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Mini Review

*Corresponding author
David W. Harrison, PhD
Director
Behavioral Neuroscience Laboratory
Psychology Department
College of Science
Virginia Polytechnic Institute
Blacksburg, VA 24061-0436, USA
Tel. (540) 231-4422
E-mail: dwh@vt.edu

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Brain Mechanisms in Blood Glucose Mobilization and Absorption: The Role of the Left and the Right Frontal Regions in the Regulatory Control of Blood Glucose Levels

Benjamin B. DeVore, MS; David W. Harrison, PhD*

Department of Psychology, Virginia Polytechnic Institute and State University, Blacksburg, VA 24061, USA

With the ravaging effects of glucose related diseases (such as diabetes) on the rise, an increased understanding of the central mechanisms involved in glucose mobilization and absorption, and the potential development of the metabolic syndrome, is becoming increasingly important. Although, substantive efforts have been expended to better understand the peripheral mechanisms involved with the systemic processing of glucose, there remains a paucity of research dedicated to the central neural aspects largely involved in the mobilization and absorption of blood glucose. Despite this lack of research, the relationship between emotional states of anger or fear and those oppositional processes associated with quiescent states or digestive uptake have been clearly related to blood glucose levels.[1-3] Moreover, and perhaps most relevant here, is that the differential emotional states just described have been established with origins in cerebral laterality and with regulatory control mechanisms largely relegated to the frontal lobes and executive brain systems.[4-6]

We have provided evidence with the potential to bridge this gap between brain theory and research on peripheral mechanisms with specializations of the right brain for intense emotional states and sympathetic drive[7-10] and with somewhat oppositional specializations of the left brain for quiescent states and perhaps parasympathetic drive. Functional cerebral systems theory[11-14] demonstrates the regulatory control over sympathetic drive by the frontal lobe executive regions, where incremental blood pressure, heart rate, sweating, cholesterol levels, and blood glucose levels may provide the biological resources and reserves for the fight with relevance to insure success in meeting the potentially coercive threat or challenge. Furthermore, cerebral balance theory[7] supports oppositional mechanisms with quiescent states and the establishment of resource reserves largely by left cerebral systems. This brief review of current neuropsychological research will present a theoretical foundation, based upon Alexander Luria's functional cerebral systems theory, for the preferential activation of glucose metabolism by the right cerebral hemisphere (Figure 1).

Fundamental to the presented argument is the theoretical construct, that the majority of emotional processing, particularly intense emotions such as anger or fear, are lateralized to the right hemisphere.[15] Research in our lab looking at violent-prone individuals has consistently supported this theory by showing decreased frontal lobe regulation of right posterior anger and negative emotionally responsive brain regions.[4,16] Of further import to the theory of right hemispheric glucose mobilization is evidence showing sympathetic response is substantially under right hemispheric control and that overall cardiovascular recruitment is driven by right hemispheric activation. Current research efforts,[17] comparison studies of the left-versus-right sided cerebrovascular accidents,[18] and unilateral intracarotid sodium amobarbital injections (UISAI) [Wada technique][18] all support the relative role of the right hemisphere in sympathetic response.

Given the integral role of blood glucose as the major fuel source for the brain, it follows

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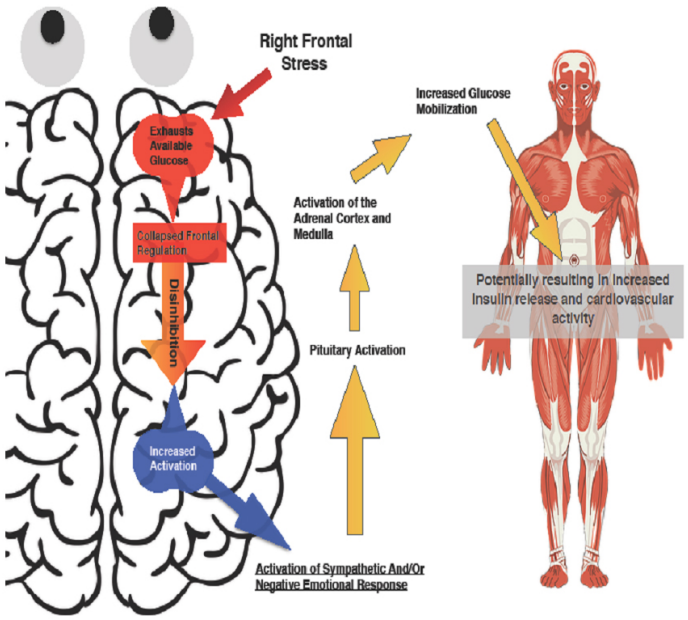
Figure 1: Right Frontal Regulatory Role Over Glucose Mobilization Depicting Capacity Limitations.



that processes such as intense emotion or increased sympathetic drive would require increase levels of glucose for mobilization of action.[2] To help illustrate how glucose may be regulated (or deregulated in certain cases), our lab has proposed the quadrant theory of neural functioning. Anatomically, the anterior and posterior "quadrants" of the brain communicate within each hemisphere *via* the longitudinal tract. Similarly, the anterior and posterior regions of each hemisphere communicate with the parallel region across the corpus callosum.[19] Given this general wiring of the various regions, each quadrant appears to compete for cerebral resources, specifically glucose, for a given function. Due to the overall regulatory role of the frontal lobe, if the right frontal region were to exhaust the general supply of glucose available, posteriorly there would be an "unbridling" or cortical release of processes typically under frontal control. Right posterior release or activation has been shown to result in increased sympathetic response and heightened emotional intensity with underlying sympathetic nervous system activation.[20] These more intense and often negatively valenced emotional responses further result in an overall increase in blood-glucose levels.[21] Chronic or pervasive stress or negatively valenced emotional biases appear to have far reaching health implications, possibly including the development of diabetes and the metabolic syndrome. Systematic research efforts in our laboratory have provided evidence that inadequate capacity for right frontal regulatory control over negative or intense emotions and over sympathetic activation is sufficient for the reactive elevation of blood glucose levels.[2,3] This is apparent in high hostile violent-prone men with chronic effects connected to the increased likelihood of developing metabolic syndrome.[3]

While a good amount of research is still needed, the evidence for the role of the right hemisphere in glucose mobilization and the potentially opposition role of the left hemisphere in glucose absorption, digestive advance, and quiescent emotional states cannot be ignored. With the increasing costs and health risks associated with glucose related diseases, efforts must continue to be made to both determine the specific role of the right hemisphere in both glucose mobilization and gluconeogenesis. With greater understanding of these processes within lateralized brain regions, cause specific treatment methodologies can be identified and utilized.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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Research

*Corresponding author
Makiko Nakade, RD, PhD
Faculty of Health and Welfare
Tokai Gakuin University
5-68 Nakakirino-cho
Kakamigahara, Gifu 504-8511, Japan
Tel. +81 (58) 389-2200
Fax: +81 (58) 389-2205
E-mail: nakade_m@tokaigakuin-u.ac.jp

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Associations of Waist-to-Height Ratio with Various Emotional and Irregular Eating, and Making Environment to Promote Eating in Japanese Adults: The Saku Cohort Study

Makiko Nakade, RD, PhD[1*]; Naomi Aiba, RD, PhD[2]; Akemi Morita, MD, PhD[3]; Motohiko Miyachi, PhD[4]; Kijo Deura, MD[5]; Fumie Soyano, RN[6]; Shaw Watanabe, MD, PhD[7]; for Saku Cohort Group

[1]Faculty of Health and Welfare,Tokai Gakuin University, 5-68 Nakakirino-cho, Kakamigahara, Gifu 504-8511, Japan
[2]Department of Nutrition and Life Science, Kanagawa Institute of Technology, 1030 Shimo-ogino, Atsugi, Kanagawa 243-0292, Japan
[3]Department of Nutrition, Koshien University, 10-1 Momijigaoka, Takarazuka, Hyogo 665-0006, Japan
[4]Department of Health Promotion and Exercise Program, National Institute of Health and Nutrition, National Institutes of Biomedical Innovation, Health and Nutrition,1-23-1 Toyama, Shinjuku-ku, Tokyo 162-8636, Japan
[5]Dock Center, Saku Central Hospital Nagano Prefectural Federation of Agricultural Cooperatives for Health and Welfare,197 Usuda, Saku-City, Nagano 384-0301, Japan
[6]The Graduate School of Nursing, Saku University, 2384 Iwamurada, Saku, Nagano 385-0022, Japan
[7]Life Science Promotion Foundation, 25-3-1004, Daikyo-cho, Shinjuku-ku, Tokyo 160-0005, Japan

ABSTRACT

Objective: The waist-to-height ratio (WHtR) has started gaining attention as a measure of abdominal obesity. While the associations between various eating behaviors and high BMI or obesity or overweight determined by BMI have been reported, studies focusing on the relationship between eating behaviors and the WHtR in adults are scarce. This study aimed to clarify eating behaviors associated with a high WHtR in Japanese adults.
Study design: Cross-sectional study.
Methods: Subjects were 1674 men and 1144 women aged 20 to 75 years who participated in a baseline assessment of Saku cohort study in Japan from 2009 to 2011. The subjects underwent a physical examination and answered a questionnaire regarding various eating behaviors (emotional eating, irregularity of eating (including having late-night snacks, eating between meals, having many occasions to go to drinking parties, skipping breakfast and having dinner late), eating fast, eating until full, external eating and making environment to promote eating), lifestyles, and stage of change regarding diet. The relationship between the WHtR (<0.5 as a reference) and each eating behavior was examined using multiple logistic regression analysis adjusting for age, sex, lifestyles, and stages of change regarding diet.
Results: After adjusting for covariates, the WHtR showed significant positive relationships with eating behaviors regarding all items of emotional eating, having late-night snacks, eating between meals, having many occasions to go to drinking parties (in the irregularity of eating category), eating fast, eating until full, all items of external eating and making environment to promote eating. Skipping breakfast and having dinner late (in the irregularity of eating category) did not show significant associations with the WHtR.
Conclusions: Some eating behaviors were associated with a higher WHtR in adults. Putting more emphasis on modifying these specific eating behaviors may effectively decrease the WHtR and prevent cardiovascular diseases.

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KEY WORDS: Waist-to-height ratio; Obesity; Overweight; Eating behaviors; Eating habit; Environment; Adults; Cardiovascular disease; Behavior modification.

ABBREVIATIONS: WHtR: Waist-to-Height Ratio; BMI: Body Mass Index; WC: Waist Circumference; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure.

