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Original Research

Rationale Diagnostic Criteria of the Metabolic Syndrome

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ABSTRACT

Purpose

Metabolic syndrome is a preceding risk of diabetes, hypertension and/or dyslipidemia, so the diagnosis of metabolic syndrome is important for further treatment. In 2005, the international diabetes foundation (IDF) reported a new diagnostic criterion of metabolic syndrome, making abdominal obesity an essential factor required in the diagnosis. Waist circumference (WC) is used as a surrogate marker of abdominal obesity, but it is defined based on the national cutoff point of each country. This study examined the validity of diagnostic criteria ofmetabolic syndrome, especially focusing on the different criteria of WC, for international standardization.

Method

We compared the efficacy of our previous weight-loss intervention by Japanese and IDF criteria by reanalyzing Saku control obesity program (SCOP). In IDF, the cutoff point of WC for men is 90 cm and 80 cm for women. On the contrary, the cutoff point of WC is 85 cm for men and 90 cm for women in Japan. Factors for diagnosis was evaluated, and the prevalence of metabolic syndrome at baseline and 1 year later was compared by the different diagnostic criteria.

Result and Discussion

In Japanese criteria, the rate of metabolic syndrome among men decreased from 100% to 97.3%, and among women 96.6% to 88.6%. However, when we applied the IDF criteria, the rate of metabolic syndrome among men decreased from 97.4% to 88.5%, and among women 100% to 100%. These results suggested that the prevalence of metabolic syndrome by IDF criteria is underdiagnosis in men and over-diagnosis in women compared to the Japanese criteria. Japanese cutoff point is calculated by the computed tomography (CT) scan data in which 100 cm^2 abdominal fat area corresponds to nearly 100 cm WC. The standardization of diagnostic criteria is important to compare the efficacy of intervention and prevention of diseases between countries.

Keywords

Metabolic Syndrome; Obesity; Waist circumference; Visceral fat; Adiponectin; Leptin.

INTRODUCTION

Conflicting Diagnostic Criteria of Metabolic Syndrome

The increase in obesity over the past 30 years has been fueled by a complex interplay of unhealthy diet and physical inactivity, environmental, social, economic, and behavioral factors, acting on a background of genetic susceptibility.[1-3] Obesity is a common risk factor for diabetes, hypertension, dyslipidemia and other lifestyle related diseases, and the preclinical condition has been summarized under the diagnosis of metabolic syndrome. The concept of metabolic syndrome was proposed by several committees, although there had been a considerable disagreement over the definition and diagnostic criteria. The use of definitions in conducting research into the metabolic syndrome resulted in wide-ranging prevalence rates, inconsistencies and confusion, and spurred on the vigorous debate regarding how the metabolic syndrome should be defined.[4-6]

Excess abdominal fat is an important and independent risk factor for metabolic syndrome. Research has shown that waist circumference is directly associated with abdominal fat and can

be used in the assessment of risks associated with excess weight and obesity.[7,8] The above Japanese cutoff point (85 cm for men and 90 cm for women) was calculated based on the CT scan data (100 cm^2 abdominal fat area). In recent years, abdominal computed tomography (CT) has become available to determine the amount of abdominal fat directly and accurately.[7]

Fortunately, people who have a body mass index (BMI) of 30 or greater can improve their health by losing weight. A loss of 5-10% of initial body weight can do much to improve health by lowering blood pressure and other risk factors for obesity-related diseases.[9] In addition, research showed that a goal of at least 7% weight loss from initial body weight brought by moderate diet and exercise could delay or possibly prevent type 2 diabetes in nondiabetic people.[10]

Longitudinal Epidemiological and Clinical Study in Saku

We have carried out a series of epidemiological and clinical studies in Saku, Nagano prefecture in Japan.[11-15] Since 1990 a population-based Japan Public Health Center cohort study, consisting of 40-59-year-old residents, has been conducted in Saku. In Saku Health Dock Center each year about 7,000 examinees have come to the center for health checkups, including an oral glucose tolerance test (OGTT) by 75 g glucose intake, endoscopy, and recently abdominal CT, in addition to the routine laboratory test and physical check-up. The Saku Health Dock Center database contains approximately 196,000 records connecting to the hospital database.

The purpose of the cohort study was to identify cancer and cardiovascular disease risks, and it represented a novel approach that incorporated biological markers as health screening data, blood, urine, and gene storage for future analyses. We selected this area because of a long collaborative history for primary prevention of chronic diseases.[16]

Objective of this Study

The objective of this study was to examine the validity of diagnostic criteria of metabolic syndrome, especially focusing on the different criteria of waist circumference (WC) (International Diabetes Foundation (IDF) and Japanese criteria). We reanalyzed the data of our previous clinical study (saku control obesity program (SCOP)) and compared the efficacy of SCOP intervention (i.e. change in the rate of metabolic syndrome before and after the intervention) by using the Japanese and IDF criteria.

METHODS

Evidence-Based Approach: Saku Control Obesity Program (SCOP)

The saku control obesity program (SCOP), the details of which have been described previously.[11] The SCOP study protocol included 235 Japanese obese subjects (116 men and 119 women) recruited from the database of medical health check-up of Saku Central Hospital Human Dock Center. The study participants were selected from medical records since 2000 and were aged 40-64-years-old with a body mass index (BMI: kg/m^2) greater than 28.3 (the upper 5 percentile of all examinees). They were asked to participate in an intervention program for weight loss.

The number of participants was 116 males and 119 females, aged 52.9±6.6 and 54.4±6.5 years, respectively. Basal metabolic rate, measured in one-tenth of the participants, was 1659±226 kcal in males and 1477±210 kcal in females, and physical activity energy expenditure (PAEE) was 271±127 kcal in males and 246±102 kcal in females. Average body weight was 86.4±11.8 kg in males and 75.2±9.5 kg in females. Average BMI was 30.4±3.5 kg/m^2 in males and 31.1±3.1 kg/m^2 in females.

A cognitive-behavioral treatment was employed in a randomized intervention trial by diet and physical activity.[13] All participants were randomly divided into two groups: Group A received intervention in year 1 and will be followed-up in years 2 and 3; Group B will receive intervention in year 2 and will be followed up in year 3. A diary to record body weight, body fat, number of steps, and success in achieving the established plan (e.g., not eating snacks, increase of 3,000 steps/day), as well as a dietary record, was given to each participant. The equipments for body weight and body fat scale and accelerometer (Lifecorder), were also provided.

The participants received individual counseling (30 minutes) by a registered dietician after physical examination and group sessions about effective exercise (20 minutes) by exercise instructors. Body composition parameters were measured at baseline and at 1, 3, 6 and 9 months during the intervention period.

Statistical Analysis

In this study, we undertook further analysis of the data of the SCOP. Body fat %, total fat area, subcutaneous fat area and visceral fat area after 1-year intervention in the intervention and control groups were compared by Student's *t*-test. Spearman correlations were used to test the association among body weight, BMI, waist circumference and CT fat area. The significance of differences among the biomarkers at the baseline, after 1 year and 1-year follow-up were analyzed with repeated measure analysis of variance (Friedman test was used for adiponectin and leptin). The Japanese criteria of metabolic syndrome was defined as follows; WC≥85 cm for male and WC≥90 cm for female and having two or more the following risk factors: dyslipidemia (triglyceride≥150 mg/dl and/or HDL cholesterol<40 mg/dl), hypertension (systolic blood pressure≥140 mmHg and/or diastolic blood pressure≥90 mmHg) and hyperglycemia (fasting plasma glucose≥110 mg/dl). The IDF criteria was defined as follows; WC≥90 cm for male and WC ≥80 cm for female and the other criteria are as same as Japanese criteria.

RESULTS

At baseline, the prevalence rate of the risk factor of metabolic syndrome was as follows; hypertension; 27.2% and 42.7% for males and females, respectively, hyperglycemia; 39.5% and 40.2%, dyslipidemia; 57.9% and 35.9% for males and females, respectively (Table 1).

People who are obese could reverse an earlier metabolic syndrome by adopting a healthy lifestyle and losing weight.

Table 1. *Prevalence of Each Risk Factor of Metabolic Syndrome at Baseline*

	Males n=116	%	Females n=119	%
Hypertension	31	27.2	50	42.7
Hyperglycemia	45	39.5	47	40.2
Dyslipidemia	66	57.9	42	35.9

*Hyperglycemia is more than 7 mM by OGTT.

In males, the number of risk factors decreased from 40.4% to 35.1% with one factor, 15.8% to 19.3% with two factors, and 14.0% to 7.0% with three factors. In females, 28.1% to 35.1% with one factor, 26.3% to 15.8% with two factors, 7.0% to 3.5% with three factors (Table 2).

Table 2. *Number of Risk Factors Before and After the Intervention*

	Baseline				After 1yr intervention			
	Males n	%	Females n	%	Males n	%	Females n	%
No risk factor	17	29.8	22	38.6	22	38.6	26	45.6
1 risk factor	23	40.4	16	28.1	20	35.1	20	35.1
2 risk factors	9	15.8	15	26.3	11	19.3	9	15.8
3 risk factors	8	14.0	4	7.0	4	7.0	2	3.5
	57		57		57		57	

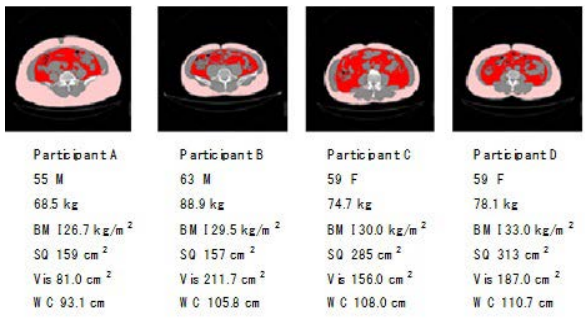
A goal of 5% reduction of body weight attained more than half, and about one fourth achieved 10 kg reduction of body weight. Group A showed 4.5±4.4 kg decrease by the one-year intervention, and group B decreased by 5.4±6.1 kg body weight.

Anthropometric and Laboratory Data of SCOP

The waist circumference was measured twice at the umbilicus level while the subject was in a standing position using a fiberglass measuring tape; the average measurement was used for the analysis.

Total fat areas were assessed by a CT scan at the level of the umbilicus, with the subjects in the supine position, and calculated using the software (Fat Scan; N2 System Corp, Osaka, Japan) (Figure 1).

