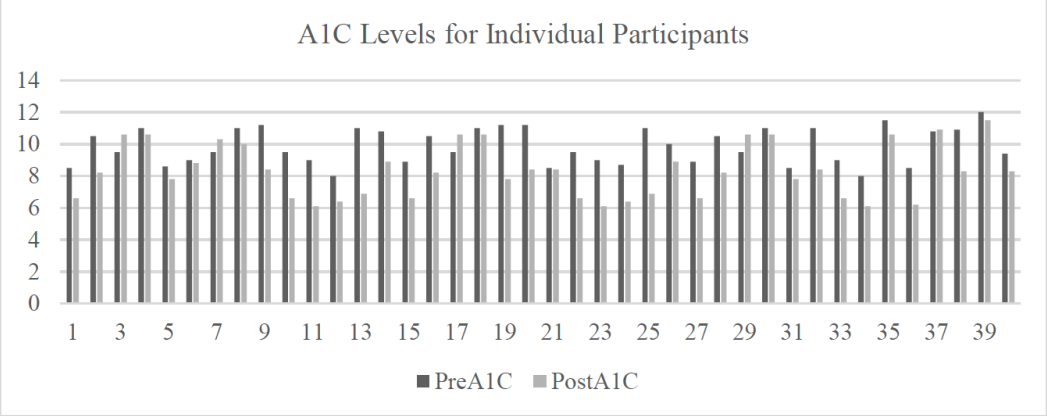


Figure 2. A1C Levels for Individual Participants

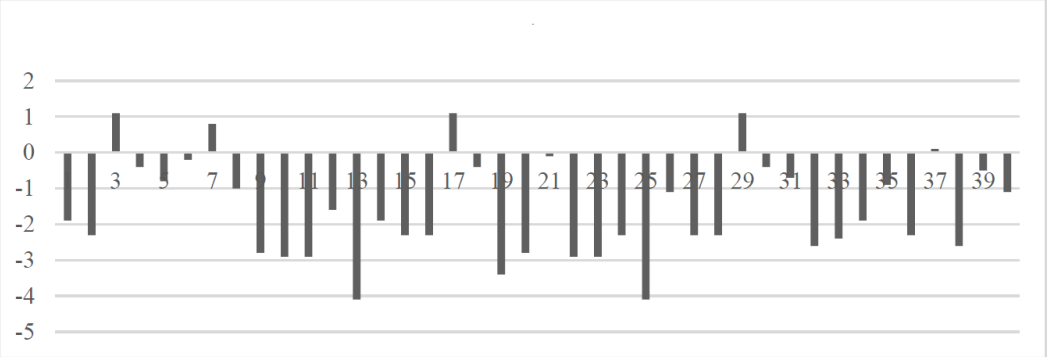


Figure 3. Changes in A1C Levels for Individual Participants

Table 3

Distribution of Participants (A1C Change Achieved)

Change	Patient	Preintervention A1C	Postintervention A1C	A1C Change
Positive	3	9.5	10.6	1.1
	17	9.5	10.6	1.1
	29	9.5	10.6	1.1
	7	9.5	10.3	0.8
	37	10.8	10.9	0.1
Minimal	21	8.5	8.4	-0.1
	6	9.0	8.8	-0.2
	4	11.0	10.6	-0.4
	18	11.0	10.6	-0.4
	30	11.0	10.6	-0.4
	39	12.0	11.5	-0.5
	31	8.5	7.8	-0.7
	5	8.6	7.8	-0.8
	35	11.5	10.6	-0.9
	8	11.0	10.0	-1.0
Moderate	26	10	8.9	-1.1
	40	9.4	8.3	-1.1
	12	8.0	6.4	-1.6
	1	8.5	6.6	-1.9
	14	10.8	8.9	-1.9
	34	8.0	6.1	-1.9
	24	8.7	6.4	-2.3
	36	8.5	6.2	-2.3
	2	10.5	8.2	-2.3
	15	8.9	6.6	-2.3
	16	10.5	8.2	-2.3
	27	8.9	6.6	-2.3
	28	10.5	8.2	-2.3
	33	9.0	6.6	-2.4
Maximal	32	11.0	8.4	-2.6
	38	10.9	8.3	-2.6
	9	11.2	8.4	-2.8
	20	11.2	8.4	-2.8
	10	9.5	6.6	-2.9
	11	9.0	6.1	-2.9
	22	9.5	6.6	-2.9
	23	9.0	6.1	-2.9
	19	11.2	7.8	-3.4
	13	11.0	6.9	-4.1
	25	11	6.9	-4.1