INTRODUCTION

Adiposity is a serious public health concern, causing many lifestyle diseases such as hypertension, dyslipidemia, hyperuricemia, and type 2 diabetes.[1] A recent World Health Organization (WHO) report indicated that, worldwide, 34% of adult men and 35% of adult women aged 20 years or above were overweight and that 10% of men and 14% of women were obese.[2] In Japan, the prevalence of obesity and/or overweight was lower than the WHO's report; however, the prevalence has increased in all age groups of men aged ≥20 years and in middle-aged women over the last 2 or 3 decades.[3,4] While the prevalence of obese or overweight women has slightly decreased, the prevalence of obese or overweight men has remained unchanged for almost a decade.[5]

A widely used measure to determine adiposity is the body mass index (BMI), calculated by height and weight. However, this measure does not distinguish between fat mass and lean mass, or capture distribution of body fat.[6]

Recently, positive associations between abdominal obesity and cardiovascular disease risk factors such as hypertension,[7] type 2 diabetes,[8] and plasma lipids[9] have been reported. Waist circumference (WC) is a simple and frequently used measurement for estimating abdominal obesity. However, there is disagreement as to whether the degree of cardiovascular disease risk may differ by height, in cases with similar WCs.[10,11] Therefore, a waist-to-height ratio (WHtR), or WC divided by height, has been proposed. Many studies comparing the WHtR and other adiposity measures such as BMI or WC as a predictor of cardiovascular disease have been conducted, and a systematic review of 78 studies concluded that the WHtR and WC were stronger predictors than BMI.[10] The review also indicated that the WHtR may be a more useful screening tool than WC, proposing a WHtR of 0.5 as a suitable global boundary value in clinical screening.[10]

Adiposity occurs due to an imbalance of energy intake and expenditure. Eating behavior is one of the factors that affects energy intake. An assessment of eating behavior is less complicated than calculating energy intake, which requires detailed information about food intake, and therefore is likely to be a practical tool for dietary intervention.[12]

Previous studies have examined relationships between various eating behaviors and BMI or obesity or being overweight determined by BMI in adults. For example, eating quickly has been associated with being overweight or obese, as shown in some cross-sectional studies,[12-15] and with weight gain in a prospective longitudinal study.[16] Ohkuma et al[17] conducted a meta-analysis using 23 cross-sectional or longitudinal studies and concluded that eating quickly is positively associated with excess body weight. Other behaviors which have shown positive relationships with BMI or obesity or being overweight were emotional eating,[18,19] skipping breakfast,[20] night eating (awake during the night to eat)[21,22] and eating until full.[12,14] Eating between meals[23] and external eating[24] (eating in response to food-related stimuli, regardless of the internal state of hunger or satiety[25]) were also associated with substantial weight gain. On the other hand, there have been reports of eating behaviors that did not show significant association with being overweight: skipping breakfast,[15] eating late evening meals,[15] late-night snacking,[12] and eating between-meals.[12]

In respect of the WHtR, positive relationships with skipping breakfast in 9 to 11-year-old children[26] and eating quickly in 12- to 13-year-old children have been reported.[27] However, to our knowledge, no study has examined the relationships between the WHtR and eating behaviors in adults. Identifying eating behaviors that positively affect the WHtR, and recommending people avoid these behaviors is likely to be useful in preventing or reducing abdominal obesity in adults. Therefore, the present study aimed to examine the relationships between the WHtR and various eating behaviors among adults in Japan.

METHODS

Study Subjects

All subjects were participants in a cohort study conducted at the Saku General Hospital Human Dock Center in Nagano Prefecture in Japan. Recruitment was carried out among people aged 20 to 75 years who visited the Dock Center from 2009 to 2013. By 2011, a total of 3620 men and women agreed to participate in the study and underwent a baseline assessment including anthropometric measurement, blood-pressure measurement, blood test and a questionnaire about eating behaviors, lifestyles, and stage of change regarding diet. Written information, including the purpose of study, a right to refuse participation, and assurances on the security of personal information, was handed to each participant. Written informed consent was obtained from all participants. The study protocol was approved by the Ethics Committee of the National Institute of Health and Nutrition (#R201409-01).

Outcome Measures

Height was measured with footwear removed, and body weight was measured wearing light clothing for all participants (Inner Scan BC-200: TANITA, Japan). All measurements were undertaken in the morning, prior to eating. The BMI was calculated from the body weight (kg) divided by the height squared (m^2). The WC was measured in the upright position using a cloth tape measure. To standardize the WC measurement, a cloth tape mea-

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sure was looped around each participant's waist and back horizontally, at the level of the umbilicus, and measurements were taken to the nearest 0.1 cm after the participant exhaled freely. The WHtR was calculated from the WC (cm) divided by the height (cm).

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured twice using an automatic manometer (HEM-907, Omron Healthcare Co., Ltd., Kyoto, Japan) after the subject had sat at rest. The average of two blood pressure measurements was used for the analysis. Blood samples were collected from the anterior cubital vein from the subjects in an overnight fasting state and HDL cholesterol (HDL-C), LDL cholesterol (LDL-C), triglyceride (TG), HbA1c and fasting plasma glucose (FPG) levels were analyzed in the Saku General Hospital Human Dock Center.

Eating behaviors were assessed using a questionnaire developed by the Japan Society for the Study of Obesity (JSSO).[28] This questionnaire included 51 items regarding eating behaviors. After referring to previous studies examining the relationship between eating behaviors and BMI or WHtR,[12-24,26,27] and a Dutch eating behavior questionnaire,[25] we selected 13 items from the JSSO questionnaire and categorized into emotional eating, irregularity of eating, eating fast, eating until full, and external eating (See Appendix). In addition, because it is suggested that the availability of foods at home has been positively associated with the actual consumption of foods among adolescents,[29] we chose four items from the JSSO questionnaire as "making environment to promote eating" (Appendix). We did not use JSSO's eating behavior categories,[28] because different items are included for men and women, even within categories having the same name, thus making it difficult to compare results using JSSO's categories with those of previous studies. A four-point Likert scale (disagree/sometimes agree/agree/strongly agree) was used as a response alternative in the questionnaire.

Questions on stages of change regarding diet and on lifestyles were included in the questionnaire. As to stages of change regarding diet, subjects chose one of the following five stages: 1) *pre-contemplation* (participants are not seriously considering changing dietary behavior), 2) *contemplation* (participants are considering changing dietary behavior, but they have no intention of carrying this out within the next month), 3) *preparation* (participants are considering changing dietary behavior and they intend to carry this out within the next month), 4) *action* (participants have already changed dietary behavior within the last 6 months), and 5) *maintenance* (participants have already changed dietary behavior for at least 6 months).

Lifestyle information, such as smoking status (currently smoking, past smoking, have never smoked), frequency of exercise (3 times or more per week, 1 to 2 times per week, 1 to 3 times per month, less than 1 time per month), and frequency of alcohol intake (every day, 4 to 6 days per week, 1 to 3 days per week, less than 1 day per week), were also assessed.

Statistical Analysis

Analyses were performed on 2818 people (1674 men [59.4%] and 1144 women [40.6%]) who had fully completed the questionnaire and provided completed anthropometric data.

We determined a cutoff value for WHtR of 0.5, referring to a previous systematic review[10] and previous studies.[30-35] To examine the association between the WHtR and cardiovascular disease risk factors, subjects were classified into two groups (WHtR<0.5 and WHtR≥0.5), and the prevalence of cardiovascular disease risk factors (hypertension, dyslipidemia [high TG, high LDL-C or low HDL-C], and hyperglycemia) by chi-squared test. These risk factors were defined based on the criteria set by the Japanese Society of Hypertension,[36] Japan Atherosclerosis Society[37] and the Japan Diabetes Society.[38] Specifically, hypertension was defined as SBP ≥140 mmHg and/or DBP ≥90 mmHg, high TG as TG ≥150 mg/dL, high LDL-C as LDL-C≥140 mg/dL, low HDL-C as HDL-C <40 mg/dL and hyperglycemia as HbA1c ≥ 6.5 % and/or FPG ≥126 mg/dL. These definitions also included the subjects currently taking medication.

The mean age, lifestyles and stages of change regarding diet between the two groups were also compared by student's *t*-test or chi-squared test. Binary logistic regression analysis was then performed, with WHtR category (WHtR<0.5=0 and WHtR≥0.5=1) as a dependent variable and each eating behavior as an independent variable. Binary logistic regression analysis adjusting for age, sex, lifestyles, and stages of change regarding diet was also conducted. Crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. For the analysis, the following responses were operationalized as either binary or categorical variables: stages of change regarding diet (pre-contemplation, contemplation, preparation/action, maintenance) and eating behaviors (strongly disagree/sometimes disagree/agree, strongly agree).

All statistical analyses were carried out using Statistical Package for the Social Sciences (SPSS) for Windows (version 24.0; SPSS Inc., Tokyo, Japan). Statistical significance was defined as a two-tailed $p<0.05$ for all analyses.

Results

Characteristics of the Subjects

The mean age of the subjects was 59.0±9.5years (Table 1). Mean BMI, WC, and the WHtR were 23.2±3.1kg/m^2, 83.5±8.7 cm and 0.51±0.05, respectively (Table 1).

Comparison of the Prevalence of Cardiovascular Disease Risk Factors between Two Groups Classified by WHtR Cutoff Values

Table 2 shows the prevalence of cardiovascular risk factors (hypertension, high TG, high LDL-C, low HDL-C, and hyperglyce-

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Table 1: Characteristics of Subjects.

Variables	Mean±SD
Age (yr)	59.0±9.5
Height (cm)	162.9±8.5
Body weight (kg)	61.8±11.1
BMI (kg/m^2)	23.2±3.1
WC (cm)	83.5±8.7
WHtR	0.51±0.05
SBP (mmHg)	117.8±15.7
DBP (mmHg)	73.6±11.6
TG (mg/dl)	111.1±67.6
LDL-C (mg/dl)	121.4±28.8
HDL-C (mg/dl)	59.2±14.5
FPG (mg/dl)	102.7±17.1
HbA1c (%)	5.4±0.6
Sex	n (%)
Men	1674 (59.4)
Women	1144 (40.6)
Smoking status	
Never	1480 (52.5)
Past smoking	955 (33.9)
Current smoking	383 (13.6)
Frequency of alcohol intake	
Less than 1 day/week	1206 (42.8)
1-3 day(s)/week	580 (20.6)
4-6 days/week	415 (14.7)
Every day	617 (21.9)
Frequency of exercise	
Less than 1 time/month	967 (34.3)
1-3 time(s)/month	401 (14.2)
1-2 time(s)/week	576 (20.4)
3 times or more/week	874 (31.0)
Stages of change regarding diet	
Pre-contemplation, contemplation, preparation	1920 (68.1)
Action, maintenance	898 (31.9)

BMI: body mass index; WC: waist circumference; WHtR: waist-to-height-ratio; SBP: systolic blood pressure; DBP: diastolic blood pressure; TG: triglyceride; LDL-C: LDL cholesterol; HDL-C, HDL cholesterol; FPG: fasting plasma glucose.

Table 2: The Prevalence of Cardiovascular Disease Risk Factors in the Two Groups by WHtR Cutoff Value.

	WHtR<0.5 (n=1200)	WHtR≥0.5 (n=1618)	*p* value*
	n %	n %	
Hypertension	191 (24.2)	597 (75.8)	<0.001
High TG	198 (26.4)	552 (73.6)	<0.001
High LDL-C	334 (32.7)	686 (67.3)	<0.001
Low HDL-C	125 (26.0)	355 (74.0)	<0.001
Hyperglycemia	58 (25.6)	169 (74.4)	<0.001

*Chi-squared test was conducted. WHtR: waist-to-height-ratio. TG: triglyceride; LDL-C: LDL cholesterol. HDL-C: HDL cholesterol.

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mia) between the two groups (WHtR<0.5 and WHtR≥0.5). The prevalence of all cardiovascular risk factors in the WHtR≥0.5 group were significantly higher than those in the WHtR<0.5 group.

Comparison of Characteristics between Two Groups Classified by WHtR Cutoff Value

Mean age, sex distribution, lifestyle, and stages of change regarding diet in the two groups (WHtR<0.5 or WHtR≥0.5) are shown in Table 3. The mean age was significantly higher in the WHtR≥0.5 group compared to the WHtR<0.5 group. The sex distribution was also significantly different between the groups. There were no significant differences in smoking status, frequency of alcohol intake and exercise, and stages of change regarding diet.