Figure 1. *Abdominal Computed Tomography of Visceral Fat and Subcutaneous Fat*



SQ: Subcutaneous fat area, Vis: visceral fat area

Abdominal CT photo was taken annually and total fat, subcutaneous and visceral fat was separately measured by the computer software. Body fat % was measured by InBody (body composition measurement by impedance) and change in fat measurements by 1-year intervention was compared (Table 3).[17]

Table 3. *Changes of Fat Volume and CT Area by 1year Intervention*

	Intervention group (Males (n=56))		Control group (M(n=49))		
Males	Baseline	After 1 year	Baseline	After 1 year	p
Age (years)	53.7±6.7		53.9 ± 6.3		
Body fat (%)	28.5±3.6	26.8±4.4	29.2±4.6	29.6±5.1	**
Total fat area (cm2)	393±82	333±81	417±137	397±104	**
Subcutaneous fat area (cm^2)	243±66	207±62	253±114	238±96	*
Viscera fat area (cm^2)	150±48	126±46	164±48	159±48	**
	Intervention group (Females (n=52))		Control group (F(n=52))		
Females	Baseline	After 1 year	Baseline	After 1 year	p
Age (years)	55.0±6.6		54.5±6.2		
Body fat (%)	39.7±5.2	37.8±5.9	41.8±5.4	41.8±5.8	**
Total fat area (cm^2)	467±98	402±93	468±123	455±108	**
Subcutaneous fat area (cm^2)	343±80	302±76	335±100	326±88	
Viscera fat area (cm^2)	125±47	100±38	133±47	130±45	**

Means±SD. Significant level between two groups after 1 year; *p<0.05 **p<0.01

The correlations among body weight, BMI, WC, and total fat, subcutaneous and visceral fat area (cm^2) by CT are shown in Table 4. BMI, WC and total fat area showed a significantly high association, and the visceral fat area only showed a mild association with total fat area and body weight. Visceral fat area had poor association with subcutaneous (SQ) fat area in female subjects.

Table 4. *Correlation between Body Weight, BMI, Waist Circumference and CT Fat Area*

M n=116 F n=119	Weight	BMI	Waist	Total fat	SQ fat	Visceral fat
Weight		0.863**	0.890**	0.837**	0.798**	0.539**
BMI	0.823**		0.879**	0.907**	0.874**	0.567**
Waist	0.798**	0.769**		0.917**	0.877**	0.585**
Total fat	0.766**	0.788**	0.903**		0.926**	0.697**
SQ fat	0.739**	0.719**	0.857**	0.906**		0.375**
Visceral fat	0.371**	0.458**	0.461**	0.593**	0.197*	

* p<0.05 **p<0.01

Upper part (yellow) is the correlation among men, and lower part (red) is among women.

Even though the WC increases, the increase of visceral fat area is the lowest compared to the subcutaneous fat area (Figure 2).

Following an overnight fast, blood samples were collected for biological analyses at the time of each health check-up. HDL cholesterol (HDL-C), LDL cholesterol (LDL-C), triglyceride (TG) and HbA_{1c} levels were analyzed in the clinical laboratory of

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the Saku Central Hospital. High-molecular-weight form (HMW) adiponectin (μg/mL) and leptin (ng/mL) were measured by ELISA. Clinical and biological parameters were assessed at baseline (0 month), the end of intervention (12 months) and the end of follow-up (24 months).

Body weight, BMI, and other biological change are noted. Most of the biomarkers were significantly improved at the 12 and 24 months as compared with baseline (Table 5).

Changes in adiponectin and leptin were a good biomarker for the trend in body weight decrease and rebound (Figure 3).

Figure 2. *Relationship between Waist Circumference and CT Estimated Fat Area*

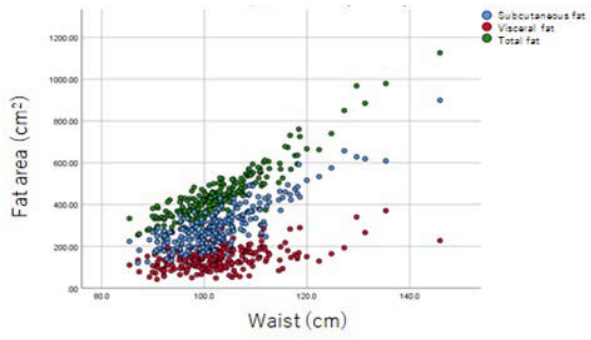


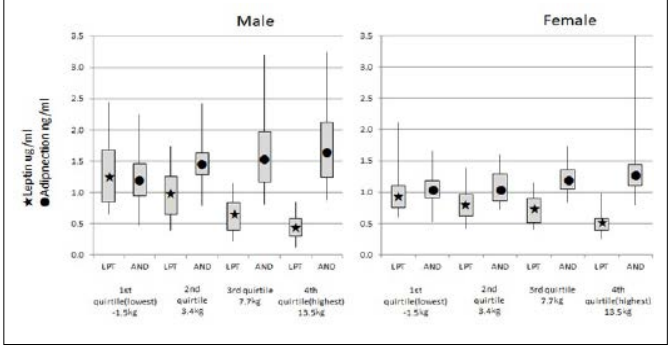
Table 5. *Change of Biomarkers at the Baseline, After 1year Intervention, and 1year Follow-up*

Males (n=56)	unit	Baseline	After 1year intervention	1 year follow-up	*p*
Weight	kg	84.2±8.5	79.3±8.7	80.5±1.2	**
BMI	kg/m^2	29.8±2.3	28.1±2.5	28.5±2.6	**
Systolic blood pressure	mmHg	131.9±15.4	125.8±14.3	128.3±12.6	**
Diastolic blood pressure	mmHg	81.1±14.2	79.3±11.2	80.4±10.1	
Waist circumference	cm	100.0±6.5	96.0±7.5	96.7±7.3	**
Total fat area	cm^2	393.3±82.2	333.1±80.7	350.3±82.0	**
Total cholesterol	mg/dl	205.4±29.3	203.3±34.1	196.6±29.9	**
HDL cholesterol	mg/dl	48.3±10.8	50.3±12.7	51.4±14.6	**
LDL cholesterol	mg/dl	123.2±28.9	124.4±30.9	120.8±31.2	
Triglyceride	mg/dl	169.7±98.1	142.8±74.4	146.4±81.9	*
HbA1c	%	5.7±1.1	5.5±0.8	5.7±0.7	**
Adiponectin	ug/ml	2.2 (1.5-3.6)	3.2 (2.1-5.9)	2.6 (1.6-4.8)	**
Leptin	ng/ml	6.7 (4.2-9.1)	5.7 (3.8-8.8)	5.2 (3.6-7.3)	**
Females (n=52)					
Weight	kg	74.5±8.4	70.7±9.3	71.9±1.3	**
BMI	kg/m^2	31.0±2.9	29.4±3.4	29.9±3.3	**
Systolic blood pressure	mmHg	132.6±16.1	126.8±17.3	126.1±17.4	**
Diastolic blood pressure	mmHg	81.3±11.4	79.8±11.7	78.9±10.9	**
Waist circumference	cm	103.2±8.1	99.2±9.6	100.7±9.2	**
Total fat area	cm^2	467.4±97.6	402.0±93.0	420.5±90.8	**
Total cholesterol	mg/dl	210.3±35.5	210.1±26.8	206.4±27.6	
HDL cholesterol	mg/dl	56.2±11.8	57.2±13.0	59.0±13.4	*
LDL cholesterol	mg/dl	128.0±31.8	129.2±25.9	126.8±25.0	
Triglyceride	mg/dl	130.8±60.7	118.4±57.9	112.9±53.9	*
HbA1c	%	5.9±1.2	5.6±1.0	5.9±1.0	*
Adiponectin	ug/ml	5.1 (4.1-8.4)	6.8 (5.1-10.2)	5.8 (4.8-8.5)	**
Leptin	ng/ml	17.7 (13.2-23.5)	15.7 (10.7-20.7)	14.2 (9.5-18.2)	**

*p<0.05, **p<0.01 by repeated measure ANOVA (by Friedman test for adiponectin and leptin)

Means±SD. Adiponectin and leptin showed median and range (25 percentile and 75 percentile).

Figure 3. *Leptin and Adiponectin Corresponding to the Quartile of Body Weight Decrease*



Adiponectin is associated with insulin sensitivity and atherosclerosis. Despite adiponectin being secreted from adipose tissue, plasma levels are lower in individuals with obesity, insulin resistance and type 2 diabetes (T2D). Leptin continued to decrease throughout 24 months despite weight regain between follow-up periods (Table 5). HDL-C continued to increase from baseline to 24 months. At 24 months, HDL-C was significantly higher than at baseline for both men and women.

Evaluation of efficacy of SCOP intervention by Japaneseand IDF criteria

We evaluated the efficacy of SCOP intervention (i.e. change in the rate of metabolic syndrome before and after the intervention) by using the Japanese and IDF criteria.When we applied Japanese criteria, the rate of metabolic syndrome among men decreased from 100% to 97.3%, and among women 96.6% to 88.6% (Table 6). Three and 8% reduction in males and females occurred. However, when we applied the IDF criteria, the rate of metabolic syndrome among men decreased from 97.4% to 88.5%, and among women 100% to 100%. Metabolic syndrome rate decrease was found 9% in men, and none in women.

Table 6. *Number of Subjects by Japan and IDF Criteria*

Baseline	Japan criteria				IDF criteria			
	M	%	F	%	M	%	F	%
MS -	0	0	4	3.4	3	2.6	0	
MS +	116	100	115	96.6	113	97.4	119	100
total	116		119		116		119	
After 1 year intervention	Japan criteria				IDF criteria			
	M	%	F	%	M	%	F	%
MS -	3	2.7	13	11.4	13	11.5	0	0
MS +	110	97.3	101	88.6	100	88.5	114	100
total	113		114		113		114	

MS; metabolic syndrome, -; none, +; present, M; males, F; Females

DISCUSSION

Different Prevalence of Metabolic Syndrome by Japanese, WHO and IDA Criteria

The first definition of criteria referring to abdominal obesity was proposed by the National Cholesterol Education Program Adult Treatment (ATPIII) in 2001. ATPIII adopted abdominal obesity estimated by the WC rather than by BMI in addition to hypertriglyceridemia, low High-Density Lipoproteins (HDL)-cholesterol, high blood pressure, and hyperglycemia.

In 2005, the International Diabetes Foundation (IDF) reported a new diagnostic criterion of metabolic syndrome, making abdominal obesity an essential factor required in the diagnosis.[4] The representatives of the IDF, the International Atherosclerosis Society, and the American Heart Association/National Heart, Lung and Blood Institute agreed that abdominal obesity should not be a prerequisite for the diagnosis, requiring the present of any three of five factors. They also suggested that abdominal obesity should be defined based on the national cutoff point of each country.[4] Most countries accept the criteria of IDF.

Matsuzawa[5,18] accumulated data of abdominal CT scan in relationship to adiposity and diseases, and the Japanese committee adopted a cutoff point of 100 cm^2 of the visceral fat area for both men and women because the risk of metabolic syndrome increased over this point in both men and women simultaneously. WC that corresponded to visceral fat of 100 cm^2 was 85 cm in men and 90 cm in women.

When we compare the efficacy of intervention by Japanese criteria, the rate of metabolic syndrome among men decreased from 100% to 97.3%, and among women 96.6% to 88.6% (Table 6). Three and 8% reduction in males and females occurred. However, when we applied the IDF criteria, metabolic syndrome rate decrease was found 9% in men, and none in women. Such unbalance is curious in biological response. It also suggests the prevalence of metabolic syndrome by IDF criteria is underdiagnosis in men and overdiagnosis in women compared to the Japanese criteria.