Data Analysis Results

The researcher then proceeded with the inferential statistical analysis to address the research questions. As shown in Table 4, there was a decrease in the mean scores from the preintervention A1C (M = 9.8225, SD = 1.11964) to the postintervention A1C (M = 8.3100, SD = 1.68032). Table 5 contains the results of the paired samples t test, which indicate that the decrease between pre- and postintervention A1C is statistically significant ($t(34) = 7.038$, $p < .001$). Based on these results, the null hypothesis was rejected and the alternative hypothesis, which stated "The receipt of personalized instructions will significantly reduce the level of hemoglobin A1C over a 3-month time period" was accepted.

Table 4

Results of Paired Samples t test – Descriptive Statistics

		M	*N*	*SD*	*SEM*
Pair 1	Pre-A1C	9.8225	35	1.11964	.17703
	Post-A1C	8.3100	35	1.68032	.26568

Table 5

Results of Paired Samples t test

			Paired Differences					
				95% Confidence Interval				
	Mean	SD	Std. Error Mean	Lower	Upper	*t*	df	Sig. (2-tailed)
Pair 1	Pre-A1C – Post A1C	1.51250	1.35915	.21490	1.07782	1.94718	7.038	34

Clinical significance, which pertains to whether the differences identified in the study are critical enough to result in changes in practice [19],

should also be considered for the clinical treatment of type 1 diabetes. While change in A1C levels was statistically significant, it does not necessarily equate to clinical significance.

Supplementary Evidence

To provide supplementary evidence, the researcher presented results from a separate within-subject trial conducted in Barranquilla and Cali in Colombia. A group of 100 individuals with early onset type 2 diabetes or pre-diabetes were enrolled in a t-dependent trial using the Lower 6 phone application developed by the researcher to measure how use of the application would affect their A1C levels between 2017 and 2018. The Lower 6 application provides information regarding the glycemic index and glycemic load of foods and recipes. Participants were tested biannually for A1C.

Results of this trial showed that the Lower 6 application helped participants improve their A1C profile. Figure 4 displays the mean A1C levels of the participants, showing a decline from 2017 when the trial was started to 2018. This supplementary evidence provides additional support for the use of telemedicine for patients with type 1 or type 2, as well as pre-diabetes.