Eating Behaviors Associated with WHtR

Results of the binary logistic regression analysis are shown in Table 4. In the crude model, subjects who answered "sometimes agree" and/or "agree/strongly agree" to the following eating behaviors showed significantly higher odds ratio of WHtR≥0.5 than those who answered "disagree" (reference): all items of emotional eating category, eating between meals, having many occasions to go to drinking parties (irregularity of eating category), eating fast, eating until full, all items of external eating and all items of making environment to promote eating.

Furthermore, after adjusting for age, sex, smoking status, frequency of exercise, alcohol consumption and stages of change regarding diet, significantly higher odds ratios of the WHtR≥0.5 were seen in the "sometimes agree" responses for the following eating behaviors: eating when being irritated or stressed (in the emotional eating category), having many occasions to go to drinking parties (irregularity of eating category), eating favorite foods even if finishing a meal (external eating category) and being unable to avoid cooking more than enough (making environment to promote eating category).

As to the items of having a late-night snacking (irregularity of eating category), no significant relationship was seen in the crude model but both the "sometimes agree" or "agree/strongly agree" responses showed a significantly higher odds ratio of the WHtR≥0.5, after adjusting for the covariates. On the other hand, a significantly lower odds ratio of the WHtR≥0.5

Table 3: Comparison Chracteristics between the Two Groups by WHtR Cutoff Value.

	WHtR<0.5 (n=1200)	WHtR≥0.5 (n=1618)	*p* value*
Age	56.7±9.9	60.7±8.9	<0.001
Sex	n%	n%	
Men	744 (62.0)	930 (57.5)	0.016
Women	456 (38.0)	688 (42.5)	
Smoking status			
Never	647 (53.9)	833 (51.5)	0.108
Past smoking	381 (31.8)	574 (35.5)	
Current smoking	172 (14.3)	211 (13.0)	
Frequency of alcohol intake			
Less than 1 day/week	485 (40.4)	721 (44.6)	0.101
1-3 day(s)/week	255 (21.3)	325 (20.1)	
4-6 days/week	194 (16.2)	221 (13.7)	
Every day	266 (22.2)	351 (21.7)	
Frequency of exercise			
Less than 1 time/month	415 (34.6)	552 (34.1)	0.715
1-3 time(s)/month	164 (13.7)	237 (14.6)	
1-2 time(s)/week	255 (21.3)	321 (19.8)	
3 times or more/week	366 (30.5)	508 (31.4)	
Stages of change regarding diet			
Pre-contemplation, contemplation, preparation	701 (58.4)	947 (58.5)	0.952
Action, maintenance	499 (41.6)	671 (41.5)	

Age was shown as mean±SD.
*Student's *t*-test was conducted for age. Chi-squared test was conducted for sex, smoking states, frequency of alcohol intake and exercise, and stages of change regarding diet.
WHtR: waist-to-height ratio.

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Table 4 Associations between WHtR and Eating Behaviors by Multiple Logistic Regression Analysis.

	n (%)	Crude	Adjusted*
		OR (95% CI)	OR (95% CI)
Emotional eating			
I tend to eat when I am irritated or stressed			
Disagree	1,890 (67.1)	1.00 (reference)	1.00 (reference)
Sometimes agree	596 (21.1)	1.06 (0.88-1.28)	1.27 (1.04-1.55)*
Agree/strongly agree	332 (11.8)	1.65 (1.29-2.11)***	2.20 (1.68-2.88)***
I tend to eat anything when I have nothing to do			
Disagree	1,883 (66.8)	1.00 (reference)	1.00 (reference)
Sometimes agree	697 (24.7)	1.29 (1.08-1.54)**	1.43 (1.19-1.73)***
Agree/strongly agree	238 (8.4)	2.19 (1.62-2.94)***	2.39 (1.75-3.26)***
Irregularity of eating			
I often have late-night snacks			
Disagree	2,155 (76.5)	1.00 (reference)	1.00 (reference)
Sometimes agree	475 (16.9)	1.03 (0.84-1.26)	1.35 (1.09-1.68)**
Agree/strongly agree	188 (6.7)	1.25 (0.92-1.69)	1.69 (1.22-2.34)**
I often eat between meals			
Disagree	1,440 (51.1)	1.00 (reference)	1.00 (reference)
Sometimes agree	894 (31.7)	1.27 (1.07-1.50)**	1.42 (1.19-1.71)***
Agree/strongly agree	484 (17.2)	1.78 (1.44-2.21)***	2.04 (1.61-2.58)***
I don't eat breakfast			
Disagree	2,493 (88.5)	1.00 (reference)	1.00 (reference)
Sometimes agree	178 (6.3)	1.07 (0.79-1.46)	1.35 (0.98-1.88)
Agree/strongly agree	147 (5.2)	1.02 (0.73-1.43)	1.35 (0.94-1.93)
I have dinner late			
Disagree	1,485 (52.7)	1.00 (reference)	1.00 (reference)
Sometimes agree	581 (20.6)	0.81 (0.67-0.99)*	1.01 (0.83-1.24)
Agree/strongly agree	752 (26.7)	0.84 (0.70-1.00)	1.13 (0.93-1.37)
I have many occasions to go to drinking parties			
Disagree	1,623 (57.6)	1.00 (reference)	1.00 (reference)
Sometimes agree	767 (27.2)	0.98 (0.83-1.17)	1.23 (1.01-1.49)*
Agree/strongly agree	428 (15.2)	1.39 (1.12-1.74)**	1.95 (1.52-2.51)***
Eating fast			
I eat a meal fast			
Disagree	769 (27.3)	1.00 (reference)	1.00 (reference)
Sometimes agree	606 (21.5)	0.99 (0.80-1.22)	1.14 (0.91-1.42)
Agree/strongly agree	1,443 (51.2)	1.47 (1.23-1.76)***	1.75 (1.45-2.11)***
Eating until full			
I'm not satisfied unless I eat my full			
Disagree	1,060 (37.6)	1.00 (reference)	1.00 (reference)
Sometimes agree	829 (29.4)	1.24 (1.03-1.49)*	1.42 (1.17-1.72)***
Agree/strongly agree	929 (33.0)	1.68 (1.40-2.01)***	2.13 (1.76-2.59)***

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External eating			
I can eat my favorite foods even if I have finished a meal			
Disagree	696 (24.7)	1.00 (reference)	1.00 (reference)
Sometimes agree	1,036 (36.8)	1.16 (0.95-1.40)	1.25 (1.02-1.52)*
Agree/strongly agree	1,086 (38.5)	1.55 (1.27-1.87)***	1.82 (1.47-2.24)***
I tend to eat when I see others eating			
Disagree	1,321 (46.9)	1.00 (reference)	1.00 (reference)
Sometimes agree	951 (33.7)	1.29 (1.09-1.52)**	1.52 (1.27-1.82)***
Agree/strongly agree	546 (19.4)	1.99 (1.62-2.46)***	2.59 (2.05-3.27)***
I tend to eat fruits and sweets when I see them			
Disagree	983 (34.9)	1.00 (reference)	1.00 (reference)
Sometimes agree	1,069 (37.9)	1.11 (0.93-1.32)	1.15 (0.96-1.38)
Agree/strongly agree	766 (27.2)	1.47 (1.21-1.78)***	1.54 (1.25-1.90)***
I tend to eat leftover food because I don't want to waste it			
Disagree	756 (26.8)	1.00 (reference)	1.00 (reference)
Sometimes agree	1,055 (37.4)	1.21 (1.01-1.46)*	1.37 (1.12-1.66)**
Agree/strongly agree	1,007 (35.7)	1.59 (1.31-1.92)***	2.00 (1.63-2.45)***
Making environment to promote eating			
I'm unconfortable unless I keep enough food left in a refrigerator			
Disagree	2,223 (78.9)	1.00 (reference)	1.00 (reference)
Sometimes agree	374 (13.3)	1.10 (0.88-1.37)	1.15 (0.91-1.44)
Agree/strongly agree	221 (7.8)	1.61 (1.20-2.16)**	1.62 (1.19-2.20)**
I always keep food around			
Disagree	2,032 (72.1)	1.00 (reference)	1.00 (reference)
Sometimes agree	468 (16.6)	1.39 (1.13-1.71)**	1.53 (1.23-1.91)***
Agree/strongly agree	318 (11.3)	2.11 (1.63-2.74)***	2.20 (1.67-2.89)***
I cannot avoid buying more food than necessary			
Disagree	1,368 (48.5)	1.00 (reference)	1.00 (reference)
Sometimes agree	815 (28.9)	1.09 (0.91-1.30)	1.15 (0.96-1.39)
Agree/strongly agree	635 (22.5)	1.66 (1.36-2.02)***	1.70 (1.38-2.10)***
I cannot avoid cooking more than enough.			
Disagree	1,422 (50.5)	1.00 (reference)	1.00 (reference)
Sometimes agree	702 (24.9)	1.17 (0.98-1.41)	1.30 (1.07-1.57)**
Agree/strongly agree	694 (24.6)	1.66 (1.37-2.00)***	1.78 (1.46-2.18)***

¶: Adjusting for age, sex, smoking status, frequency of exercise and alcohol intake and stages of change regarding diet. *p<0.05, **p<0.01, ***p<0.001. WHtR, waist-to-height ratio.

was seen in the "sometimes agree" response in the item of having dinner late (irregularity of eating category) in the crude model. However, this significance disappeared after adjusting for the covariates. Significant relationships were not seen in the item of skipping breakfast (irregularity of eating category) in both crude and adjusted model.

DISCUSSION

We examined the relationship between various eating behaviors and WHtR among adults in Japan. While an association between various eating behaviors and a higher BMI or obesity or being overweight has been reported,[12-24] the results of some eating behaviors remains controversial.[12,15] In addition, there are only a few studies focused on the relationship between eating behaviors and WHtR[26,27] and studies in adults are scarce.

We examined the relationships between the WHtR and various and specific eating behaviors to provide more specific dietary advice for people in clinical settings. For example, emotional eating in previous studies was expressed as an emotional eating score.[18,19] However, emotional eating includes several situations (stress and boredom, etc.). External eating also includes many situations such as extra eating of favorite foods

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even after finishing a meal, eating when seeing others eat, eating food just because it is there, and eating leftover food. We hypothesized that associations with the WHtR differ by situations, even within the same eating categories. In this study, the eating behavior category of ''making environment to promote eating'' was also included. Because we thought adults have more opportunity for buying and cooking foods, four items (always keeping food around, keeping enough food in the refrigerator, buying more food than necessary, and cooking more than enough) were included. As far as we know, only one study has examined the relationship between the home environment and obesity[39] and no study has examined these factors regarding the WHtR in adults.

Our study showed significant positive relationships between the WHtR and all the items of making environment to promote eating. A previous study also reported that obese people had greater number of refrigerators, freezers and highly visible foods,[39] suggesting highly accessible to foods contribute to obesity and higher WHtR.

In this study, the WHtR showed significant positive relationships with all the items of emotional eating, having a late-night snack, eating between meals, having many occasions to go to drinking parties, eating fast, eating until full, all the items of external eating and making environment to promote eating after adjusting for covariates.

Previous studies in adults reported significant positive relationships between BMI/obesity/overweight/weight gain and following eating behaviors: emotional eating,[18,19] night eating,[21,22] eating between-meals,[23] eating fast,[12-17] eating until full[12,14] and external eating.[24] In addition, although the subjects were children, it has been reported that eating quickly demonstrated a positive relationship with WHtR,[27] which was consistent with our results.