Biological Rationale of the Japanese Criteria Based Upon the Abdominal Fat Area by CT

Controversies on the significance and cutoff point of WC may have arisen from a misunderstanding of the purpose and the significance of the measurement of WC.[18]

The adipose tissue had been considered as just an energy storage tissue, but recent studies reported that the tissue synthesizes and secretes various bioactive substances called adipocytokines, such as leptin, adiponectin, tumor necrosis factor-α (TNF-α), free fatty acids (FFAs), resistin and angiotensinogen.[19] Many studies have been investigated about adiponectin and leptin among various adipocyte-derived cytokines, and it is thought to be related in the process of metabolic syndrome to the disease.[20,21]

So far, visceral adiposity measured by CT scan is a golden standard, and it fits into the pathophysiology of metabolic syndrome.

The cutoff point in Japan was the only one that was

based on the visceral fat area for the prevalence of diseases. The first nationwide lifestyle intervention program to improve the risk factors for metabolic syndrome in healthy adults was recently reported by Tsushita et al.[22] They used the registry of Specific Health Checkups and Specific Health Guidance focusing on metabolic syndrome in middle aged adults, 40 to 74 years of age, beginning in 2008 with follow-up period of 3 years. Number of participants to the program was 31,790 and non-participated controls were 189,726. Body weight reduction was 1.98 kg (participants) and 0.42 kg (non-participants) and WC reduction was 2.34 cm in men and 2.98 cm in women by the intervention, while among controls it was unchanged for 3 years.

So, the standardization of diagnostic criteria is important to compare the efficacy of intervention and prevention of diseases. It could be conclusive that the WC of Japanese criteria is appropriate avoiding both over-diagnosis and under-diagnosis. WC reflects both visceral fat and subcutaneous fat of the abdominal wall, women in middle age usually have more subcutaneous fat than visceral fat. A similar distribution is found among *sumou* wrestlers. The subcutaneous fat area did show a low correlation with visceral fat area (CC=0.197) in women (Table 4).

As developing countries are simultaneously facing increasing obesity and lifestyle diseases, collaboration in research and programs is urgently needed to prevent disease through dietary and lifestyle intervention.

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ETHICAL ISSUE

The protocol of SCOP was approved by the National Institute of Health and Nutrition and the SAKU General Hospital. The Ministry of Health, Labour and Welfare supported the study by funding.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

REFERENCES

1. Watanabe S, Mizuno S, Hirakawa A. Effects of brown rice on obesity: GENKI Study I (cross sectional epidemiological study.) *J Obesity Chronic Dis.* 2018; 2(1): 12-19. doi: 10.17756/jocd.2018-013

2. Poirier P, Giles TD, Bray GA, et al. Obesity and cardiovascular disease: Pathophysiology, evaluation, and effect of weight loss. *Arterioscler Thromb Vasc Biol.* 2006; 26: 968-976. doi: 10.1161/01.ATV.0000216787.85457.f3

3. Ford ES, Williamson DF, Liu S. Weight change and diabetes incidence: Findings from a national cohort of US adults. *Am J Epidemiol.* 1997; 146(3): 214-222. doi: 10.1093/oxfordjournals.aje.a009256

4. Zimmet P, Magliano D, Matsuzawa Y, Alberti G, Shaw J. The metabolic syndrome: A global public health problem and a new definition. *J Atherosclerosis Thromb.* 2005; 12(6): 295-300. doi: 10.5551/jat.12.295

5. Matsuzawa Y. Pathophysiology and molecular mechanisms of visceral fat syndrome: The Japanese experience. *Diabetes Metab Rev.* 1997; 13(1): 3-13. doi: 10.1002/(sici)1099-0895(199703)13:1<3::aid-dmr178>3.0.co;2-n

6. Watanabe S. Waist circumference in the diagnosis of metabolic syndrome: Debate and solution. *Ann Nutr Food Sci.* 2018; 2(3): 1022.

7. Examination Committee of Criteria for 'Obesity Disease' in Japan; Japan Society for the Study of Obesity. New criteria for 'obesity disease' in Japan. *Circ J.* 2002; 66(11): 987-992.

8. The IDF consensus worldwide definition of the metablolic syndrome. Volume 2005. International Diabetes Federation. 2005.

9. Wing RR, Lang W, Wadden TA, et al. Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes. *Diabetes Care.* 2011; 34(7): 1481-1486. doi: 10.2337/dc10-2415

10. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med.* 2002; 346(6): 393-403. doi: 10.1056/NEJMoa012512

11. Watanabe S, Morita A, Aiba N, et al. Study design of the SAKU Control Obesity Program (SCOP). *Anti-aging Med.* 2007; 4(2): 70-71. doi: 10.3793/jaam.4.70

12. Morita A, Ohmori Y, Suzuki N, Ide N, Morioka M, et al. Anthropometric and clinical findings in obese Japanese: The Saku Control Obesity Program (SCOP). *Anti-aging medicine.* 2008; 5(1): 13-16. doi: 10.3793/jaam.5.13

13. Nakade M, Aiba N, Suda N, et al. Behavioral change during weight loss program and one-year follow-up: Saku Control Obesity Program (SCOP) in Japan. *Asia Pac J Clin Nutr.* 2012; 21(1): 22-34.

14. Watanabe S. Population-based strategy for preventing diabetes and its complications. *Diabetes Res Open J.* 2018; 4(1): e1-e4. doi: 10.17140/DROJ-4-e011

15. Nakade M, Aiba N, Morita A, et al. 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. *Diabetes Res Open J.* 2017; 3(2): 20-30. doi: 10.17140/DROJ-3-132

16. Watanabe S, Tsugane S, Sobue T, Konishi M, Baba S. Study design and organization of the JPHC study. Japan public health center-based prospective study on cancer and cardiovascular diseases. *J Epidemiol.* 2001; 11 (6 Suppl): S3-S7.

17. Kawashima N, Watanabe S, Morita A, et al. Changes of fat volume and adipocytokines by the randomized intervention program for obesity control program (SCOP). *Diabetes Res Open J.* 2015; 1(5): 136-146. doi: 10.17140/ DROJ-1-122

18. Matsuzawa Y. Specific health guidance, the nationawide lifestyle intervention program targeting metabolic syndrome, seems to be successful in Japan. *J Atheroscler Thromb.* 2018; 25(4): 304-305. doi: 10.5551/jat.ED092

19. Matsuzawa Y, Funahashi T, Nakamura T. Molecular mechanism of metabolic syndrome X: Contribution of adipocytokines adipocyte-derived bioactive substances. *Ann N Y Acad Sci.* 1999; 892: 146-154. doi: 10.1111/j.1749-6632.1999.tb07793.x

20. Arita Y, Kihara S, Ouchi N, et al. Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. *Biochem Biophys Res Commun.* 1999; 257(1): 79-83. doi: 10.1006/bbrc.1999.0255

21. Cnop M, Havel PJ, Utzschneider KM, Carr DB, Sinha MK, et al. Relationship of adiponectin to body fat distribution, insulin sensitivity and plasma lipoproteins: Evidence for independent roles of age and sex. *Diabetologia.* 2003; 46(4): 459-469. doi: 10.1007/s00125-003-1074-z

22. Tsushita K, Hosler AS, Miura K, et al. Rationale and descriptive analysis of specific health guidance: The national wide lifestyle intervention program 2010 targeting metabolic syndrome in Japan. *J Atheroscler Thromb.* 2018; 25(4): 308-322. doi: 10.5551/jat.4

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Systematic Review based Hypothesis

Fatty Acid Escape Hypothesis: The Pathway to Type-2 Diabetes

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ABSTRACT

Background
Obesity and Type 2 diabetes mellitus (T2DM) are closely related such that together these are generally called diabesity, the underlying causes of which revolve around the functioning of insulin.

Methods
PubMed was searched using the following Mesh [("*Adipocytes/classification*"[Mesh] OR "*Adipocytes/cytology*"[Mesh] OR "*Adipocytes/metabolism*"[Mesh] OR "*Adipocytes/pathology*" [Mesh] OR "*Adipocytes/physiology*"[Mesh]) OR "*Fatty acids* (FA)" [Mesh].

Results
The interaction of insulin with the whole body systems is extensive and resistance to insulin can occur due to multiple reasons including sepsis, Cushing's syndrome, or even with pregnancy. In this review of literature, our focus is primarily on insulin resistance that is associated with obesity. Insulin promotes lipogenesis in the liver and promotes glucose uptake by skeletal muscles and adipose tissues. Also, insulin inhibits lipolysis in adipose tissue to allow triacylglycerides (TAG) storage in the anhydrous droplet form. When insulin resistance ensues, the delicate balance will tilt to a self-enabling cycle that culminates in the development of T2DM "Diabesity".

Conclusion
This review of literature also discusses the hypothetical cascade of defective expansion of adipose tissue due to fatty acids escape, chronic inflammatory state, and ectopic fat deposition in the omentum, liver and skeletal muscles that underlie the pathogenesis of this disease process.

Keywords
Adipose tissue; Diabetes; Fatty acid; Insulin; Resistance; Obesity.

Abbreviations
AS-160: Aktsubstrate of 160kDa; ASP: Acylation stimulating protein; DAG: diacylglycerol; DIC: Decarboxylase carrier; FA: Fatty acid; FFA: Free Fatty acid acid; G-6-P: Glucose-6-phosphate; GPCR-40: G-protein coupled receptors-40; HIF-1: Hypoxia inducible factor-1; IKKβ: I-kappa B kinase β; imTG: Intramuscular triglyceride; IR: Insulin binding to its receptor; IRS: Insulin receptor substrate; LCFAs: Long-chain fatty acids; LPL: Lipoprotein lipase; MCFAs: Medium-chain fatty acids; mTOR: Mammalian target of rapamycin; OMF: Omental fat; PEPCK: Phosphoenolpyruvate carboxykinase; PKCζ: Protein Kinase Cζ; ROS: Reactive oxygen species; SCFAs: Short-chain fatty acid; SCF: Subcutaneous fat (SCF); STZ: Streptozococin; T1DM: Type-1 diabetes mellitus; T2DM: Type-2 diabetes mellitus; TNF-1α: Tumor necrosis factor-1α; UCP-1: Uncoupling protein-1; VF: Visceral fat; VLDL: Very low density lipid; WHO: World Health Organization.