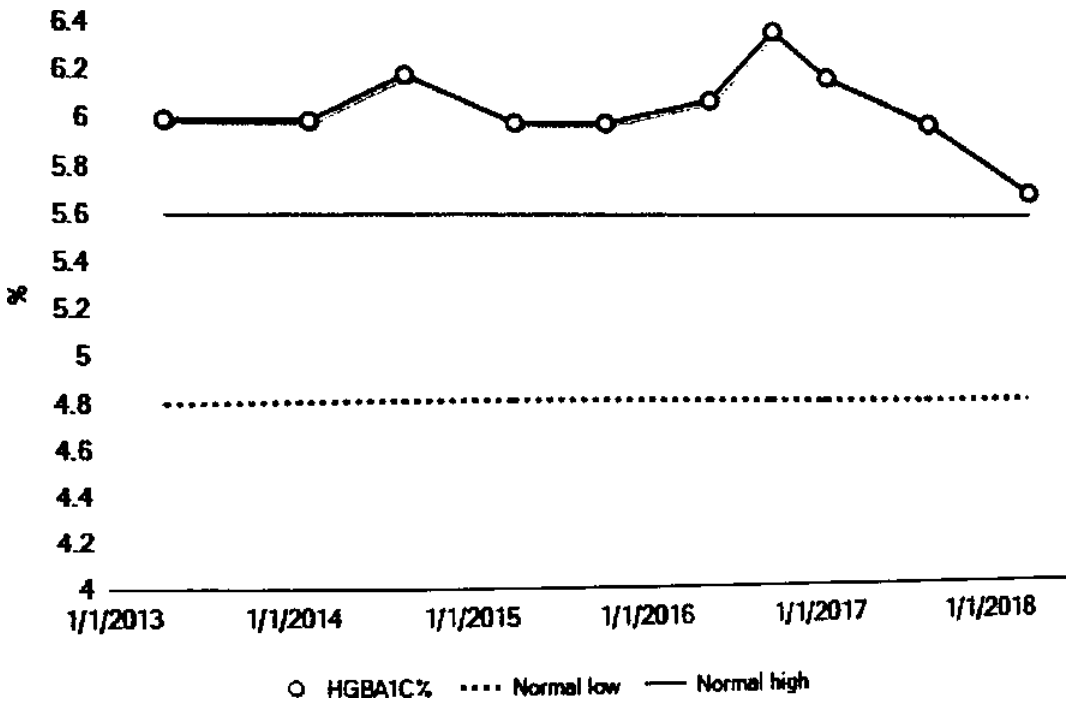


Figure 4. Changes in Mean A1C Levels of Participants

Discussion

The efficacy of a cell phone application that could help patients with diabetes improve their diets was tested in this study. The researcher hypothesized that using a mobile phone application to communicate personalized dietary instructions to patients with type 1 diabetes who live in rural California over a 3- month time period would reduce A1C levels. Ninety-seven percent of all participants experienced a decline from pre- to postintervention A1C levels.

Based on the collected data, the average preintervention A1C was at 9.8, while average postintervention A1C was at 8.3. The results of the paired samples *t* test indicated that there was a statistically significant decrease from pre- to postintervention A1C levels.

The decrease in the A1C levels may be attributed to the fact that lifestyle- related dietary management or nutrition medical therapy is considered a major factor for controlling type 1 and type 2 diabetes [20]. As part of the intervention, participants were given specific advice on how to improve blood glucose control through eating smaller portion sizes, eating fewer servings of specific types of food, or completely eliminating specific types of food from their diet. These dietary changes may have accounted for the statistically significant changes in the A1C levels. Thus, this provides support for the findings from previous researchers indicated that changes in the diet would have an effect on A1C levels of patients with diabetes [20,21]. The supplementary evidence regarding the use of Lower 6 application further supported this notion with the decrease in mean A1C levels of participants after receiving dietary information from the mobile phone application.

As shown by the results of this study, changes in diet alone had a statistically significant, although not clinically significant, effect on the A1C levels of the study participants. To be clinically significant, an A1C level within the range of 6-8 indicates the patient has maintained optimal blood glucose control for the period immediately preceding the measure [22]. Although the decrease in A1C levels of the participants from 9.8 to 8.3 was statistically significant, it was not clinically significant. These results suggest that this method of telemedicine, despite improving access to healthcare providers, providing personalized dietary advice, and reducing A1C levels, does not by itself improve medical outcomes for patients with type 1 diabetes.

It should also be noted that statistical significance relates only to the likelihood that the results were not due to chance [19]. Clinical significance, which pertains to whether differences identified in the study are critical enough to result in changes in practice [19], is what determines the use of an intervention in actual treatment. Thus, despite its effectiveness in reducing A1C levels among participants, the decision to use such telemedicine interventions for clinical treatment cannot be based solely on the results of this study. Further research is recommended including lifestyle changes in general and insulin bolusing, which may result in changes that are more clinically significant.

Conclusions

This study supports findings from previous research that found merit in the use of telemedicine intervention to support self-management and adherence to treatment regimens in patients with chronic diseases [23,24]. A majority of the participants in this study achieved statistically significant reductions in their A1C change score; however, the decrease was not great enough to be considered clinically significant. The attention given to patients with chronic diseases in rural settings has proved to be a viable avenue to resource stewardship; the cost to operate a program that utilizes smartphone technology is lower than the alternative of a patient hospitalization or in-person check-ups. Face-to-face medical care is important in treatment plans for people with long-term care conditions. That said, there is indication that the interspersed distance-care, when personalized to the idiosyncratic needs of individual patients, and when attended by experts in chronic disease, can facilitate the overall care and treatment of

people with chronic healthcare needs that require timely, if not intense, intervention.