There are many studies focused on eating quickly. One of the possible reason of obesity/overweight/weight gain caused by eating quickly is considered high energy intake. A previous systematic review, examining the effects of manipulating the eating rate on the concurrent energy intake, concluded that a slower eating rate was associated with a lower energy intake.[40] It is possible that the speed of eating and the frequency of chewing influence hormones affecting satiety, and that eating speed influences food intake through differing stomach distension sensitivities.[40] Although these mechanisms remain under investigation, they may have also contributed to a higher WHtR in our study.

Night eating may also affect energy intake and metabolism. A previous study reported night eaters consumed significantly more total energy, arising from their higher energy intake during night-time eating.[22] In the study, night eaters gained significantly more weight compared to non-night eaters during the follow-up period. Another previous study showed eating at night significantly increased total and LDL cholesterol, while reduced fat oxidation, suggesting that eating at night changes fat metabolism and increases the risk of obesity.[41]

In respect to skipping breakfast, Lento et al. reported positive relationships between the WHtR and skipping breakfast in 9 to 11-year-old children.[26] This was inconsistent with our results, possibly owing to the response alternative in our questionnaire. While the previous study assessed frequency of eating breakfast,[26] in this study, subjects chose an answer from a four-point Likert scale (disagree/sometimes agree/agree/strongly agree). Because ''agree'' is a subjective response, this may have distorted our skipping breakfast assessment. More studies using standardized breakfast definitions are needed to examine the effect of breakfast on the WHtR.

This study reports no significant relationship between having dinner late and the WHtR after adjusting for the covariates. This is consistent with the results of one previous study.[15] However, another report found that a late time for the last meal and a short duration of time between the last meal and sleep onset were predictors of a higher total caloric intake.[42] Considering the previous study, [42] careful interpretation of our results is required, because dinner times and the duration between dinner and sleep onset were not evaluated in this study. It is possible that our study participants may have eaten dinner at an earlier time than they reported and/or that the time duration between their dinner and sleep onset was longer. Because no standard measurements have been established to define either a late dinner or a time duration between dinner and sleep onset, studies using more detailed definitions may be needed.

There are some limitations to this study. First, because of its cross-sectional design, we were unable to determine causal relationships. Secondly, the subjects were not representative of the Japanese population because the study was conducted in only one Dock Center in the Nagano prefecture. However, almost 3000 subjects were included for this study and it is worth noting that this is the first study to examine the relationship between eating behaviors and the WHtR in adults. More studies are needed to find the specific eating behaviors that relate to the WHtR.

CONCLUSIONS

In this study, we aimed to clarify eating behaviors that are associated with the waist-to-height ratio (WHtR) in Japanese adults. After controlling for covariates, our study showed that many specific eating behaviors including making environment to promote eating were associated with the WHtR. Putting more emphasis on modifying these eating behaviors may be effective for decreasing the WHtR and preventing cardiovascular diseases.

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in Saku General Hospital.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

AUTHORS' CONTRIBUTION

NA, AM, MM, KD, FS and SW started and managed the cohort study conducted in the Saku General Hospital Human Dock Center. They also critiqued the manuscript. MN conducted data collection, data analysis and wrote the manuscript. All authors read, modified, and approved the final manuscript.

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APPENDIX

Appendix: Eating Behaviors and Items in the Questionnaire.

Eating behavior	Items
Emotional eating	I tend to eat when I am irritated or stressed.
	I tend to eat anything when I have nothing to do.
Irregularity of eating	I often have late-night snacks.
	I often eat between meals.
	I don't eat breakfast.
	I have dinner late.
	I have many occasions to go to drinking parties.
Eating fast	I eat a meal fast.
Eating until full	I'm not satisfied unless I eat until full.
External eating	I can eat my favorite foods even if I have finished a meal.
	I tend to eat when I see others eating.
	I tend to eat fruits and sweets when I see them.
	I tend to eat leftover food because I don't want to waste it.
Making environment to promote eating	I'm unconfortable unless I keep enough food left in a refrigerator.
	I always keep food around.
	I cannot avoid buying more food than necessary.
	I cannot avoid cooking more than enough.

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*Corresponding author
Hiroshi Bando, MD, PhD, FACP
Lecturer
Tokushima University and
Medical Research
Nakashowa 1-61
Tokushima 770-0943, Japan
Tel. +81-90-3187-2485
E-mail: pianomed@bronze.ocn.ne.jp

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Investigation of Uric Acid and Cystatin C on Low-Carbohydrate Diet (LCD)

Hiroshi Bando, MD, PhD, FACP[1*]; Koji Ebe, MD, PhD[2]; Tetsuo Muneta, MD, PhD[3]; Masahiro Bando, BSc[4]; Yoshikazu Yonei, MD, PhD[5]

[1]Tokushima University and Medical Research, Tokushima, Japan
[2]Takao Hospital, Kyoto, Japan
[3]Muneta Maternity Clinic, Chiba, Japan
[4]Department of Nutrition and Metabolism, Institute of Biomedical Sciences, Tokushima University Graduate School, Tokushima, Japan
[5]Anti-Aging Medical Research Center, Graduate School of Life and Medical Sciences, Doshisha University, Kyoto, Japan

ABSTRACT

Background: As to nutritional therapy, continuous discussions were observed concerning calorie restriction (CR) and low-carbohydrate diet (LCD). Authors and colleagues have applied LCD for lots of diabetic patients and reported the detail relationship with ketone bodies and Morbus (M) value.
Methods: Ninety-three patients with type 2 diabetes mellitus (T2DM) were considered as subjects in the study, among which 41 were male and 52 were female, 58.3±13.2 years old on average, 60 years old in median. Methods were as follows: 1) patients were admitted and provided formular diet, which included CR diet (60% carbohydrates, 1400 kcal/day) on day 1-2, and LCD (12% carbohydrate, 1400 kcal/day) on day 3-14; 2) several biomarkers on fasting were measured on day 2, 4 and 14; 3) daily profile of blood glucose were done on day 2 and day 4.
Results: According to the M-value, subjects were classified into 4 groups, which were less than 25, 26-100, 101-250, more than 251, and number was 24, 24, 24, 21, respectively. The average HbA1c in 4 groups were 6.6%, 7.4%, 8.5% and 9.5% respectively. The median M-values decreased from day 2 to 4, which were 10.4 to 9.1, 53.5 to 7.7, 150 to 19.1 and 438 to 87, respectively. The average uric acid in each group revealed significant increase from day 2 to day 14. There were significant correlation between uric acid increment and creatinine increment, and among creatinine, creatinine clearance (CCr) and Cystatin C.
Conclusion: LCD showed efficacy for glucose variability with significant decrease in glucose and M-value. Renal study showed increase of serum uric acid. In addition to correlations of Cystatin C and biomarkers, current results would be from some dehydrated state and/or relative decrease of total calorie intake. These findings would become the fundamental data of efficacy of LCD and its physiological influences for renal function.

KEY WORDS: Low-carbohydrate diet (LCD); Morbus value (M-value); Cystatin C; Creatinine; Type 2 diabetes mellitus (T2DM).

ABBREVIATIONS: LCD: Low-Carbohydrate Diet; CR: Calorie Restriction; T2DM: Type 2 Diabetes Mellitus; MAGE: Mean Amplitude of Glycemic Excursions; M-value: Morbus value; CGM: Continuous Glucose Monitoring, SMBG: Self-Monitoring of Blood Glucose; CKD-EPI: Chronic Kidney Disease-Epidemiology Collaboration; MDRD: Modification of Diet in Renal Disease; CCr: Creatinine Clearance, eGFR: estimated Glomerular Filtration Rate; GFR: Glomerular Filtration Rate; T1DM: Type 1 Diabetes Mellitus; UA: Uric Acid.

INTRODUCTION

As to adequate nutritional therapy with metabolic and diabetic patients, the discussion has been

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continued for long in the light of calorie restriction (CR) and low-carbohydrate diet (LCD).[1,2] Several researcher showed the predominant efficacy of LCD compared with CR.[3-8] Recently, Bernstein and Feinman have suggested adequate definition and treatment of LCD, in addition to the statement of American Diabetes Association (ADA).[1]

In Japan, authors and colleagues have treated lots of patients with diabetes mellitus, and investigated the efficacy of LCD.[9-11] For medical and social development of LCD, we proposed 3 types of actual LCD in daily life, which are petit, standard and super LCD.[9,12,13] We have also reported the significant role of ketone bodies in LCD and physiological role for pregnant female and fetus newborn axis.[11,14]

Furthermore, we investigated the clinical significance of Morbus (M) value in the treatment of LCD for the patients with type 2 diabetes mellitus (T2DM).[11,12] M-value is useful marker in the evaluation for blood glucose variability in diabetic patients that expresses both elevated glucose level and increased mean amplitude of glycemic excursions (MAGE).[15-17] When glycemic control gets better, numerical value of M-value decreases highly, which is simple and helpful for clinical and medical practices and research.

In this study, we have treated T2DM patients for super LCD and investigated the changes of average blood glucose, M-value and renal biomarkers such as uric acid, creatinine and Cystatin C.

SUBJECTS AND METHODS

The subjects were 93 patients with T2DM, including 41 males and 52 females, with 58.3±13.2 years old (mean±SD), and 60 years in median value. They were admitted for 14 days, and received the same treatment protocol for endocrine, metabolic and renal examination.

The methods included formula diet and examination. On admission, CR diet was given on day 1 and 2, including 60% carbohydrates, 25% lipids and 15% protein with 1400 kcal/day. After that, LCD was given from day 3 until day 14, including 12% carbohydrates, 64% lipids and 24% protein with 1400 kcal/day, which is so-called super LCD formula used for long years in our investigation.[9-12]

We measured several biomarkers on day 2, 4 and 14. On day 2, the basal biomarkers such as blood glucose/HbA1c, M-value and sera levels of uric acid, creatinine, cystatin C, and daily profile of blood glucose were measured. On day 4, daily profile of blood glucose was measured. On day 14, uric acid, creatinine and other biomarkers were measured.

One subject who is 64-years-old man with HbA1c 7.3% had 3 times of daily profile of glucose. The average glucose and M-value were calculated for that subject.

Analysis for M-value

The M-value (Morbus value) stands for the combination of two factors. One is the level of blood gluose, and another is the MAGE. It is a logarithmic transformation of the deviation of glycemia from an arbitrary assigned "ideal" glucose value.[15-17] The formula is as follows: $M = M^{BS}+M^{W}$, where M^{W}=(maximum blood glucose-minimum glucose)/20; M^{BS}=the mean of MBSBS; MBSBS=individual M-value for each blood glucose value calculated as (absolute value of [10×log (blood glucose value/120)]^3).

$$\text{M-value}=\frac{\Sigma}{N}\left|\text{M}\frac{BS}{BS}\right|+\text{W}/20 \quad \text{where} \quad \text{M}\frac{BS}{BS}=\left|10\log\frac{PG}{120}\right|^3$$

For the M-value, the standard range is <180, borderline is 180-320 and abnormal is >320. Whereas in the M-value, the standard range is <5, borderline is 5-10 and abnormal is >10. It was reported that multiple sampling and a 7-point glycemic trial per day would have yielded similar results.[17]

Statistical Analyses

In current study, data was represented as the mean±standard deviation, and also represented median, quartile of 25% and 75% in biomarkers. For statistical analyses, correlation coefficients were calculated using the Microsoft Excel analytical tool.[18] Furthermore, we used JMP (Version 8) statistical analysis software (JMP Japan Division of SAS Institute Japan Ltd., Minato-ku, Tokyo, Japan) and Microsoft Excel analytical tool. A significance level of less than 5% obtained using a two-tailed test was considered to be statistically significant.