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INTRODUCTION

The recent updates from world health organization (WHO) indicate that the number of patients with diabetes in the world has quadrupled to an estimated 422 million since the publication of first report by WHO in 1980.[1] Likewise, obesity has doubled globally during the same time-period with more than 1.9 billion overweight and over 600 million obese adults worldwide.[2] Given the clinical manifestations, Type-2 diabetes mellitus (T2DM) has always been considered as glucose-centric pathology, characterized by the legendary Hippocratic three "Ps", i.e., polyuria, polydipsia and polyphagia.[3] The underlying cause of T2DM is the loss of glucose homeostasis, a condition which is also shared by Type-1 diabetes mellitus (T1DM). In terms of metabolic derangement, T1DM and T2DM are on the opposing ends of the disease spectrum: the former is depicted by hypoinsulinemia whereas the latter is characterized by hyperinsulinemia that emanates from body's adaptive response to the tissue insulin resistance.[4] Experimental animal studies have provided genetic evidence supporting the novel dogma that fatty acid (FA)-induced hyperinsulinemia is a driving factor for diet-induced obesity rather than directly inducing obesity on its own.[5] Hyperinsulinemia has also been associated with obesity both in animal models and humans where excessive insulin is considered as a predictor of obesity.[6,7] The tetrad of insulinemia, insulin resistance, hyperglycemia and diabetes are closely related with each other in a way that most T2DM patients will show all these features. In the light of this interplay of the tetrad, we redefine the state of T2DM which biochemically is considered as blinding of body tissues to the level of both glucose and insulin circulating in the blood that leads to a constant influx of high energy substrates like free fatty acids (FFAs) and glucose into the circulation. Based on review of literature, we attempt to define a commonality between T1DM and T2DM in terms of body's shift to use lipids as fuel for energy when insulin sensitivity of the tissues or availability of insulin is low in the light of second-wave hypothesis of adipocytes.

INTERACTION BETWEEN FFAS AND INSULIN

FFAs are classified as short-chain (SCFAs; 1-6), medium-chain (MCFAs; 6-12) and long-chain (>12 carbon atoms; LCFAs) fatty acids with a significant role as energy substrates in the body.[8] One of the mechanism by which FFAs contribute to glycolysis, gluconeogenesis and lipogenesis is *via* regulation of insulin secretion from the pancreatic β-cells.[9] While short-term exposure of the β-cells to FFAs enhances insulin secretion, long-term exposure may cause significantly reduced insulin secretion due to lipotoxicity of the β-cells.[10] Rodent and human islets of Langerhans showed increased secretion of insulin when challenged with FFAs in a glucose-dependent manner.[11] More interestingly, the LCFAs, especially with higher saturation degree, were more effective than medium- and short-chain FFAs. At molecular level, they (especially the LCFAs) interact with G-protein coupled receptors-40 (GPCR-40) in the pancreas to regulate insulin secretion and negatively influence insulin-mediated glucose uptake by the body tissues.[9,12] Mechanistically, this is attributed to reduced glycogen synthesis and reduction in carbohydrate metabolism *via* early interruption of insulin signaling by FAs. It is speculated that increased lipid oxidation might be the underlying cause of diabetes and obesity associated insulin resistance. The postulated mechanism is that increased FFA oxidation cause elevation of the intra-mitochondrial acetyl-CoA/CoA and nicotinamide adenine dinucleotide (NADH/NAD) ratios with subsequent inactivation of pyruvate dehydrogenase.[13,14] This in turn causes the citrate concentration to raise that leads to inhibition phosphofructokinase and subsequent accumulation of glucose-6-phosphate (G-6-P) that inhibits hexokinase-II thus resulting in lower glucose uptake. However, subsequent studies have revealed decrease in the cellular G-6-P instead of elevated level needed to inhibit hexokinase-II.[15]

FFAs also have a direct effect on insulin-mediated glucose uptake and phosphorylation by amending the responsiveness of insulin receptors.[16] Saturated FFAs have been generally implied in the development of insulin resistance whereas unsaturated FAs have protective effect on the metabolism. This distinction is based on their respective inflammatory and anti-inflammatory properties to disrupt insulin signaling in the cells.[17] More recent studies have implied differential effects of FFAs on insulin signaling and glucose uptake relevant to their structure and saturation level.[18] Treatment of human skeletal myotubes with palmitate (saturated FA) and oleic acid (unsaturated FA) and their combination significantly impaired 3H-labeld 2-deoxy-D-glucose uptake. However, at molecular level, assessment of the myotubes showed impaired insulin-stimulated activation of Akt-serine473, AS-160 (Aktsubstrate of 160k Da protein), Glycogen synthase kinase 3 beta (GSk3B) phosphorylation and induction of stress-signaling phospho-Extracellular signal-regulated kinases (ERK) and c-Jun N-terminal kinases (JNK) (54k Da isoform) by palmitate treatment while these molecular changes were inhibited by combined treatment with oleic acid.[18] These data explain a differential role of FFAs by which they interfere with insulin signaling but really fail to translate this affect into insulin-independent glucose uptake by the cells thus pointing to the interference and influence of other concomitantly working signaling mechanisms.

Despite sufficient evidence in the published data that FFAs cause insulin resistance, some contriving reports in this regard from early investigators attribute their effect to the duration FFAs in the blood.[19] Assessment during acute phase (within 90 minutes) of FFAs infusion showed no effect in terms of insulin resistance while chronic exposure to FFAs increased insulin resistance irrespective of the rate of infusion.[20] A common feature of these studies is the time duration of only 2 hours of FFAs infusion to impart their effect which is insufficient for the FFAs to modulate the insulin receptor activity. This information is critical and explains that the rapid postprandial rise in the plasma level of triacylglycerides (TAG) does not cause insulin resistance; rather chronically high plasma level TAG in most T2DM patients would play a major role in insulin resistance in these patients.[21] In summary, the saturation status of FFAs and duration of exposure to FFAs are important determinants of tissue insulin resistance.

EFFECT OF GLUCOSE ON ADIPOSE TISSUE (SECOND-WAVE ADIPOCYTE HYPOTHESIS)

Insulin promotes euglycemia *via* tissue uptake of glucose while blood glucose homeostasis is swayed towards hyperglycemia due

to tissue insulin resistance.[22] Akin to any other body cell, adipocytes are sensitive to glucose changes in their microenvironment. With better understanding of their role in energy balance, they are being considered as critical integrators of glucose homeostasis.[23] Studies with 3T3-L1 adipocytes showed that the cells cultured in 5 mM glucose grew with normal phenotype and were responsive to insulin mediated glucose uptake and inhibition of lipolysis pathways as compared to the 3T3-L1 cells cultured in 25 mM glucose.[24] More importantly, high glucose culture conditions significantly influenced the insulin-induced 3T3-L1 adipose cell differentiation besides influencing differentiation-directed insulin signaling pathways in glucose concentration-dependent fashion. Long-term exposure to high glucose concentration during adipogenesis and short-term exposure of mature adipocytes to glucose promote TAG accumulation in the 3T3-L1 cells.[25] These molecular changes have been attributed to the impaired metabolic functions in the adipocytes upon exposure to high glucose concentration. A direct comparison of 3T3-L1 adipocytes cultured in 4 mM and 25 mM glucose also showed that the cells cultured in high glucose culture conditions developed insulin resistance. Similar observations were made in the adipocytes from rats with Streptozococin (STZ)-induced diabetes.[26]

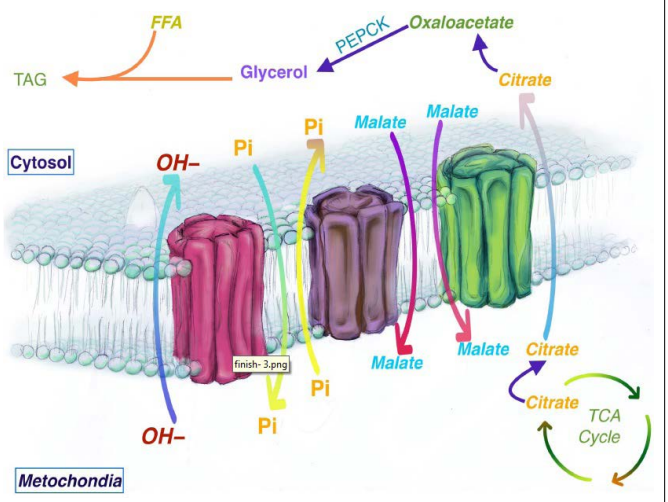
Molecular studies *in vitro* as well as *in vivo* using adipocytes isolated from STZ-treated hyperglycemic rats have also shown elevated levels of ROS with simultaneous low level secretion of pro-inflammatory interleukin-6.[26] ROS levels in the 3T3-L1 adipocytes can be reduced either by pharmacological treatment of the cells with the drugs which reduce mitochondrial membrane potential or by the over expression of uncoupling protein-1 (UCP-1) (27), which is essential role for optimal mitochondrial function.[27] Transduction of adipocytes with adenovirus encoding for UCP-1 showed that phosphorylated Akt levels were not affected by insulin despite significant reduction of review of systems (or symptoms) (ROS) in UCP1 expressing adipocyte. Moreover, insulin receptor substrate-1 (IRS-1) significantly increased in the insulin-induced phosphorylation of serine^{307} and serine^{636} under hyperglycemic conditions, both of which have been implicated in the reduced insulin-sensitive state.[28,29] Phosphorylation of tyrosine^{608} that is important for interaction between IRS-1, phosphatidylinositol 2-kinase and PTP2C was significantly increased under normoglycemic conditions. These data support the idea that adipose tissue adopts insulin-resistant phenotype when exposed to hyperglycemia. It is pertinent to mention that induction of adipogenic phenotype using high glucose concentration (25 mM) has little clinical relevance. This high glucose-induced adipose tissue in the biological system functions in a limited range of biological activity. For example, adipose tissue maintains a relatively steady flux of TAGs into the blood during fasting. On the other hand, the time for the adipose tissue to buffer the blood FFAs is prolonged after dietary ingestion of high caloric diet due to inherent insensitivity.[30] Such deleterious activity of the adipose tissue during hyperglycemia deteriorates glucose homeostasis even further.

^{14}C-integration analysis in genomic DNA has shown 50% adipose tissue renewal in the body in 9-years, with 10% fat cell renewal/year without any change in the total number of adipocytes at all adult ages.[31,32] These data has led to the hypothesis of a second-wave of adipocytes that show genetic changes as an adaptive response against glucotoxicity. The second-wave adipocytes which achieve adaptive genetic priming not only show insulin resistance but are also slow to restore their insulin sensitivity. If this hypothesis holds good, it explains the chronicity of T2DM and stress the significance of developing early screening program for patients that would alter the treatment outcome.[33]

ADIPOCYTE MITOCHONDRIAL RESPONSE TO ELEVATED SUBTRATE LEVELS

The mitochondria has significant role in lipolysis and lipogenesis such that obesity is associated with mitochondrial dysfunction.[34] The mitochondria in the adipocytes contain several proteins, i.e., decarboxylase carrier (DIC) and phosphoenolpyruvate carboxykinase (PEPCK) that facilitate the exchange of metabolites across its membrane. While DIC is involved in the transport of citrate, PEPCK-2 (the mitochondrial isozyme PEPCK-M encoded by PCK2 gene) catalyzes the GTP-stimulated conversion of oxaloacetate to phosphoenolpyruvate for glyceroneogenesis that allows the synthesis of glycerol backbone for FA re-esterification.[35] Transgenic overexpression of PEPCK increased glycerogenesis, re-esterification of FFAs, adipose mass and body weight in mice.[36] Contrarily, gene deletion of cytosolic PEPCK caused severe hypoglycemia by day 2 after birth in a mice model besides 2-3 fold higher liver triglyceride contents as compared to the normal control littermates.[37] At molecular level, it involves co-operative action of citrate, dicarboxylate and phosphate carriers. Whereas citrate-carrier mediates efflux of citrate from mitochondrial matrix into the cytoplasm in exchange for malate, DIC mediates the exchange of malate with phosphate, and phosphate-carrier then mediates the exchange of phosphate with hydroxyl ion, resulting in a net transport of citrate to the cytoplasm (Figure 1). DIC as a mitochondrial membrane protein has a pivotal role in FA metabolism and its expression is regulated by the substrates and by insulin;

Figure 1. *Transport of Citrate Across the Mitochondrial Membrane into the Cytosol*



The mitochondrial transporters cooperate for citrate flux into the cytosol where it is converted into oxaloacetate before phosphoenolpyruvate carboxykinase (PEPCK) enzyme converts it into enolpyruvate for further use in glyceroneogenesis. Glycerol thus synthesized is esterified with free fatty acids for the formation of triacylglycerides(TAG).