To find out about a cell phone application created as a result of this study go to; www.lower6app.com

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Chapter 4: Estrogen Treatments

Estrogen treatments and risk of Alzheimer's Disease

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Abstract

Background: Since the publication of the Women's Health Initiative (WHI) trials, prescription of hormone therapy (HT) for menopausal women have declined. With interest on the potential benefits of HT being renewed, more researchers have examined its effects on cognition and risk of developing Alzheimer's Disease (AD). **Objective:** This systematic review was conducted to synthesize data regarding the use of HT during menopausal transition and its relationship with the risk of AD. **Methods:** A systematic literature search was conducted using the databases PubMed, Web of Science, and Google Scholar. **Results:** 40 articles were included in the review based on inclusion and exclusion criteria. The studies focused on themes of AD trends, biological mechanisms of AD, menopausal transition, menopause management, and effects of estrogen treatment. **Conclusion:** Generally, results from the studies have indicated potential cognitive benefits of estrogen, and in turn HT, on women in menopausal transition who are at risk for AD.

Introduction

The world is experiencing a surge of the aging population, with projections indicating adoubling of the number of individuals aged 65 and above by the year 2050 (Derby, 2020).

Within this aging population, the number of menopausal women is also projected to double (Ward & Deneris, 2018). Menopausal women undergo significant changes in their physical, mental, and sexual health (Heidari et al., 2019). These changes can have negative impacts on menopausal women's lifestyle, career, social activities, and their overall quality of life (Heidariet al., 2019). It is thus vital that menopausal women receive well-informed care (Ward & Deneris, 2018). Receiving such care would ensure that women can make proper decisions overtheir own health.

One of the most significant changes in menopausal women is the depletion of estrogen levels (Heidari et al., 2019). To compensate for this depletion and treat menopausal symptoms, hormone therapy (HT), or more specifically, estrogen treatment has been used on menopausal women (Scheyer et al., 2018). Estrogen treatment has been the gold standard for menopausal symptoms such as vasomotor and genitourinary symptoms (Santoro et al., 2021); however, results from the Women's Health Initiative (WHI) trials in 2002 have shown negative effects of HT, including a greater risk for dementia in women older than 65 years, among others (Caretto etal., 2018; Langer et al., 2021). The WHI randomized controlled trials involved the use of conjugated equine estrogens (CEE) with medroxyprogesterone acetate (MPA), and included women aged 50 to 79 in the United States (Chester et al., 2018). It was considered one of the largest studies on women's health, and as such, created monumental controversy in the field of women's healthcare.

Before the WHI publication, researchers have suggested a negative relationship between HT and dementia (Langer et al., 2021). Dementia, particularly Alzheimer's Disease (AD) represents another significant problem for the aging population (Ghanbari Gohari & Akhlagi, 2018; Hlavka et al., 2019; Weller & Budson, 2018). The risk of developing dementia increases with age and it was estimated that new cases of dementia would appear somewhere in the world every 4.1 seconds (Ghanbari Gohari & Akhlagi, 2018). The rate of deaths related to AD has also substantially increased, by as much as 89% in the United States between 2000 and 2014 (Weller & Budson, 2018), making it the 6th leading cause of death in the United States and 5th worldwide (Derby, 2020). It has also been cited as an economic burden, accounting for around 500 billion USD of the United States healthcare budget per annum (Weller & Budson, 2018). There remains to be a cure for AD, which highlights the importance of prevention (Ghanbari Gohari, & Akhlagi, 2018; Hlavka et al., 2019). Hormone therapy may be a potential factor to be considered in analyzing the risks of AD.