Ethical Considerations

Current study was conducted in compliance with the ethical principles of the Declaration of Helsinki and Japan's Act on the Protection of Personal Information along with the Ministerial Ordinance on Good Clinical Practice (GCP) for Drug (Ordinance of Ministry of Health and Welfare No. 28 of March 27, 1997). No ethical committee meeting was held. Informed consent was obtained from the subjects related to this research. The study was registered with UMIN #R000031211.

RESULTS

Fundamental data

The results obtained from 93 subjects were shown in Table 1. By the level of M-value, subjects were classified into 4 groups. Group 1-4 revealed the M-value, less than 25, 26-100, 101-250, more than 251, with the number of the cases 24, 24, 24, 21, respectively.

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Table 1: General Data of the Subjects.

Categorization	Group 1	Group 2	Group 3	Group 4
Number	24	24	24	21
Sex (male/female)	13/11	8/16	9/15	11/10
Age in average (y.o.)	56.2±13.3	59.1±15.1	62.8±7.4	54.7±15.1
Age in median (y.o.)	57 (47-64)	63 (50-72)	63 (58-68)	60 (50-65)
Body Mass Index (kg/m^2)	23.8±3.0	24.2±5.2	25.4±4.2	27.3±5.2
M-value on day 2	4-25	26-100	101-250	251-1285

The results were expressed by Mean±SD.
The results of age were also expressed by median (25%-75%).

Glucose Metabolism and M-value

The results for HbA1c, fasting glucose and M-value were shown in Table 2. M-value in 4 groups decreased from day 2 to 4, which was 10.4 to 9.1, 53.5 to 7.7, 150 to 19.1 and 438 to 87, respectively (Figure 1). The average glucose and M-value of 64-years-old patient with T2DM were shown in Table 3.

Renal Function

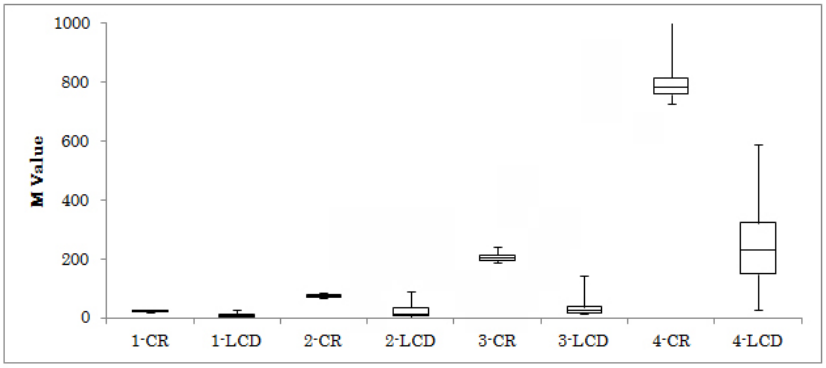
Renal biomarkers on day 2 and day 14 were shown in Table 4. The average uric acid (UA) level in each group revealed significant increase from day 2 to day 14. (Figure 2) There was significant correlation between UA increment and creatinine increment on day 2 and day 14 (Figure 3). Other markers did not

Table 2: HbA1c, Glucose and Morbus (M) Value of the Subjects.

Categorization	Group 1	Group 2	Group 3	Group 4
HbA1c				
HbA1c on day 2 in average (%)	6.6±1.1	7.4±1.3	8.5±1.2	9.5±1.7
HbA1c on day 2 in median (%)	6.4 (6.1-6.8)	7.3 (6.3-8.2)	8.4 (7.6-9.4)	9.0 (8.6-10.6)
Fasting Glucose				
Fasting Glucose on day 2 (mg/dL)	117.3±20.4	146.5±31.3	183.5±42.5	226.5±38.5
Fasting Glucose on day 4 (mg/dL)	110.5±42.7	125.2±27.0	147.7±30.6	186.8±43.3
Fasting Glucose on day 14 (mg/dL)	98.9±15.0	110.3±21.3	119.2±24.4	133.1±42.1
Average Glucose				
average glucose on day 2 (mg/dL)	128.2±11.8	163.6±46.2	211.1±20.3	298.6±46.3
average glucose on day 4 (mg/dL)	111.6±19.2	135.5±32.2	159.0±21.7	198.2±47.7
Morbus value				
M value on day 2	10.4 (6.2-17.7)	53.5(41-67)	150 (125-194)	438 (343-701)
M value on day 4	9.1 (4.4-14.3)	7.7 (3.9-19.9)	19.1 (14.0-29.9)	87.0 (33-148)

The results were expressed by Mean±SD.
The results of HbA1c and M value were expressed by median (25%-75%).

Figure 1: Changes of M-value on Day 2 and 4 in 4 Groups.



The M-values in 4 groups were investigated on day 2 and 4. The median levels on day 2 to day 4 in 4 groups were 10.4 to 9.1, 53.5 to 7.7, 150 to 19.1 and 438 to 87, respectively. All subjects were provided calorie restricted (CR) diet on day 1 and 2, and low carbohydrate diet (LCD) on day 3 and 4. Abbreviation: 1-CR means group 1 and Calorie Restriction on day 2, and 4-LCD means group 4 and Low Carbohydrate Diet on day 4.

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Table 3: Average Glucose and M-value of Patient with T2DM.

	Blood Glucose level (mg/dL)								M-value
Time (h)	8	10	12	14	17	19	21	Average	
Day 2	180	315	288	335	268	333	304	289	426.0
Day 4	140	191	185	180	152	166	160	168	29.0
Day 14	97	124	112	125	86	104	93	106	7.4

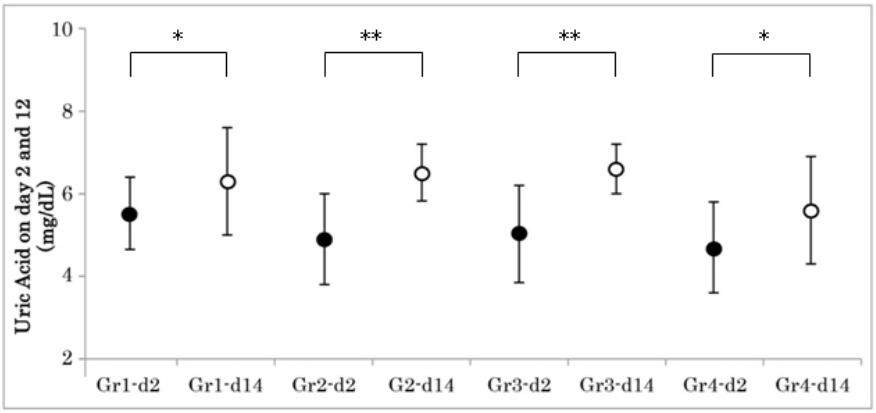
The patient was 64-years-old male with HbA1c 7.3%.
He was on CR on day 1,2 and LCD on day 3-14.
Blood glucose was measured 7 times a day from 08:00 h to 21:00 h.
M-value stands for combined implication of both average glucose and Mean Amplitude of Glycemic Excursions (MAGE).

Table 4: Renal Function of the Subjects.

Categorization	Group 1	Group 2	Group 3	Group 4
Uric Acid				
Uric Acid on day 2 (mg/dL)	5.45±1.37	4.90±1.46	5.33±1.36	4.89±1.40
Uric Acid on day 14 (mg/dL)	6.59±1.92	6.19±.2.01	6.18±1.29	5.90±1.63
Uric Acid increment (mg/dL)	1.01±1.03	1.12±1.02	1.22±1.06	1.12±1.03
Creatinine				
Creatinine on day 2 (mg/dL)	0.75±0.15	0.70±0.17	0.76±0.21	0.64±0.15
Creatinine on day 14 (mg/dL)	0.81±0.18	0.77±0.16	0.80±0.23	0.72±0.17
Blood Urea Nitrogen				
BUN on day 2 (mg/dL)	18.5±5.0	18.3±4.8	19.3±7.4	17.5±4.3
BUN on day 14 (mg/dL)	22.3±7.2	21.2±5.3	21.6±11.1	17.9±3.8
Other markers				
Cystatine C on day 2 (mg/L)	0.81±0.18	0.79±0.17	0.83±0.32	0.69±0.15
CCr on day 4 (ml/min)	99.7±25.3	96.3±29.7	95.9±27.2	115.3±25.3
eGFR on day 4 (ml/min)	78.6±19.9	75.9±23.4	75.6±21.4	90.9±19.9
u-uric acid/creatinine	0.42±0.11	0.52±0.18	0.53±0.13	0.61±0.22

The results were expressed by Mean±SD.

Figure 2: Changes of Uric Acid on Day 2 and 14 in 4 Groups.



Uric acid (UA) levels were investigated in group 1-4 on day 4 and day 14. The average UA level in each group revealed significant increase from day 2 to day 14. The asterisk represents as follows: *p<0.05, **p<0.01.
Gr1-d2: Group 1 day 2; Gr4-d14: Group 4 day 14.

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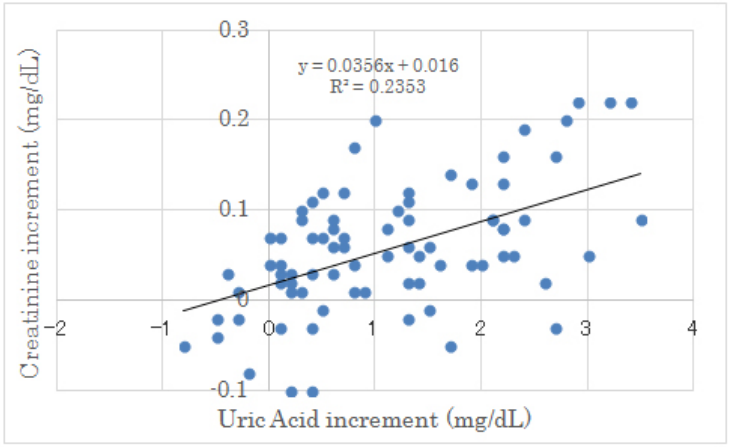
Figure 3: Correlation between Uric Acid Increment and Creatinine Increment on Day 2 and Day 14.



There were significant correlation between both factors (p<0.05).

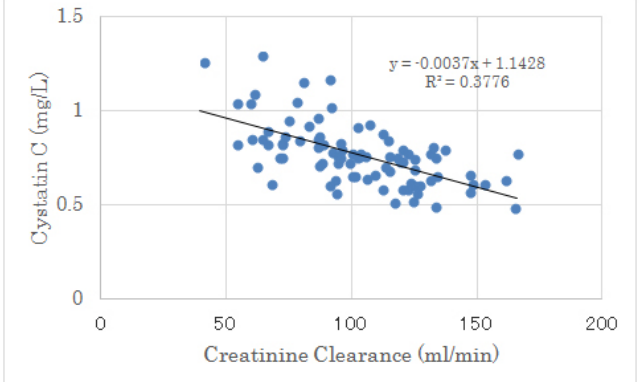
show any significant difference in 4 groups.

There was no significant correlation between UA increment from day 2 to 14 and Cystatin C. There was negative significant correlation between Creatinine Clearance (CCr) and Cystatin C. (Figure 4). There was positive significant correlation between Creatinine and Cystatin C (p<0.01) (Figure 5).