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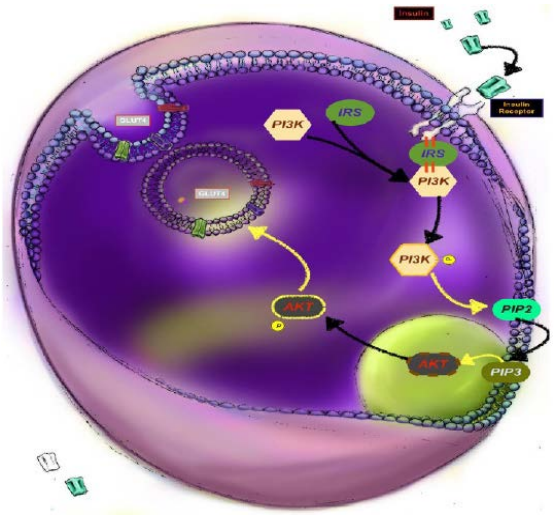
abundance of FFAs and glucose upregulates while insulin down regulates DIC protein in the mitochondria.[38] Higher DIC expression is associated with mitochondrial membrane hyperpolarization that leads to increased ROS which causes tissue irresponsiveness to insulin.[39]

MOLECULAR PATHWAY OF INSULIN RESISTANCE IN ADIPOCYTES (FATTY ACID ESCAPE HYPOTHESIS PART-I)

Loss of glucose and lipid homeostasis is linked to many bioactive molecules released from the visceral adipocytes, i.e., tumor-necrosis factor-α (TNF-α), resistin, leptin, and adiponectin besides.[40] Lipid-overloaded hypertrophied adipocytes are resistant to insulin without the involvement of adipocytes inflammatory status as a contributory factor.[41] From amongst the FFAs, monounsaturated FFAs cause hypertrophy whereas saturated FFAs cause pro-inflammatory response in the adipocytes. The hypertrophied adipocytes, characterized by the presence of uni-locular lipid droplets, show impaired insulin-dependent glucose uptake which was accompanied by defective Glucose transporter type 4 (GLUT4) trafficking.

A dysregulated FFA metabolism is one of the primary causes of insulin resistance due to preferential oxidation of FFAs over glucose in T2DM thus supporting FFAs as a novel target to treat insulin resistance in T2DM.[18,42] Signals from apparently unrelated pathways can inhibit insulin signaling by heterologous desensitization. Studies have focused on Ser/Thr phosphorylation of internal revenue service (IRS) proteins as a key feedback control mechanism to abrogate signal transduction in response to insulin.[43,44] TNFα, FFAs and cellular stress play a significant role in activation of Ser/Thr kinases to phosphorylate the IRS proteins and inhibit their function *via* their uncoupling from their upstream and downstream effectors in response to insulin to promote insulin resistance.[45,46]

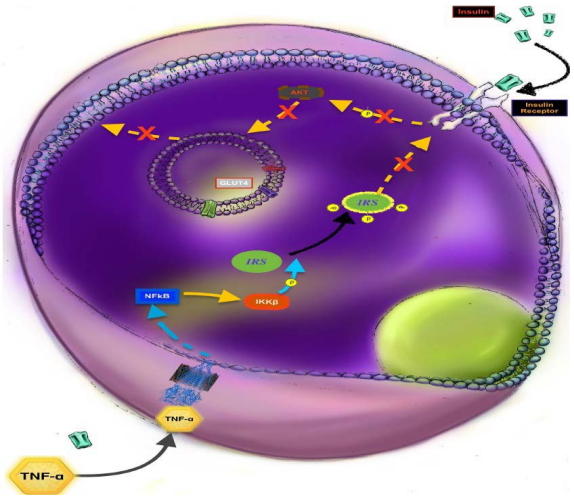
Figure 2A. *Insulin Signaling Pathway and the "Insulin Sensitive State"*



Insulin binding with its receptor (IR) activates the insulin receptor substrate-1 (IRS-1) which is the major substrate of the insulin receptor. Downstream to the activation of IRS-1, activity of phosphoinositol triphosphate kinase (PI3K) which is an integral part this signaling complex, generates phosphoinositol 3,4-biphosphate and phosphoinositol 1,3,4-triphosphate that lead to the activation of Protein Kinase B (Akt2). The activation of Akt thus causes membrane trafficking of GLUT4 transporter to permit glucose uptake from the circulation.

Insulin binding to its receptor (IR) autophosphorylates its tyrosine residues followed by downstream activation of Akt, Protein Kinase Cζ (PKCζ), mammalian target of rapamycin (mTOR) and IKKβ (I-kappa B kinase β). The excessive presence of FFAs and TNFα effects insulin signaling in the tissues by activation of the downstream signals i.e., PKC, IKKβ, through different pathways that allow them to phosphorylate and inhibit IRS even before insulin binds to its receptor. As the level of inhibitors rise as part of the disease process, IRS fails to activate Akt thus abrogating translocation of GLUT-4 transporter from the cytoplasm to the cell membrane thus leading to much reduced glucose uptake (Figures 2A, 2B).[47]

Figure 2B. *The State of Insulin Resistance "TNF-α Signaling Pathway"*



The binding of (TNF-α) with its receptor leads to activation of NFkβ-IKKβ pathway that causes failure of insulin receptor and insulin receptor substrate-1 (IRS-1) activation in response to insulin binding with its receptor on the cell surface. These molecular events impairs the activation of Protein Kinase B (Akt) thus resulting in failure of membrane trafficking of Glut-4 transporter and development of resistance to glucose uptake in response to insulin binding with its receptor.

THE FATTY ACID ESCAPES HYPOTHESIS PART-2: ADIPOCYTES RESPONSE TO ENERGY FLOOD

Excessive energy intake provokes the adipose tissue to undergo dynamic remodeling characterized by adipocyte hypertrophy and hyperplasia. Whereas these two modes of remodeling diverge in many aspects including adipocyte size and number, recruitment of inflammatory cells, release of adiponectin and pro-inflammatory cytokines, hypoxia and fibrosis (all increasing in case of hypertrophy), they have a common feature in terms of FFAs release.[48] Both of these modes of remodeling are part of adipocytes' contribution to energy homeostasis.

Adipocytes are active secretors of bioactive molecules which, besides protecting themselves, also contribute towards metabolism, immunity, inflammation, matrix remodeling, vasculogenesis and many more physiological functions.[49] IKKβ-deficient mice are at a higher risk of increased adipocyte death; higher macrophage infiltration and defective adaptive adipose remodeling that also lead to increased lipolysis, higher release of FFAs and impaired insulin signaling.[50] Molecular studies have shown a key role for IKKβ in adipocyte survival. Histological studies in high

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fat diet-fed obese mice show an increase in hypoxia induced factor-1 alpha (Hif-1α) due to large adipocyte volume and the higher oxygen demand that might not be compensated by neo-angiogenesis and hence remains instrumental in adipocyte apoptosis while knockdown of Hif-1α decreased adiposity with concomitant improvement in insulin sensitivity.[51,52] These molecular changes are accompanied by gross infiltration by immune cells including M1 and M2 macrophages which participate in the remodeling process as the key players.[53] These cells release a plethora of pro- and anti-inflammatory adipokines, i.e., leptin, resistin, adiponectin, vistatin as well as cytokines and chemokines, i.e., IL6, TNF-α and monocyte chemo attractant protein-1 (MCP-1) which act in autocrine, paracrine and systemic manner to produce their effects.[54,55]

As the pro-inflammatory and anti-inflammatory molecules outbalance each other and the degree of inflammation in the adipose tissue increases beyond the level of healthy expansion, a spill-over of inflammatory cytokines into the blood causes a low grade chronic inflammatory state. These molecular changes cause loss of sensitivity to insulin with a simultaneous increase in lipolysis, which initiates FFAs escape to the circulation thus augmenting a vicious cycle that climaxes into global tissue insulin resistance. FFAs and chronic inflammation together form an ominous combination to induce insulin resistance in other tissues *via* ectopic fat deposition with the former and receptor signaling into cells by the latter.

ECTOPIC FAT DEPOSITION "VISCRAL FAT"

Visceral fat (VF) and subcutaneous fat (SCF) have distinct cellular and molecular characteristics and diverge in terms of anatomical distribution.[56] Besides other differences, VF and its resident macrophage population release more inflammatory cytokines i.e., TNF-α and IL-6, show higher lipoprotein lipase activity and higher release of FFAs as compared to SCF.[57,58] Epidemiological studies have substantiated these observations and report that in comparison with SCF, VF correlates more with insulin resistance.[59] However, SCF cell volume change is more strongly correlated with insulin sensitivity rather than fat cell number which remain nearly constant.[60]

In view of the FFA escape hypothesis discussed earlier, SCF will be the prime site for fat disposition albeit with marked variability among individuals due to wide variety of factors not discussed here. This may result in the development of "obesity-healthy phenotype (OH-phenotype)" in healthy-obese subjects whereas in lean subjects with "insulin resistance phenotype (IR-phenotype)". In other words, when SCF storage capacity doesn't match with the positive energy balance then FFAs will be re-routed to deposit as VF thus leading to high circulatory FFAs. This also makes VF to positively correlate with metabolic syndrome. A direct comparison of adipocytes from different fat tissues shows that the percentage of small size adipocytes is higher in SCF and omental fat (OMF) in normoglycemic subjects as compared to the hyperglycemic patients.[61] A similar but statistically insignificant trend has also been observed in the mesenteric fat derived adipocytes. VF adipocytes show higher catecholamine-induced lipolysis and reduced sensitivity to insulin-mediated lipogenesis thus maintaining a higher level of circulating FFA in the blood that would augment tissue insulin resistance.[62] VF tissue shows enhanced responsiveness to the lipolytic effect of circulating catecholamine that makes VF sensitive to exercise.[63]

VF adipocytes also show a distinct genetic profile as compared to SCF and epigastric adipose tissue that may be an important contributory factor towards their insulin resistance and therefore, can be classified as "IR-phenotype".[64] The steady-state messenger ribonucleic acid (mRNA) levels for lipoprotein lipase (LPL) as well as LPL mass are lower in omental fat (OMF) than subcutaneous fat (SCF); however, the specific LPL activity is greater in OMF as compared with to SCF tissue.[65] Insulin increases the levels of LPL mRNA and LPL activity in abdominal SCF but not in the OMF, whereas glucocorticoids increase the LPL mRNA and LPL activity more in OMF, particularly in men.[66] Moreover, insulin and glucocorticoids synergistically affect the activity of LPL in both OMF and SCF; however SCF is more sensitive to glucocorticoids in the presence of insulin. The LPL activity normally is higher in OMF than SCF. Insulin not only effects LPL mRNA expression, it also regulates the LPL activity *via* posttranslational mechanism which is more significant in the SCF tissue as compared to OMF tissue and the latter is inherently insensitive to insulin.[67] It is important to mention that LPL activity needs to be coupled with acylation stimulating protein (ASP) enzymes which will upregulate the process of reesterification and TAG formation.[68] As this mechanism is more significant in SCF tissue in comparison with OMF tissue, it renders the former more effective in TAG clearance *via* rapid incorporation of the formed FFA into intracellular TAG. On the contrary, OMF tissue releases more FFA in the circulation because the hydrolysis is not accompanied with TAG formation.[68] When insulin resistance is developed in SCF tissue, it practically adopts OMF tissue phenotype thus losing its ability to clear the endogenous or exogenous TAG. The OMF tissue expansion thus becomes more prominent during this stage as it also competes with SCF in the storage. This derangement culminates into OMF tissue expansion with higher portal FFA level that is going to affect the liver insulin sensitivity as discussed in the next section.