Physicians had customarily prescribed HT for the prevention of various chronic diseases prior to the WHI publication (Chester et al., 2018). Since the WHI publication, there has been a significant decline in the prescription of HT as well as the training in menopause management around the world (Caretto et al., 2018; Chester et al., 2018). Although the WHI results have caused alarm, it should be noted that they used CEE rather than human-identical hormones, which may have had a different effect (Gersh & Lavie, 2020). Furthermore, researchers have called attention to the possibility that the late administration of HT on women well into their postmenopausal years may have generated the undesired effects (Langer et al., 2021). The WHI results may thus have been an overestimation of risks, especially if the patient was younger and presented with low risks of chronic disease (Ward & Deneris, 2018). As such, researchers have

sought to reassess the effects of HT, provide a deeper understanding of its nuances, andovercome any misunderstandings regarding the WHI results.

Hormone therapy has since been revisited and reassessed for its relationship with chronicdiseases (Caretto et al., 2018; Ward & Deneris, 2018). Two pivotal studies, the Kronos Early Estrogen and Prevention Study (KEEPS) and the Early Versus Late Intervention Trial (ELITE), were published, showing support for the safety of HT when used in healthy women within a certain period (Chester et al., 2018). With the revived interest in HT, the North American Menopause Society (NAMS) amended their standpoint, indicating that HT should be prescribed on a case-to-case basis and within a window of time around the onset of menopause (Ward & Deneris, 2018). With these steps, various studies have since been published surrounding HT, including studies on the cognitive effects of HT; however, results of various trials appear to be inconsistent (Pertesi et al., 2019). As such, the problem being tackled in this systematic review involves the use of estrogen treatments during menopausal transition and its relationship with therisk of AD.

Alzheimer's Disease

Alzheimer's Disease (AD) is a progressive disease that falls under the category of dementia. Dementia is used as the general term describing two or more neurodegenerative symptoms including impaired memory, executive function, and/or language skills, among others,which affect their daily living (Alzheimer's Association, 2021; Weller & Budson, 2018). The specific term, AD, is used to describe the type of dementia that is purported to be caused by certain changes in the brain, particularly in terms of hippocampal and cortical atrophy, as well asloss of synapses (Chávez-Gutiérrez & Szaruga, 2020). Alzheimer's Disease is the most prevalenttype of dementia, accounting for around 60% to 80% of dementia cases (Alzheimer's

Association, 2021; Derby, 2020). As an age-related set of diseases, dementia, and particularlyAD, is considered a significant public health and social issue (Derby, 2020; Trevisan et al., 2019). Almost all elderly individuals gain increased risks of dementia as they age (Trevisan etal., 2019). Prevention of AD has thus been a topic of interest healthcare.

The history of AD can be traced back to 1906 when German Psychiatrist Alois Alzheimerpresented a case of a 51 year old female patient, who showed signs of cognitive decline and behavioral changes (Derby, 2020; Trevisan et al., 2019). The case was presented during the Southwestern German Psychiatrists' 37th convention; however, the disease was actually named by his colleague, Emil Kraepelin in 1910 (Liu et al., 2019). Alzheimer's Disease received modestattention up until 1963, when medical researchers Robert Terry and Michael Kidd sparked renewed interest in the disease through their electron microscopy analysis of neuropathological lesions. The analysis was performed on two patients with advanced AD, and revealed neurofibrillary tangles within the brains (Liu et al., 2019). Since then, various developments in AD research have led to the current conceptualization of AD as a pathologic process that can be identified by certain biomarkers including beta-amyloid deposition and tau pathology (Blennow & Zetterberg, 2018).

The developments in AD studies have led to the establishment of clinical diagnostic criteria published by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) in1984 (Derby, 2020). A clinical diagnosis of AD comprised evidence of progressive memory deterioration alongside a degradation of language, motor function, and perception that are not explained by other disorders. These clinical symptoms were historically assumed to be related tounderlying neuropathology (Derby, 2020). When patients met these criteria, a diagnosis of

probable AD was given, which could only be considered as *definite AD* with an autopsy investigation upon death (Blennow & Zetterberg, 2018). A diagnosis of definite AD would require microscopic assessment of several brain areas using staining methods, taking note of lesion morphology and density, as well as their topographic distribution (DeTure & Dickson,2019).