DISCUSSION

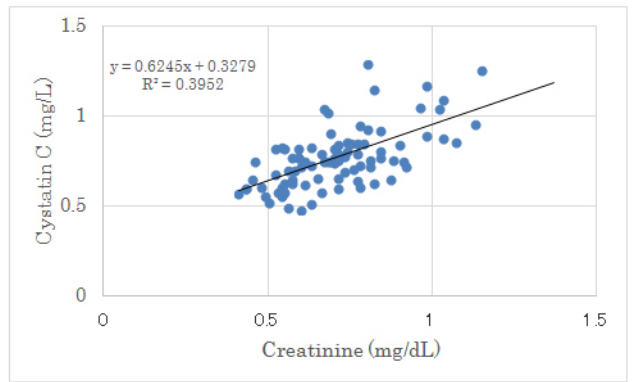
LCD was introduced by Bernstein and Atkins, and got developed for long years.[19,20] Successively, the effect of LCD have been reported.[21-24] In Japan, we have continued clinical study and research concerning LCD, and reported effect of weight reduction, elevated ketone bodies and its physiological role and

Figure 4: Correlation between Creatinine Clearance and Cystatin C.



There were negative significant correlation between both factors (p<0.01).

Figure 5: Correlation between Creatinine and Cystatin C.



There were positive significant correlation between both factors (p<0.01).

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significant evaluation using M-value.[11,12]

M-value is a useful biomarker to express the variability of blood glucose including glucose level and fluctuation. There were discussions concerning how many times of sampling per day is necessary. It was reported that multiple sampling and a 7-point glycemic trial per day would have yielded similar results.[25-27]

M-value reveals similar result for continuous glucose monitoring (CGM) for 48 hours which is considered as ideal research method.[28] There are rare reports concerning M-value. Patients with T1DM were investigated for blood glucose fluctuations 3 times and more per day, using CGM and self-monitoring of blood glucose (SMBG).[29]

In this study, the data of M-value and HbA1c in 4 groups showed parallel relation. M-value on day 4 was decreased than that on day 2, suggesting clinical short effect of LCD.

In previous reports, microalbuminuria and glomerular filtration rate (GFR) were followed 14 years, and they did not vary in relation to diabetes status.[30,31] Continuing LCD with 14% carbohydrate for 1 year, obese adults with T2DM had no adverse affect on clinical markers of renal function or on preexisting kidney disease.[32] Similar results were obtained for creatinine, eGFR, albuminuria, or fluid and electrolyte balance.[33-34]

LCD is as safe as CR and Mediterranean, in preserving/improving renal function among moderately obese participants with or without type 2 diabetes.[35] Potential improvement is likely to be mediated by weight loss-induced improvements in insulin sensitivity and blood pressure. For LCD for a year, patients with stage 1-3 renal disease had an improvement in renal function, whereas patients with hyperfiltration had a decrease in the GFR.[36]

Our current study showed that uric acid was significantly elevated from day 2 to day 14 in 4 groups. One of the causes of elevated uric acid was supposed to be some dehydrated status i.e., less water intake than expected. This is compatible with the result of significant correlation with elevated uric acid and elevated creatinine, with similar elevated tendency of BUN. Another probable cause would be the relative decrease of total calorie intake. When nutrition changes from CR to LCD, total calorie often decreases compared with that of previous status. Third possible cause would be the hyperfiltration of glomerulus in early stage of diabetic nephropathy. As the degree of hyperfiltration becomes less, creatinine and uric acid values could be increased.[36] These speculation are possible because of accumulative reports for years.

In comparison with previous reports for years, our study is based on a short period of 2 weeks. Consequently, our speculation would be possibility due to limited research protocol.

In this study, Cystatin C showed significant positive correlation with creatinine and negative correlation with creatinine clearance. Serum Cystatin C alone provides GFR estimates that are nearly as accurate as serum creatinine adjusted for age, sex and race.[37] The chronic kidney disease-Epidemiology collaboration (CKD-EPI) creatinine equation was reported to be more accurate than the modification of diet in renal disease (MDRD) Study equation.[38] Recently, the combined creatinine-Cystatin C equation have been precise and useful for various patho-physiological states including T2DM.[39-41] Our results would become reference data among renal biomarkers in clinical terms which represents actual interrelationship on LCD in the patients with T2DM.

Our study has small and limited research situation, then further research will be necessary concerning the renal functions in LCD.[1] LCD would be highly evaluated for treatment of diabetes with the clinical research of influence for renal function.

CONCLUSION

In this study, the changes of M-value on CR/LCD, creatinine, uric acid and Cystatin C were investigated in patients with T2DM. Decreased M indicates the efficacy of LCD for short period, and influence for renal biomarkers in detail relationship will be studied in the future.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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Case Report

*Corresponding author
Hazel Su Pin Chan, MDCM, MMed
Department of Anaesthesia and Surgical Intensive Care
Singapore General Hospital
Outram Road, 169608 Singapore
Tel. +6581217865
E-mail: hazel.chan.s.p@singhealth.com.sg

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Unanticipated Difficult Laryngoscopy in a Diabetic Patient Undergoing Coronary Artery Bypass Graft Surgery

Hazel Su Pin Chan, MDCM, MMed*; Sophia Tsong Huey Chew, MBBS, MMed, FANZCA

Department of Anaesthesia and Surgical Intensive Care, Singapore General Hospital, Outram Road, 169608 Singapore

INTRODUCTION

Difficult laryngoscopy has been shown to be more frequent in cardiac surgery *versus* general surgery. In one study, the incidence of difficult laryngoscopy in cardiac surgery was almost double that compared to general surgery patients.[1] The incidence of difficult laryngoscopy is also higher in diabetic patients, with an incidence reported to be as high as 30% in long-term diabetics.[2] In Singapore, the prevalence of diabetes mellitus in patients presenting for coronary artery bypass grafting (CABG) is high and despite a seemingly normal airway examination based on head and neck examination, one may encounter unexpected difficulties.

CASE REPORT

We present a 53-year-old man diagnosed with triple vessel coronary artery disease (CAD) scheduled for CABG. He weighed 64.4 kg, was 163 cm tall and had a body mass index (BMI) of 24.2. He had a significant 30-year history of juvenile onset diabetes with a fair blood glucose control demonstrated by a recent HbA1C of 7.9%. He was on a subcutaneous insulin regiment of Mixtard 34 units in the morning, 15 units at night, and oral Metformin 250 mg twice a day.

His complications related to diabetes include hypertension and ischemic heart disease. He had suffered two previous myocardial infarctions that were treated with percutaneous coronary interventions. His pre-operative transthoracic echocardiogram showed a left ventricular ejection fraction (LVEF) of 20% and he had multiple previous hospital admissions for congestive heart failure. His renal function was otherwise normal with an estimated glomerular filtration rate (eGFR) of 102 ml/min. He did not have retinopathy or neuropathy prior to surgery.

On examination of his airway, his mouth opening (>3 finger breadths), thyromental distance (6 cm), and neck mobility were normal. Mallampati score was II and his dentition was normal. No difficulty with intubation was anticipated.

Standard monitors (e.g., 5 lead ECG, pulse oximetry), a right radial arterial line, and right internal jugular central venous catheter were placed prior to induction. Following induction of general anaesthesia, successful bag mask ventilation was confirmed before neuromuscular blockade was given.

Direct laryngoscopy with a Macintosh blade revealed only the tip of the epiglottis. The laryngoscope blade was advanced deep into the vallecula, but lifting the epiglottisto visualise the vocal cords was difficult as it was very stiff. Attempts to intubate with a stylet or a bougie using a video laryngoscope were also unsuccessful. A straight Miller blade was then used, which just lifted the tip of the epiglottis, allowing a tactile blind maneuver of a bougie through the vocal cords. An endotracheal tube was then successfully railroaded over the bougie into the trachea.

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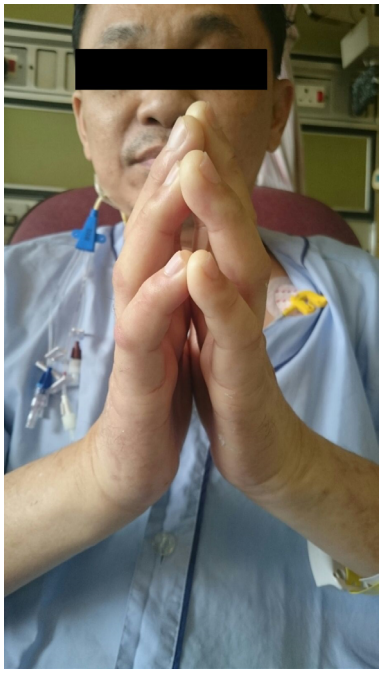
The surgery was uneventful and the patient made a full recovery. Post-operatively, the patient was assessed for limited joint mobility associated with diabetes mellitus and he demonstrated a positive Prayer sign. (Figure 1)

Figure 1: Limited Joint Mobility Syndrome Demonstrated by the "Prayer Sign".



DISCUSSION

Limited joint mobility syndrome (LJMS) or diabetic cheiroarthropathy is a long-term complication of diabetes mellitus with an incidence of 8-58%.[3] It is associated with microvascular and macrovascular complications of diabetes.

LJMS typically affects metacarpophalangeal and proximal interphalangeal joints. It manifests as progressive, painless stiffness in the hands and fingers, fixed flexion contractures of metacarpophalangeal joints with thick, waxy scleroderma-like skin appearance. Patients are unable to approximate the palmar surfaces of the phalangeal joints, exhibiting what is termed the "prayer sign".

LJMS may also affect other joints of the body leading to other sequelae. For example, involvement of the joints of lower limbs, increase the risk of falls in diabetic patients.[3] It has also been proposed that this joint rigidity may also affect the cervical and laryngeal areas making laryngoscopy more difficult.[4] Salzarulo et al[5] were the first to report "Stiff Joint Syndrome" as a cause of difficult intubation back in 1986. They attributed their difficulties to the limitation of movement at the atlanto-occipital joint.

The palm print has been used as an objective assessment of the degree of interphalangeal joint involvement. It is obtained by painting the palm of the dominant hand and pressing it firmly, with fingers spread, against a white piece of paper. A palm print score from 0-3 based on the degree of visibility of phalangeal areas on a piece of paper has been assessed as a factor to predict difficult laryngoscopy.[4-7] Several studies have compared it to other common clinical airway indices such as the Modified Mallampati score, thyromental distance and degree of neck extension and have found it to be the most sensitive predictor of difficult laryngoscopy in diabetic patients with sensitivity ranging from 75-100%.[6,7] The palm print test when used in combination with other airway assessment indices may improve the predictability of difficult laryngoscopy.

CONCLUSION

In conclusion, the palm print test is a useful and easy bedside test which can be used in combination with other clinical indices to help better predict difficult laryngoscopy in long-term diabetic patients.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

CONSENT

Consent has been taken from the patient for purpose of using patient photograph for publication in print or on the internet.