ECTOPIC FAT DEPOSITION "LIVER"

Insulin from the pancreas and the VF derived FFAs pass through the liver and get partially cleared before their drainage into the systemic circulation. Hence, the level of insulin in the portal circulation is much higher as compared to systemic circulation. Similarly, liver has a significant role in the trafficking of FFAs. FFAs with greater whole body flux as compared to the lean tissue in obese than non-obese individuals undergo conversion to TAG in the liver, packaged into VLDL and poured back into systemic circulation to cause hypertriglyceridemia.[69] A chronically increased flux of systemic as well as visceral FFAs overloads the liver to cause hepatic changes thus leading to decline in hepatic insulin clearance which will occur when hepatic insulin resistance develops.[70] Hepatic glucose uptake is independent of insulin stimulation; however, insulin action in the liver is important to direct excess glucose to glycogenesis. When insulin action on the hepatocytes is abrogated, the metabolic pathway will revert to gluconeogenesis with efflux of glucose to the systemic circulation to cause hyperglycemia.[70]

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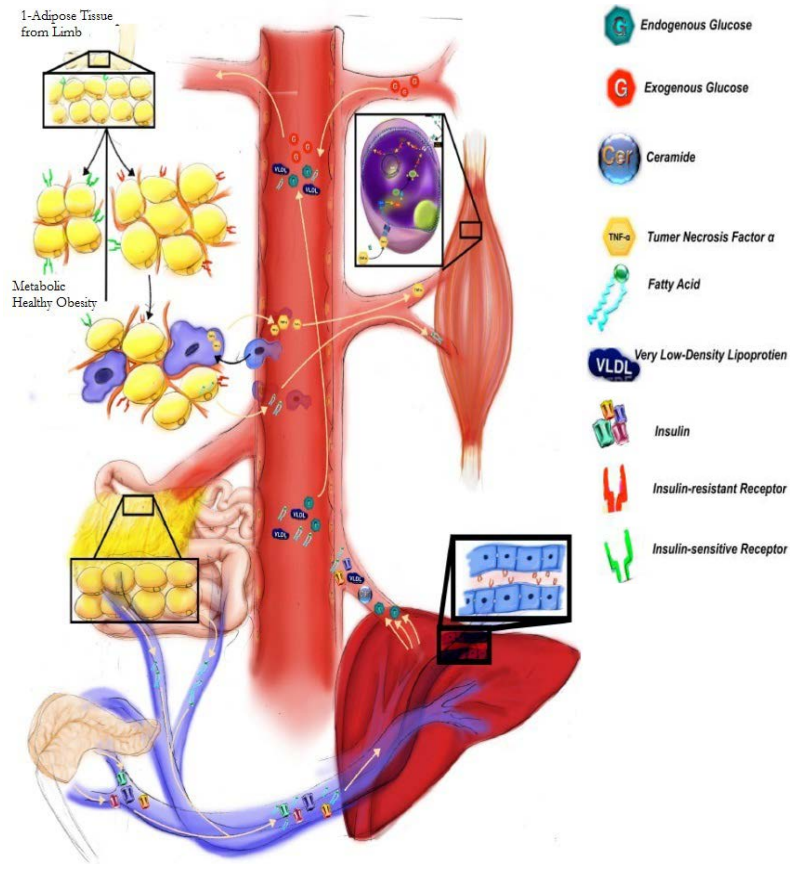
ECTOPIC FAT DEPOSION IN SKELETAL MUSCLES

TAGs in the muscle tissue form intramuscular triglyceride (imTG) pool and constitute dynamic lipid storage in the cytoplasm of the skeletal muscle cells.[71] The imTG pool generally gets expanded in the event of excess lipid availability and provides a source of energy substrate when required.[72] It is assumed that the imTG pool is replenished by FFAs from the plasma which is transported into intramuscular cytosol prior to undergoing mitochondrial oxidation. In an interesting study, infusion of 14C-labeled oleic acid led to $^{14}CO_2$ release within 30-minutes of treatment even though the steady state of FA uptake was achieved within 5-10 minutes.[73] The release of $^{14}CO_2$ continued for 7 days of observation which showed that the FA after infusion became part of the imTG pool before undergoing oxidation in the mitochondria. A similar study with improved methodology using Pulse-chase, dual-isotope, muscle biopsy approach has shown that imTG stores are used primarily, if not solely, as local oxidative fuel.[74] FFAs from plasma get incorporated into imTG during exercise thus accounting for a stable imTG pool size after the exercise session and concomitantly contribute to obviate FFA-induced insulin resistance.[75] Put together, these studies imply that fat disposition in skeletal muscles involves multi-stepα enzyme-controlled processes for TAG formation which are then hydrolyzed to FAs ordained for oxidation.

Athletes have a large imTG pool, however with preserved insulin sensitivity which is also known as athlete's paradox.[76] In other words, the imTG pool in the skeletal muscles of athletes is primed to provide substrate for energy production and is not primarily meant for TAG storage. On the contrary, obese individuals also have increased imTG pool which is destined for storage of the high circulating FFAs besides its association with insulin resistance.[77] This leads to accumulation of FA metabolites, i.e., diacylglycerol (DAG) as well as increased intracellular synthesis of ceramide that mediates insulin resistance. Treatment of cultured mice myocytes with insulin and/or palmitate has shown that insulin is a potent stimulator of ceramide production while combination of palmitate and insulin show a synergistic effect in ceramide synthesis.[78] It is however pertinent to mention that this is not the only insult that increases skeletal muscle insulin resistance; it combines with low grade chronic inflammatory state and the hepatic production and secretion of ceramide to interact through intracellular mechanisms culminating in the IRS inactivity and the reduction of glucose transporter translocation and decrease skeletal muscle uptake of glucose. As skeletal muscle in the body is primarily responsible for blood glucose uptake, their resistance to insulin besides the unsuppressed hepatic glucose production lead to hyperglycemia.

Figure 3. *FFA Escapes Hypothesis*



Starting from label[1] when peripheral adipose tissue undergoes healthy expansion, it may culminate into Metabolic healthy obese "MHO". However, in case that adipose tissue expansion is ineffective will be accompanied by an inflammatory response, macrophage invasion occurs. Then free fatty acids (FFAs) and TNF-α spilling over into the systemic circulation. The omental fat (OMF) expansion causes pouring of FFA into the portal circulation. Hepatic clearance of insulin gets reduced and higher level of very low density lipoprotein (VLDL) and other metabolites are produced and secreted into systemic circulation. Skeletal muscles become resistant (see picture above) and systemic insulin resistance sets in as well. Triggered by the "positive energy balance", disturbed homeostasis mentioned above gives rise to the metabolic profile observed in "Diabesity".

CONCLUSION

Increased FFA flux from adipose tissue and tissue insulin resistance together constitute major predictors of ectopic fat accumulation. While increased imTG accumulation is associated with skeletal muscle insulin resistance, cardiac steatosis is associated with left ventricular dysfunction and premature death. Similarly, deposition of fat in and around the pancreas is associated with impaired β-cell function. This aberrant fat partitioning may be explained by the FFAs escape model and the second-wave hypothesis of differentiated adipocyte population. The role of cytosolic fatty acid binding proteins which are abundantly expressed in tissue specific manner and, carnitine and their acyl esters (acylcarnitine)should be considered for their role in intracellular transport of FAs during FA catabolism. Most patients who develop "diabesity" (obesity related diabetes) would follow the sequence of derangement as depicted in Figure 3. Patients with T2DM who characteristically present with insulin resistance and "the positive energy balance" have the matching adipose tissue-relevant metabolic profile, i.e., high lipolysis and low lipogenesis, with the one observed in hormonally mediated diabetes i.e., Cushing's syndrome.Similarly, while T1DM primarily results from β-cell failure, T1DM patients also show low lipogenesis and higher lipolysis due to activation hormone sensitive lipase in the adipose tissue in the absence of insulin. Put together, low lipogenesis with concomitant higher lipolysis remain the cardinal features to diabetes irrespective of its type and underlying etiology.

Contriving the long-standing dogma that hyperglycemia is the main player in the pathogenesis of T2DM; our hypothesis implies that hyperglycemia is a mere consequence of body's shift to lipid metabolism as the primary energy source. Hence, there is a need to redefine it as a disease variant characterized by hyperglycemia which in fact is a very late manifestation of the chronically disturbed body metabolism. Furthermore, this urges the use of markers other than blood glucose, either alone or in combination, i.e., serum FFAs, ceramide, and insulin levels due to their early appearance during the disease onset. Using blood sugar level as a marker is akin to leaving the diagnosis as well as treatment until too late. Similarly, our model proposes that that T2DM can be reversed until the adipose tissue remains responsive to insulin.

In conclusion, we are aiming to establish a unifying hypothesis that would contribute in defining and future development of a holistic treatment approach that could reverse the whole body metabolic abnormalities rather than managing the blood parameters alone without addressing the root cause of the problem. Our hypothesis may explain the underlying cause of the emerging concept of 'double diabetes' as well.