Recently, researchers have striven towards establishing biological criteria of AD stemming from the works of neurologist Bruno Dubois and the International Working Group (Blennow & Zetterberg, 2018). These biological criteria involved the use of biomarkers such as tau proteins and amyloids. Individuals showing early signs of AD, classified as mild cognitive impairment (MCI), may be tested for such biomarkers to determine the need for greater prevention efforts (Blennow & Zettenberg, 2018). Neuroimaging or cerebrospinal fluid testing may be used to detect these biomarkers (Hlavka et al., 2019). Genetic markers of AD have also been explored, with mutations in either the amyloid precursor protein (APP), presenilin 1 (PSEN1), or presenilin 2 (PSEN2) genes indicating familial AD, as opposed to sporadic AD (DeTure & Dickson, 2019). Familial AD is less prevalent, accounting for only 1-5% of AD cases(Liu et al., 2019). Familial AD also has a greater association with early onset rather than late onset AD, occurring before age 65 (DeTure & Dickson, 2019).

Aside from the main symptoms of impaired memory, language and executive function, other symptoms have also been associated with AD such as emotional instability, loss of judgment, behavioral and personality changes, and disorientation (Alzheimer's Assocation, 2021; Trevisan et al., 2019). It may be difficult for individuals with AD to recognize faces, recallnames, or remember recent events. As the disease progresses, individuals with AD may have more trouble communicating, walking, or even swallowing. Although these symptoms are more

discernable as the individual ages, the onset of AD was purported to begin 20 years or more priorto these symptoms (Alzheimer's Association, 2021). Preventive measures are thus vital for the elderly at risk, even when symptoms are not yet observed.

The prevalence rates of AD around the world were found to be two to three times higher in women than men (McCarthy & Raval, 2020; Song et al., 2020). Estimates of one in five women were said to develop AD in their 60s (McCarthy & Raval, 2020), with the risks increasing immediately after menopause (Pertesi et al., 2019). Notably, women who experiencedpremature menopause also had a higher risk of AD (Song et al., 2020). Although it was initially believed that the increased risk of AD in women was primarily because they lived longer, other factors should also be considered, including biological and sociocultural differences (Alzheimer's Association, 2021).

Changes in brain metabolic status, shifting the energy sources from glucose to fatty acid and ketone bodies, which occur as individuals age was purported to contribute to AD (Wang et al., 2020). The aggregation of myelin debris caused by these changes leads to chronic system inflammation, which in turn, can lead to neurogenerative diseases such as AD (Wang et al., 2020). Furthermore, the accumulation of amyloid beta (Aß) plaques and tau neurofibrillary tangles were cited as the hallmark of AD (Alzheimer's Association, 2021; Blennow & Zetterberg, 2018; Chávez-Gutiérrez & Szaruga, 2020; Depypere et al., 2016; Derby, 2020; Liu et al., 2019; Pertesi et al., 2019). Clumps or plaques of Aß occur outside neurons while tangles of tau proteins occur inside neurons, particularly in the medial temporal lobes, causing further neurodegeneration and interrupting synapses within the brain (Alzheimer's Association, 2021; Pertesi et al., 2019). These plaques and tangles are used in the confirmation of AD during autopsy (Derby, 2020), and represent the biological onset of AD as they appear in the brain

around 20 or more years prior to the onset of symptoms (Chávez-Gutiérrez & Szaruga, 2020). Notably, irregular amounts of amyloid deposits do not necessarily translate into AD symptoms asother factors, such as genes or the environment, may also be of consequence (Depypere et al., 2016).

Tangles of tau protein were found to be abnormally hyperphosphorylated due to the activation of various protein kinase as well as phosphatase enzymes (Depypere et al., 2016). Tangles were noted to be up to three times more phosphorylated than normal tau (Blennow & Zetterberg, 2018). Such hyperphosphorylation cancels out the tau protein's function of bindingand stabilizing microtubules within the neuron and in turn, disrupts neuronal transmissions (Blennow & Zetterberg, 2018; Liu et al., 2019). Although the sequence of plaques and tangles remain unconfirmed, Aß accumulation was purported to precede and lead to tau accumulation (Alzheimer's Association, 2021). Developments regarding the mechanisms of amyloid plaquesand tau tangles have engendered a deeper understanding of AD and the possibilities of prevention.