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Research

*Corresponding author
Ben C. Szirth, PhD
Director, Tele-Ocular Program
Institute of Ophthalmology and Visual Science
the State University of New Jersey
New Jersey Medical School
90 Bergen Street, Newark
NJ 07103, USA
Tel. 973-986-2055
E-mail: szirthome@gmail.com

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Advances in Type 1 Diabetes Ocular Remote Tele-Health Screening

Loka Thangamathesvaran, BS; Christopher Khouri; Liliane Deeb, MD; Ben C. Szirth, PhD*; Albert S. Khouri, MD

Institute of Ophthalmology and Visual Science, New Jersey Medical School, Rutgers University, Newark, NJ, USA

ABSTRACT

Background: Type 1 diabetes affects approximately 3 million Americans. Subjects are on average 14-years-old at time of diagnosis. It is a systemic, chronic condition that has retinal complications. Yearly ophthalmic consultation is important to maintaining adequate ocular health. The National Institute of Health (NIH) estimates that about half of individuals affected by diabetes are not aware they have some level of retinopathy.[1] The goal of community base remote screenings is to identify at risk individuals and refer them for comprehensive clinical evaluation and possible intervention.
Methods: Retinal screenings were conducted in July 2016 in conjunction with annual *Friends for Life* convention organized by *Children with Diabetes* (http://www.childrenwithdiabetes.com). In total, 218 participants were included in a comprehensive retinal screening. Self-reported baseline measurements of body mass index (BMI), blood pressure (BP), visual acuity and pupil size were recorded. An auto-refractor (Canon, Tokyo, Japan) and automated puff tonometer (Canon, Tokyo, Japan) were used to note visual acuity and intraocular pressure (IOP). Imaging modalities used to assess ocular health included a spectral domain ocular coherence tomography (OCT) (Optovue, iVue, Fremont, California, USA), ocular coherence tomography-angiography (Optovue, iVue, Fremont, California, USA), and a non-mydriatic retinal camera (Canon, Tokyo, Japan).
Results: Our ocular screening included 218 participants, 61%female and 39% male. Ages ranged from 4 to 73 with an average of 19±12.8 years. The average blood pressure was 111/70. HbA1C ranged from 5.1 to 13.0 with an average of 7.6±1.16. Average duration of diabetes for all subjects was 10 years. Most subjects on average had been using insulin pumps and continuous glucose monitoring devices (CGM) for 7 and 3.5 years respectively. Of the 218 subjects ten had dot hemorrhages, three had flame hemorrhages and one had intraretinal microvascular abnormalities (IRMAs) affecting at least one eye. One subject required emergency referral to medical retina while 15 were referred for anterior segment evaluation for nuclear sclerosis.
Conclusions: Comprehensive remote screenings including OCT, OCT-A and non-mydriatic retinal evaluation can provide a quick, efficient way to assess ocular health in T1DM. Yearly ophthalmic consultation can help detect retinal health at an early stage and better implement lifestyle modifications to minimize further complications.

KEY WORDS: Retinopathy; Type 1 Diabetes; Diabetic retinopathy; Retinal screenings; Non mydriatic retinal camera; Ocular coherence tomography (OCT); OCT-A.

ABBREVIATIONS: T1DM: Type 1 Diabetes Mellitus; BMI: Body Mass Index; BP: Blood Pressure; IOP: Intraocular Pressure; CGM: Continuous Glucose Monitoring Devices; IRMAs: Intraretinal Microvascular Abnormalities; OCT: Ocular Coherence Tomography; OCT-A: Ocular Coherence Tomography-Angiography; VA: Visual Acuity; FA: Fluorescein Angiography; ICG: Indocyanine Green; ONH: Optic Nerve Head.

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INTRODUCTION

Type 1 diabetes mellitus (T1DM) is a disease that compromises pancreatic function and requires strict glycemic control to minimize lifelong complications. These complications can have systemic manifestations that affect vision, renal function and have the potential to decrease the life span of those affected by 13 years.[2] Education and constant vigilance are key factors in managing these complications. An organization called; *Children with Diabetes,* was created to educate affected individuals and their families about T1DM (http://www.childrenwithdiabetes.com). The participants take part in various sessions including a comprehensive non-mydriatic ocular screening program where attendees and their families learn about ocular health as it relates to diabetes. For the past decade, the Institute of Ophthalmology and Visual Science (IOVS) located at Rutgers State University (Newark, NJ, USA) has provided over 2,500 comprehensive eye exams remotely with a volunteer staff of medical professionals, medical students as well as optometry students (SUNY College of Optometry, New York, NY, USA) and pre-college students interested in the field of health care.

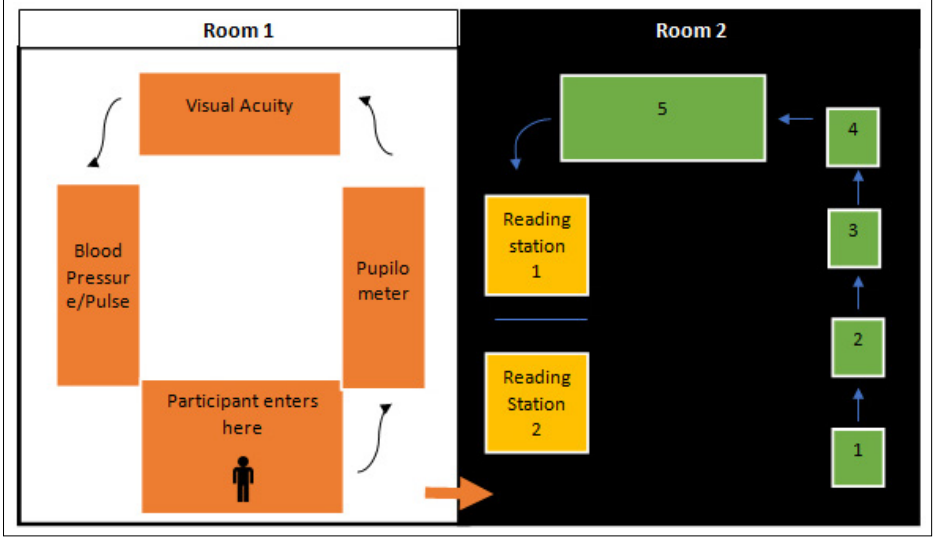
SUBJECTS AND METHODS

The comprehensive ocular screening was conducted following Health Insurance Portability and Accountability Act of 1996 (HIPPA) guidelines as well as an approved Institutional Review Board (IRB) at Rutgers University Hospital, Newark, New Jersey, USA. The screening was conducted in July 2016 and included 218 participants; 61% female and 39% male. The screening constituted of several stations divided between two rooms. As seen in Figure 1, in the first room (Left) participants provide baseline information such as; body mass index (BMI), blood pressure (BP), visual acuity (VA), and pupil size measured with a pupilometer (Neuroptics, VIP™-200 Irvine, California, USA).

The second room (Figure 1, right side) was illuminated at a level of 80 candelas in order to maintain naturally dilated pupils for optimal retinal imaging. The room consisted of 6 stations: the first station was an auto-refractor (Canon, RKF2 Tokyo, Japan), the second station was an automated puff tonometer (Canon, TX 20 Tokyo, Japan), the third station was a Spectral Domain Ocular Coherence Tomography (SD-OCT) (Optovue, iVue, Fremont, California, USA), the fourth station was an Ocular Coherence Tomography-Angiography (OCT-A) (Optovue, AngioVue, Fremont, California, USA), the fifth station was a non-mydriatic retinal camera (Canon, CR2 Plus-AF equipped with a EOS-60D SLR camera with a 45 degree view and a resolution of 18.1 mega pixel APS-C CMOS, Tokyo, Japan). Retinal photography station was placed as the last testing station since it uses a Xeon flash tube that compromises natural pupil dilation (flash setting in color imaging was 80 Watt second while auto fluorescence was 300 Watt seconds). Station six was the reading/evaluation station where all data was interpreted. This station had tele-ophthalmic connectivity through a DICOM connection to allow us access to an offsite board-certified ophthalmologist for instant consultation when needed.

All ocular testing was performed without use of mydriatic agents. Since our participants were predominantly children who were also partaking in outdoor programs we wanted to avoid dilation. Second, we wanted to avoid precipitating acute

Figure 1: Flow Chart Depicting Participant Flow during Screening. Room on the Left: Participant General Information; Pupil Size, Visual Acuity, Blood Pressure, Pulse, and Participant Intake form Consisting of Height, Weight, BMI, Diabetes Management, Family and Past Medical and Ocular History. Room on the Right: Retinal Screening Room. Number Correspondence; 1- auto-refractor (Canon, RKF2 Tokyo, Japan), 2- tonometer (Canon, TX 20 Tokyo, Japan), 3- SD-OCT (Optovue, iVue, Fremont, California, USA),4-OCT-A (Canon, TX 20 Tokyo, Japan), and 5- (Canon, CR2 Plus-AF with EOS-60D Tokyo, Japan). Two Reading Stations with Trained Retinal Readers. Low Lighting was Present in Room #2 Allowing for Maximally Dilated Pupils without using a Mydriatic Agent.



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angle-closure glaucoma *via* the use of dilating agents. Lastly, dilating agents take about 20 minutes to be effective, our total screening is under 15 minutes per participant and this additional step would reduce the number of screenings we could provide.

Technology Advantages and Limitations in this Population

Auto-refractor/keratometer: Since this is a comprehensive ocular screening; automated refraction was used in addition to visual acuity (at 20 feet). Auto-refractors use retinal reflex alterations as the subjects fixate at a given target to determine at which point the image is at focus on the retina.[3] Our screening used the Canon's RK-F2 (Tokyo, Japan) which has several key features that allowed for ease of operation. First, once the subject's head is positioned properly, the operator was able to fine tune eye alignment using an omni-directional joystick and capture bilaterally all the required data without any further operator intervention. This model had an additional advantage of including keratometry readings allowing for the simultaneous detection of astigmatism. Lastly, the 3D eye monitoring system in the ref-keratometer allows for maintenance of alignment irrespective of subject's ocular movement allowing for ease of operation especially in a pediatric setting. The average auto-refraction in our population were 0.25 OD and 0.50 OS. No age limitation was placed during this testing.

Automated puff tonometry: The automated non-contact puff tonometer used in this screening was a Canon, TX 20 (Tokyo, Japan) that measures the intraocular pressure (IOP) by delivering a measured puff of air into the subject's cornea (apex) and determines the pressure of air required to momentarily flatten the apex of the cornea. Two important criteria for characterizing IOPs as abnormal are when the IOPs are higher than 21 mm Hg and when the difference between the right and left eye IOP exceeds 3 mmHg. The average IOPs in our population were 19.58 OD and 19.60 OS, both falling within the normal range of 10-21 mm of mercury. The importance of intraocular pressure in a diabetic population is highlighted in previous studies indicating a correlation between higher IOPs and elevated glycemic levels.[4] We placed an arbitrary cut off age of 10-years-old strictly based on subjects cooperation.

Optical coherence tomography: The Ocular Coherence Tomography (OCT) (Optovue, Fremont, California, USA) has now become a standard component in all our retinal screenings. It's advent and progress since its inception in 1991 have provided eye care professionals with the ability to visualize cross-sectional images of retinal layers and quantify the thickness of these layers with a resolution of 6 microns; retinal nerve fiber layer, ganglion cell complex, and macular area. Images are captured *via* the back reflectance of light waves and the time delay in this reflectance helps to characterize the spatial differentiation between the retinal layers. Incorporation of this particular instrument was critical to our screening due to its ability to detect early macular edema, a common consequence of diabetic retinopathy due to fluid leakage from weak retinal vasculature.[5] No age limitation was applied to this testing.

Optical coherence tomography-Angiography: A new addition to our comprehensive retinal screening in T1DM started in 2015 has been the Optical Coherence Tomography Angiography (OCT-A). Traditional clinical modalities of vascular imaging systems have been fluorescein angiography (FA) and indocyanine green (ICG) imaging; however, their invasive approach associated with known risk factors and discomfort to subjects limit their use in remote telemedicine and pediatric setting such as our retinal screening.