COMPLIANCE WITH ETHICAL STANDARDS

This article does not contain any studies with human participants or animals performed by any of the authors.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

REFERENCES

1. World Health Organization (WHO). Diabetes. Global report on diabetes. Web site. http://www.who.int/diabetes/global-report/

2. World Health Organization (WHO). Obesity and overweight. Web site. http://www.who.int/mediacentre/factsheets/fs311/en/

3. Das AK, Shah S. History of diabetes: from ants to analogs. *J Assoc Phys India.* 2011; 59 Suppl: 6-7.

4. Templeman NM, Skovso S, Page MM, Lim GE, Johnson JD. A causal role for hyperinsulinemia in obesity. *J Endocrinol.* 2017; 232(3): R173-R183. doi: 10.1530/JOE-16-0449

5. Mehran AE, Templeman NM, Brigidi GS, et al. Hyperinsulinemia drives diet-induced obesity independently of brain insulin production. *Cell Metab.* 2012; 16(6): 723-733. doi: 10.1016/j.cmet.2012.10.019

6. D'souza AM, Johnson JD, Clee SM, Kieffer TJ. Suppressing hyper-insulinemia prevents obesity but causes rapid onset of diabetes in leptin-deficient $Lep^{ob/ob}$ mice. *Mol Metab.* 2016; 5: 1103-1112. doi: 10.1016/j.molmet.2016.09.007

7. Odeleye OE, de Courten M, Pettitt DJ, Ravussin E. Fasting hyperinsulinemia is a predictor of increased body weight gain and obesity in Pima Indian children. *Diabetes.* 1997; 46(8): 1341-1345. doi: 10.2337/diabetes.46.8.1341

8. Schonfeld P, Wojtczak L. Short- and medium-chain fatty acids in the energy metabolism – the cellular perspective. *J Lipid Res.* 2016; 57: 943-954. doi: 10.1194/jlr.R067629

9. Yasuaki I, Yuji K, Masataka H, et al. Free fatty acids regulate insulin secretion from pancreatic beta cells through GPR40. *Nature.* 2003; 422(69280): 173-176. doi: 10.1038/nature01478

10. McGarry JD, Dobbins RL. Fatty acid, lipotoxicity and insulin secretion. *Diabetologia.* 1999; 42: 128-138. doi: 10.1007/s001250051130

11. Gravena C, Mathias PC, Ashcroft SJH. Acute effects of fatty acids on insulin secretion from rat and human islets of Langerhans. *J Endocrinol.* 2002; 173: 73-80.

12. Boden G, Chen X, Ruiz J, White JV, Rossetti L. Mechanisms of fatty acid-induced inhibition of glucose uptake. *J Clin Invest.* 1994; 93(6): 2438-2446. doi: 10.1172/JCI117252

13. Randle PJ, Garland PB, Hales CN, Newsholme EA. The glucose fatty-acid cycle: Its role in insulin sensitivity and the metabolic

disturbances of diabetes mellitus. *Lancet*. 1963; 1: 785-789. doi: 10.1016/S0140-6736(63)91500-9

14. Randle PJ, Garland PB, Newsholme EA, Hales CN. The glucose fatty acid cycle in obesity and maturity onset diabetes mellitus. *Ann NY Acad Sci*. 1965; 131: 324-333. doi: 10.1111/j.1749-6632.1965.tb34800.x

15. Roden M. How free fatty acids inhibit glucose utilization in human skeletal muscle. *News Physiol Sci*. 2004; 19: 92-96. doi: 10.1152/nips.01459.2003

16. Roden M, Price TB, Perseghin G, et al. Mechanism of free fatty acid–induced insulin resistance in humans. *J Clin Invest*. 1996; 97(12): 2859-2865. doi: 10.1172/JCI118742

17. Sears B, Perry M. The role of fatty acids in insulin resistance. *Lipids Health Dis*. 2015; 14: 121. doi: 10.1186/s12944-015-0123-1

18. Mäkinen S, Nguyen YH, Skrobuk P, Koistinen HA. Palmitate and oleate exert differential effects on insulin signaling and glucose uptake in human skeletal muscle cells. *Endocrine Connections*. 2017; 6: 331-339. doi: 10.1530/EC-17-0039

19. Wolfe BM, Klein S, Peters EJ, Schmidt BF, Wolfe RR. Effect of elevated free fatty acids on glucose oxidation in normal humans. Metabolism.1988; 37(4): 323-329. doi: 10.1016/0026-0495(88)90131-X

20. Kelley DE, Mokan M, Simoneau JA, Mandarino LJ. Interactionbetween glucose and free fatty acid metabolism in human skeletal muscle. *J Clin Invest*. 1993; 92: 91-98. doi: 10.1172/JCI116603

21. Lv ZH, Ma P, Luo W, et al. Association between serum free fatty acid levels and possible related factors in patients with type 2 diabetes mellitus and acute myocardial infarction. *BMC Cardiovasc Disord*. 2014; 14: 159. doi: 10.1186/1471-2261-14-159

22. Cefalu WT. Insulin resistance: Cellular and clinical concepts. *Exp Biol Med (Maywood)*. 2001; 226: 13-26. doi: 10.1177/153537020122600103

23. Rosen ED, Spiegelman BM. Adipocytes as regulators of energy balance and glucose homeostasis. *Nature*. 2006; 444(7121): 847-853. doi: 10.1038/nature05483

24. Gagnon A, Sorisky A. The effect of glucose concentration on insulin-induced 3T3-L1 adipose cell differentiation.*Obes Res*. 1998; 6(2): 157-163. doi: 10.1002/j.1550-8528.1998.tb00330.x

25. Palacios-Ortega S, Varela-Guruceaga M, Martínez JA, de Miguel C, Milagro FI. Effects of high glucose on caveolin-1 and insulin signaling in 3T3-L1 adipocytes. *Adipocytes*. 2016; 5(1): 65-80. doi: 10.1080/21623945.2015.1122856

26. Lin Y, Berg AH, Iyengar P, et al. The hyperglycemia-induced inflammatory response in adipocytes: The role of reactive oxygen species. *J Biol Chem*. 2005; 280: 4617-4626. doi: 10.1074/jbc.M411863200

27. Riley CL, Bout D, Bean C, et al. UCP1 is essential for mitochondrial structural integrity and function in brown adipose tissue. *FASEB J*. 2017; 31(1).

28. Rocchi S, Tartare-Deckert S, Mothe I, van Obberghen E. Identification by mutation of the tyrosine residues in the insulin receptor substrate-1 affecting association with the tyrosine phosphatase 2C and phosphatidylinositol 3-kinase. *Endocrinol*. 1995; 136: 5291-5297. doi: 10.1210/endo.136.12.7588273

29. Bouzakri K, Roques M, Gual P, et al. Reduced activation of phosphatidylinositol-3 kinase and increased serine 636 phosphorylation of insulin receptor substrate-1 in primary culture of skeletal muscle cells from patients with type 2 diabetes. *Diabetes*. 2003; 52: 1319-1325. doi: 10.2337/diabetes.52.6.1319

30. Reaven GM, Hollenbeck C, Jeng CY, Wu MS, Chen YD. Measurement of plasma glucose, free fatty acid, lactate, and insulin for 24 h in patients with NIDDM. *Diabetes*. 1988; 37(8): 1020-1024. doi: 10.2337/diabetes.37.8.1020

31. Spalding KL, Bhardwaj RD, Buchholz BA, Druid H, Frisen J. Retrospective birth dating of cells in humans. *Cell*. 2005; 122: 133-143. doi: 10.1016/j.cell.2005.04.028

32. Spalding KL, Arner E, Westermark PO, et al. Dynamics of fat cell turnover in humans. *Nature*. 2008; 453: 783-787. doi: 10.1038/nature06902

33. Olokoba AB, Obateru OA, Olokoba LB. Type 2 Diabetes mellitus: A review of current trends. *Oman Med J*. 2012; 27(4): 269-273. doi: 10.5001/omj.2012.68

34. Yin X, Lanza IR, Swain JM, Sarr MG, Nair SK, Jensen MD. Adipocyte mitochondrial function is reduced in human obesity independent of fat cell size. *J Clin Endocrin Metab*. 2014; 99: E209-E216. doi: 10.1210/jc.2013-3042

35. Hanson RW, Reshef L. Regulation of phosphoenolpyruvate carboxykinase (GTP) gene expression. *Ann Rev Biochem*. 1997; 66: 581-611. doi: 10.1146/annurev.biochem.66.1.581

36. Franckhauser S, Muñoz S, Pujol A, et al. Increased fatty acid re-esterification by PEPCK overexpression in adipose tissue leads to obesity without insulin resistance. *Diabetes*. 2002; 51(3): 624-630. doi: 10.2337/diabetes.51.3.624

37. Hakimi P, Johnson MT, Yang J, et al. Phosphoenolpyruvate carboxykinase and the critical role of cataplerosis in the control of hepatic metabolism. *Nutr Metab (Lond)*. 2005; 2: 33. doi: 10.1186/1743-7075-2-33

38. Brun T, Scarcia P, Li N, et al. Changes in mitochondrial carriers exhibit stress-specific signatures in INS-1Eβ-Cells exposed

to glucose versus fatty acids. *PLoS One*. 2013; 8(12): e82364. doi: 10.1371/journal.pone.0082364

39. Das K, Lewis RY, Combatsiaris TP, et al. Predominant expression of the mitochondrial dicarboxylate carrier in white adipose tissue. *Biochem J*. 1999; 344(2): 313-320.

40. Arner P. The adipocyte in insulin resistance: Key molecules and the impact of the thiazolidinediones. *Trends Endocrinol Metab*. 2003; 14(3): 137-145. doi: 10.1016/S1043-2760(03)00024-9

41. Kim JI, Huh JY, Sohna JH, et al. Lipid-overloaded enlarged adipocytes provoke insulin resistance independent of inflammation. *Mol Cell Biol*. 2015; 35(10): 1686-1699. doi: 10.1128/MCB.01321-14

42. Delarue J, Magnan C. Free fatty acids and insulin resistance. *Curr Opin Clin Nutr Metab Care*. 2007; 10(2): 142-148. doi: 10.1097/MCO.0b013e328042ba90

43. Paz K, Hemi R, LeRoith R, et al. Phosphorylation of insulin receptor substrate-1 (IRS-1) by protein kinase b positively regulates irs-1 function. *J Biol Chem*. 1997; 272: 29911-29918.