Aside from the biomarkers of Aß and tau, research on genetic risk factors for AD also point to apolipoprotein E (APOE), particularly the E4 allele (APOE4; Antonelli et al., 2019; Liuet al., 2019; Pertesi et al., 2019; Wang et al., 2020). The APOE gene in chromosome 19q13.2 produces the protein also called apolipoprotein E (ApoE), which is responsible for lipid metabolism (Liu et al., 2019). The APOE4 was purported to increase Aß and promote tau hyperphosphorylation. In line with this, frequency of APOE4, as well as its heterozygous and homozygous carriers, have been associated with late-onset AD (Liu et al., 2019; Pertesi et al., 2019). Notably, this association was found to be stronger in women than in men, which may be accounted for by sex hormone modulators (Antonelli et al., 2019). The use of APOE4 genotype

in combination with metabolic phenotype was purported to be useful in identifying individuals atrisk for neurodegenerative diseases, particularly in postmenopausal women (Wang et al., 2020). The APOE4 is thus known as the strongest genetic risk factor for AD thus far (Depypere et al., 2016; Liu et al., 2019).

There has yet to be a disease-modifying therapy established for treating AD (Hlavka et al., 2019); however, patients exhibiting AD symptoms are prescribed cholinesterase inhibitors ormemantine (Weller & Budson, 2018). Although these treatments do not stop or delay the progression of the disease, they have been cited to enhance both patients' and their caregivers' quality of life (Weller & Budson, 2018). In recognition of the progressive nature of AD, more attention is being given to prevention, with current trials focusing on early stages of AD (Hlavkaet al., 2019). Women undergoing menopausal transition may thus be ideal candidates for such studies.

Menopause

Menopause represents another significant healthcare problem with the rapidly growing aging population. The number of women over the age of 45 in the United States was estimated tobe around 70 million (Perlman et al., 2018). These women may be nearing or already experiencing menopause. Although menopause is a natural life event, it can have debilitating effects on one's quality of life (Genazzani et al., 2018). It was estimated that menopausal symptoms can lead to 10-15% lower efficiency at work, 23% increase in absences from work, and 40% increase in health-related spending (Genazzani et al., 2018). The link between menopause and dementia further exacerbates the problems of this population of women. Notably,women who had an earlier onset of menopause, natural or otherwise, were purported to have

higher risks of developing dementia (Depypere et al., 2016). As such, menopause management isa vital part of preventive healthcare (Ward & Deneris, 2018).

Menopause has been defined as the last menstrual period of a woman as ovarian follicularactivity ceases (Caretto et al., 2018; Scheyer et al., 2018). Humans have a set number of follicles with around 6-7 million oocytes before birth (Genazzani et al., 2018). Due to apoptosis, the number of oocytes immediately decline, reaching approximately 300,000 at puberty and eventually being depleted during menopause (Genazzani et al., 2018). Menopause can be officially diagnosed after a woman experiences 12 months without menstruation, which usually occurs between the ages of 40 to 58, averaging at 51 years (Caretto et al., 2018; Scheyer et al., 2018). Women typically begin experiencing symptoms 2 to 8 years before menopause, a period that is termed *perimenopause* (Ward & Deneris, 2018). Perimenopause can persist between less than a year to 10 years, averaging at around 3 to 4 years (Morgan et al., 2019). Notably, heritability plays a significant role in the age of onset of menopause, with similarities between mothers, daughters, and sisters (Mishra et al., 2019).

A considerable part of menopause is the decrease of estrogen (Heidari et al., 2019). Estrogen was defined as a steroid hormone responsible for sex-related characteristics and reproductive functions (Morgan et al., 2019). Estrogen may be classified into three compounds, namely, estrone (E1), estradiol (E2), and estriol (E3), with E2 being the most potent in premenopausal women (Morgan et al., 2019). Estrogen is produced with the help of gonadotropins, including

follicle stimulating hormones (FSH) and luteinizing hormones (LH), which are discharged from the pituitary gland as regulated by the hypothalamus (Antonelli et al.,2019). An increase of FDH and LH levels, as well as significant reduction of E2, are indicative of menopause (Antonelli et al., 2019; El Khoudary et al., 2019).