Although, FA and ICG may provide effective methods in detecting neovascularization or vascular defects, they have limited capacity in providing 3D imaging and information specific regarding depth of a given pathology.[6] The OCT-A utilized in our screening has a scanning speed of 70,000 A-scans per second providing depth of about 2.5 mm and allowing for imaging from the internal limiting membrane to the choroid. In the context of diabetic retinopathy, at our screening, three important observations helped in characterizing participants control of diabetes; maintenance of foveal avascular zone, density of perifoveal area, and presence of tortuosity in retinal vasculature. No age limitation was applied to this testing.

Non-mydriatic retinal camera: A Canon CR-2 non-mydriatic camera was used in our screening. The screening room (Figure 1 Right) was kept at 80 candelas to maximize natural dilation of pupils. Our pediatric population had a natural pupil size of over 6 mm; greater than the minimum pupil size required for artifact free images, 3.2 mm. In total, five posterior pole images were captured in each subject; optic nerve head (ONH) and macula centered right and left images and ONH centered auto fluorescence image in either the right or left eye. Interposition of these images (automated montage, Canon proprietary software) allowed for a 60-degree view of the posterior pole. All images were captured on a Canon, CR2 Plus-AF equipped with a EOS-60D SLR (Tokyo, Japan) camera with a 45 degree view and a resolution of 18.1 mega pixel APS-C CMOS sensor. This sensor has a true red, green, and blue rendition giving us accurate posterior pole colors in the dark areas of the macula/fovea where about 90% of the light is absorbed whereas the optic nerve head reflects about 90% of the incident light therefore good detail is required to capture the fleshy appearance of this structure.

Reading and interpretation station : Post-screening, all data was made available either through electronic (intranet) or hard copy printout (vital signs). OCT, OCT-A, and retinal imaging was simultaneously displayed on color balanced computer monitor displays. Retinal images were evaluated for percentage of successful readable images. Success rate of imaging were scored based on the following criteria; clarity/sharpness, visualization of proper pre-selected fields, visibility of principal structures (macula, retinal vasculature, and optic nerve), and lack of external artifacts (blinking, lashes, poor centration of the camera, etc.). In situations where retinal images did not meet the im-

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Figure 2A, 2B: Left Side Image is of a 45° Field View of Retinal Image of Left Eye Taken in Non-Mydriatic Mode through a Mild Cataract. Right Side Images same 45° Field View of Retinal Image Post Capture Digital Processing Using Opacity Suppression (Canon, Tokyo, Japan).

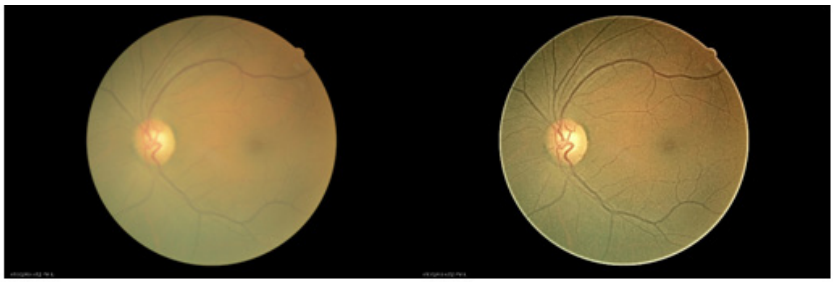

Photo curtesy of T. Russo

age quality, a post-process "Opacity Suppression" digital filter (Canon, Tokyo, Japan) was to enhance images and enable the grader to read the images (Figure 2A, 2B). Retinal imaging success rate for the 2016 screening was 90%. Screened subjects and parents were offered copies of the screening results after all findings were thoroughly discussed with them.

RESULTS

In a 4-day period spanning over 30 hours and with 16 volunteer screeners, 218 subjects with T1DM were screened. Of these 218 subjects, 70 were repeat screenings for at least one year with 39 subjects that were at least 2 years consecutive follow-up. Only one subject that had been in previous years under control lost good glycemic and blood pressure control resulting in over 440 retinal hemorrhages in both eyes. After close follow-up of this subject over a period of 8 months post screening, this individual returned to normal retinal appearance. Participant demographics are shown in Table 1.

Our ocular screening included 218 participants, 61% female and 39% male. The ages ranged from 4 to 73 with an average of 19±12.8 years. The average bp was 111/70. HbA1C levels ranged from 5.1 to 13.0 with an average of 7.6±1.16. Average duration of diabetes for all subjects was 10 years. Subjects on average had been using insulin pumps and continuous glucose monitoring devices (CGM) for 7 and 3.5 years respectively. Of the 218 individuals screened, 10 had dot hemorrhages, 3 had flame hemorrhages and 1 had intraretinal microvascular abnormalities (IRMAs) affecting at least one eye. One subject required emergency referral to medical retina while 15 were referred for anterior segment evaluation for nuclear sclerosis.

DISCUSSION

Glycemic parameters have to be maintained within a limited range. Deviation beyond these parameters can result in profound adverse effects such as diabetic coma. Although, most screened individuals did well, one individual illustrates the importance

Table 1: General Participant Demographics.

Characteristic	
Age (years)	19.13 (11-22)
Blood pressure (mmHg)	111/70 (98/62-122/78)
Average pulse (beats/minute)	84 (73-94)
Average age of type 1 diabetes onset (years)	8.7 (3.6-10.4)
Average duration of diabetes (years)	10 (4-13)
Average years of insulin pump use (years)	7 (2.5-10)
Average years of CGM use (years)	3.45 (1.5-5)
Glucose (mg/dL)	164 (112-200)
HbA1C (%)	7.57 (6.9-8.1)
Gender	Male: 38.9% Female: 61%
BMI	22.44 (18-25.7)

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of regular, consistent yearly screenings to better manage this chronic condition and prevent vision loss. The subject was a 21-year-old male who was diagnosed with T1DM in 1999. During his screening in 2012, blood glucose was 184 mg/dL, blood pressure was 128/78, and no indications of retinopathy were noted.[7] He had adequate control for 13 years.

During his visit in 2013, his self-reported blood glucose was 421 mg/dL, self-reported HbA1c level was >13%, blood pressure was 130/91 mm Hg, and pulse was 106 bpm. Retinal findings included 2 small dot hemorrhages, no flame hemorrhages, and a single Intraretinal Microvascular Abnormality (IrMA). The subject reported inconsistent use of insulin intake and glucose control.

At the time of his screening visit in 2015 (15 years post diagnosis), he had been prescribed Enalapril™ by his generalist for blood pressure control. However, he reported inconsistent use of Enalapril due to the development of numbness and pain in his legs which he attributed to the medication. He stopped taking Enalapril™. Since his previous visit, he had also altered his method of insulin administration from relying on a Medtronic™ insulin pump to self-administration of insulin subcutaneous injections due to the discomfort caused by the tubing in the Medtronic™ pump. His diet consisted primarily of fast food and carbonated sugar base drinks. These life style modifications resulted in a drastic change in both his physiological levels as well as retinal findings. His blood pressure at the time of his screening had increased to 142/62 mmHg, fasting blood glucose was 319 mg/dL, and HbA1c level was >13.5%. Retinal changes were severe with a total of 440 dot-blot and flame hemorrhages in the right and left eye primarily localized within the posterior pole consistent with diabetic retinopathy (Figure 3A and 3B).[7] The OCT-A images showed signs of retinal telangiectasia and micro-aneurysms. The subject had developed non-proliferative diabetic retinopathy, but his OCT-A findings indicating an avascular foveal pit impacted the direction of management therapy to favor more behavioral changes rather than ocular clinical treat-

Figure 3: (A) 45° Field View of Retinal Image of Left Eye Taken in Non-mydriatic Mode in July, 2015. (B) Center Image is a Montage Done without Dilation Comprised of 5 Images Captured in December 2015. (C) 45° Field View of Retinal Image Taken of Left Eye Taken in Non-mydriatic Mode in July, 2016.

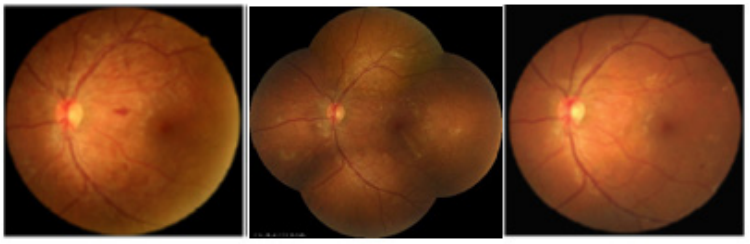

Figure 4: Top: OCT-A Image of Left Eye Taken July, 2015. Bottom: OCT-A Image of Left Eye Taken in July, 2016.

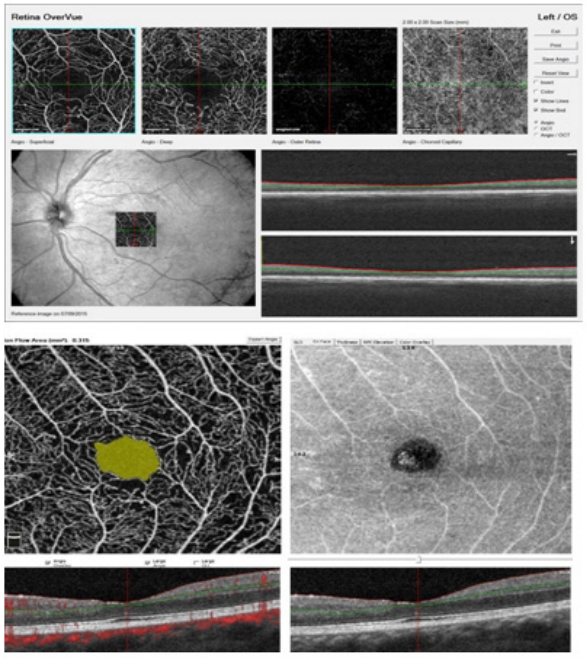

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Figure 5: "Children with Diabetes" Screening Team 2016, July 2016. Front Row: C. Khouri, B. Szirth, K. Duong, M. Shah, L Deeb, L. Thangamathesvaran, Back row: S. Mendez, K. Soules, B. Peach, R. Ragam, K. Dunlap, J. Stroud, R. Freund, H. Cope, M. Ferm, C. Weng. Photo credit: Corporate Image Photography.

ment to prevent disease progression (Figure 4).

After the 2015 retinal screening, the subject revised his approach to his diabetes management and resumed taking Enalapril for blood pressure control, Medtronic™ insulin pump for glycemic control, and started to implement healthier life style modifications. Over the course of 8 months, the subject's progress was monitored monthly both *via* retinal imaging (photography and OCT) and glycemic parameters. At the 2016 screening, his HbA1c had decreased to 8.1%, blood pressure was 110/75 mmHg, and he had two dot hemorrhages, no flame hemorrhages, and no IRMAs (Figure 3C). His positive progression emphasizes the importance of good follow-up with multi-specialty services as well as yearly retinal screenings that can monitor good glycemic and blood pressure control.

CONCLUSION

Fast paced ocular health screening programs (15 minutes) as it relates to T1DM can be successfully performed in subjects as young as 4 years of age. A non-mydriatic approach makes the experience more pleasant and convenient for the individual without compromising the quality of the images. Yearly comprehensive ocular health screenings along with T1DM related general education plays an important role in good vision control in T1DM while reminding individuals that screenings are not meant to be a replacement of a timely visit to the multi-specialty centers that can best control T1DM. One of the goals of *Friends for Life* yearly events is to create a safe learning family experience focused on establishing a lifelong support of all aspects of living with T1DM.

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CONFLICTS OF INTEREST

None of the authors have a conflicts on interest.

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