44. Liu YF, Paz K, Herschkovitz A, et al. Protein kinase c θ inhibits insulin signaling by phosphorylating irs1 at Ser1101. *J Biol Chem*. 2001; 276: 14459-14465. doi: 10.1074/jbc.C400186200

45. Ohmura E, Hosaka D, Yazawa M, et al. Association of free fatty acids (FFA) and tumor necrosis factor-alpha (TNF-alpha) and insulin-resistant metabolic disorder. *Horm Metab Res*. 2007; 39(3): 212-217. doi: 10.1055/s-2007-970421

46. Mlinar B, Marc J, Pfeifer M. Molecular mechanisms of insulin resistance, obesity and metabolic syndrome. *Bio chemia Medica*. 2006; 16(1): 8-24. doi: 10.11613/BM.2006.003

47. Le Roith D, Zick Y. Recent advances in our understanding of insulin action and insulin resistance. *Diabetes Care*. 2001; 24(3): 588-597. doi: 10.2337/diacare.24.3.588

48. Choe SS, Huh JY, Hwang IJ, Kim JI, Kim JB. Adipose tissue remodeling: its role in energy metabolism and metabolic disorders. *Front Endocrinol (Lausanne)*. 2016; 7: 30. doi: 10.3389/fendo.2016.00030

49. Rutkowski JM, Stern JH, Scherer PE. The cell biology of fat expansion. *J Cell Biol*. 2015; 208(5): 501-512. doi: 10.1083/jcb.201409063

50. Park S-H, Liu Z, Sui Y, et al. IKKb is essential for adipocyte survival and adaptive adipose remodeling in obesity. *Diabetes*. 2016; 65: 1616-1629. doi: 10.2337/db15-1156

51. Ye J. Emerging role of adipose tissue hypoxia in obesity and insulinresistance. *Int J Obes (Lond)*. 2009; 33(1): 54-66. doi: 10.1038/ijo.2008.229

52. Jiang C, Qu A, Matsubara T, et al. Disruption of hypoxia-inducible factor 1 in Adipocytes improves insulin sensitivity and decreases adiposity in high-fat diet–fed mice. *Diabetes*. 2011; 60(10): 2484-2495. doi: 10.2337/db11-0174

53. Martinez-Santibañez G, Lumeng CN-K. Macrophages and the regulation of adipose tissue remodeling. *Annu Rev Nutr*. 2014; 34(1): 57-76. doi: 10.1146/annurev-nutr-071812-161113

54. Guzik TJ, Skiba DS, Touyz RM, Harrison DG. The role of infiltrating immune cells in dysfunctional adipose tissue. *Cardiovasc Res*. 2017; 113(9): 1009-1023. doi: 10.1093/cvr/cvx108

55. Kang YE, Kim JM, Joung KH, et al. The roles of adipokines, pro-inflammatory cytokines, and adipose tissue macrophages in obesity-associated insulin resistance in modest obesity and early metabolic dysfunction. *PLoS One*. 2016; 11(4): e0154003. doi: 10.1371/journal.pone.0154003

56. Ibrahim MM. Subcutaneous and visceral adipose tissue: structural and functional differences. *Obes Rev*. 2010; 11(1): 11-18. doi: 10.1111/j.1467-789X.2009.00623.x

57. Hamdy O, Porramatikul S, Al-Ozairi E. Metabolic obesity: The paradox between visceral and subcutaneous fat. *Curr Diabetes Rev*. 2006; 2(4): 367-373. doi: 10.2174/1573399810602040367

58. Lafontan M. Differences between subcutaneous and visceral adipose tissues. [In:] Bastard JP, Fève B (eds). *Physiology and Physiopathology of Adipose Tissue*. New York City, USA: Springer. 2013. 329-349.

59. Andersson DP. Changes in subcutaneous fat cell volume and insulin sensitivity after weight loss. *Diabetes Care*. 2014; 37(7): 1831-1836. doi: 10.2337/dc13-2395

60. Preis SR, Massaro JM, Robins SJ, et al. Abdominal subcutaneous and visceral adipose tissue and insulin resistance in the Framingham heart study. *Obesity (Silver Spring)*. 2010; 18(11): 2191-2198. doi: 10.1038/oby.2010.59

61. Fang L, Guo F, Zhou L, Stahl R, Grams J. The cell size and distribution of adipocytes from subcutaneous and visceral fat is associated with type 2 diabetes mellitus in humans. *Adipocyte*. 2015; 4(4): 273-279. doi: 10.1080/21623945.2015.1034920

62. Jocken JW, Blaak EE. Catecholamine-induced lipolysis in adipose tissue and skeletal muscle in obesity. *Physiol Behav*. 2008; 94(2): 219-230. doi: 10.1016/j.physbeh.2008.01.002

63. Thompson D, Karpe F, Lafontan M, Frayn K. Physical activity and exercise in the regulation of human adipose tissue physiology. *Physiol Rev*. 2012; 92(1): 157-191. doi: 10.1152/physrev.00012.2011

64. Gerhard GS, Styer AM, Strodel WE, et al. Gene expression profiling in subcutaneous, visceral, and epigastric adipose tissues of patients with extreme obesity. *Int J Obes (Lond)*. 2014; 38(3): 371-378. doi: 10.1038/ijo.2013.152

65. Ruge T, Sukonina V, Myrnas T, et al. Lipoprotein lipase activity/mass ratio is higher in omental than in subcutaneous adipose tissue. *Eur J Clin Invest*. 2006; 36: 16-21. doi: 10.1111/j.1365-2362.2006.01584.x

66. Fried SK, Russell CD, Grauso NL, Brolin RE. Lipoprotein lipase regulation by insulin and glucocorticoid in subcutaneous and omental adipose tissues of obese women and men. *J Clin Invest*. 1993; 92: 2191-2198. doi: 10.1172/JCI116821

67. Semenkovich CF, Wims M, Noe L, Etienne J, Chan L. Insulin regulation of lipoprotein lipase activity in 3T3-L1 adipocytes is mediated at posttranscriptional and posttranslational levels. *J Biol Chem*. 1989; 264: 9030-9038.

68. Faraj M, Sniderman AD, Cianflone K. ASP enhances in situ lipoprotein lipase activity by increasing fatty acid trapping in adipocytes. *J Lipid Res*. 2004; 45: 657-666. doi: 10.1194/jlr.M300299-JLR200

69. Mashek DG. Hepatic fatty acid trafficking: Multiple forks in the road. *Adv Nutr*. 2013; 4: 697-710. doi: 10.3945/an.113.004648

70. Kotronen A, Juurinen L, Tiikkainen M, Vehkavaara S, Yki-Järvinen H. Increased liver fat, impaired insulin clearance, and hepatic and adipose tissue insulin resistance in type 2 diabetes. *Gastroenterology*. 2008; 135(1): 122-130. doi: 10.1053/j.gastro.2008.03.021

71. Badin P-M, Langin D, Moro C. Dynamics of skeletal muscle lipid pools. *Trends Endocrinol Metab*. 2013; 24(12): 589-644. doi: 10.1016/j.tem.2013.08.001

72. Shaw CS, Clark J, Wagenmakers AJ. The effect of exercise and nutrition on intramuscular fat metabolism and insulin sensitivity. *Ann Rev Nut*. 2010; 30(1): 13-34. doi: 10.1146/annurev.nutr.012809.104817

73. Dagenais GR, Tancredi RG, Zierler KL. Free fatty acid oxidation by forearm muscle at rest, and evidence for an intramuscular lipid pool in the human forearm. *J Clin Invest*. 1976; 58: 421-431. doi: 10.1172/JCI108486

74. Guo Z, Burguera B, Jensen MD. Kinetics of intramuscular triglyceride fatty acids in exercising humans. *J Appl Physiol (1985)*. 2000; 89: 2057-2064. doi: 10.1152/jappl.2000.89.5.2057

75. Schenk S, Horowitz JF. Acute exercise increases triglyceride synthesis in skeletal muscle and prevents fatty acid-induced insulin resistance. *J Clin Invest*. 2007; 117(6): 1690-1698. doi: 10.1172/JCI30566

76. Goodpaster BH, He J, Watkins S, Kelley DE. Skeletal muscle lipid content and insulin resistance: Evidence for a paradox in endurance-trained athletes. *J Clin Endocrinol Metab*. 2001; 86(12): 5755-5761. doi: 10.1210/jcem.86.12.8075

77. Li Y, Xu S, Zhang X, Zongchun Y, Cichello S. Skeletal intramyocellular lipid metabolism and insulin resistance. *Biophys Rep*. 2015; 1: 90-98. doi: 10.1007/s41048-015-0013-0

78. Hansen ME, Tippett TS. Insulin increases ceramide synthesis in skeletal muscle. *J Diabetes Res*. 2014; 2014: 765784. doi: 10.1155/2014/765784

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Hereditary Contribution Towards Development of Type 2 Diabetes Mellitus among Indian Population

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ABSTRACT

Objective
Diabetes Mellitus Type II is becoming a major disorder. This study describes the inheritance of type 2 diabetes mellitus in families with diabetes.

Methods
The study was conducted in Manipur in two districts i.e., Imphal-east and Thoubal among Muslim families. These families were considered for the present study in which one or more family members had diabetes and were involved as active participants.

Results
On tracing the genealogies of each family, a higher percentage of the participants with diabetes inherited the disease from their fathers.

Conclusions
This finding would be helpful in future research by implementing among different communities.

Keywords
Diabetes; Genealogy; Inheritance; Paternal; Manipur.

INTRODUCTION

At present, there is a dramatic rise in the incidence of diabetes all over the world. Under 3% of the absolute infection, each of diabetes, asthma, and hypertension has been accounted for among Hajjis amid the time of Hajj.[1] The exact inheritance pattern of this condition as for whether it is transmitted through the paternal side or maternal side is not found. Family history has been considered as one of the risk factors of diabetes.[2] Congregation of information on family history of the disorder for assessing the risk has been used very less in the practice of preventive medicine and early detection.[3] In order to encourage change in lifestyle and initiate interventions of the condition, medical guidelines mostly include family history as the use of this tool was more advantageous over other genomic tools.[4] In India, the studies regarding the effect of positive family history of diabetes are still required.[2]

The inheritance pattern of type 2 diabetes is quite complex to understand because many other factors are also affecting this habits, such as lifestyle patterns, physical activity status, dietary propensities and so forth the ecological components. These complex relationships between genetic factors and environmental conditions may be reflected by tracing family history.[5] Till date, molecular genetics could not find out successfully the genetic markers of this condition.[6] Type 2 diabetes is known to be a heritable condition but no specific gene has been found for the common form of diabetes.[6,7] The relative contributions of paternal and maternal influences could provide information about the parental effects on their children and hence study of the parental transmission of diabetes would be very valuable.[8] In the present study, we have endeavored to find out whether the transmission of diabetes is higher from the paternal side or from the maternal side. In fact, it will be helpful in understanding the disease more deeply.

METHODS

The study was conducted in Manipur among the Muslim communities of two districts. Four hundred participants of each gender

were actively involved in the study, out of which 200 were patients with diabetes and 200 had no diabetes. The purpose of the study was properly explained to the participants before starting the work in order to make them understand and aware of it. Those who gave written consent were only included in the study. The active participants with diabetes in this study were under medical supervision. Ethical approval was taken from the Institutional Ethical Committee before the fieldwork was carried out.

Standardized proforma was used in order to gather the required information. Socio-demographic data were also collected. Genealogies of the participants were drawn for the purpose of tracing the inheritance pattern of the disease. Only those participants who were well understood for the family history of the disease were studied in the present study. The others were not considered for genealogical tracing. Age at onset of diabetes was also recorded for each participant. Basic anthropometric measurements were taken by using anthropometer and weighing machine using the standardized procedure. The data collected were analyzed by using SPSS 17.0 version and interpreted.

RESULTS AND DISCUSSION

The demographic data of the present study is displayed in table 1. Table 1 shows sex-wise distribution of the mean and standard deviation of age (self), age of spouse, age at marriage (self) and spouse age at marriage along with its *t*-values. Mean age of males with diabetes were found to be older than females with diabetes. Mean age of spouse and age at marriage of spouse were younger among males as compared to females with highly significant *t*-value ($p<0.001$). Age at diagnosing diabetes was lower among females.

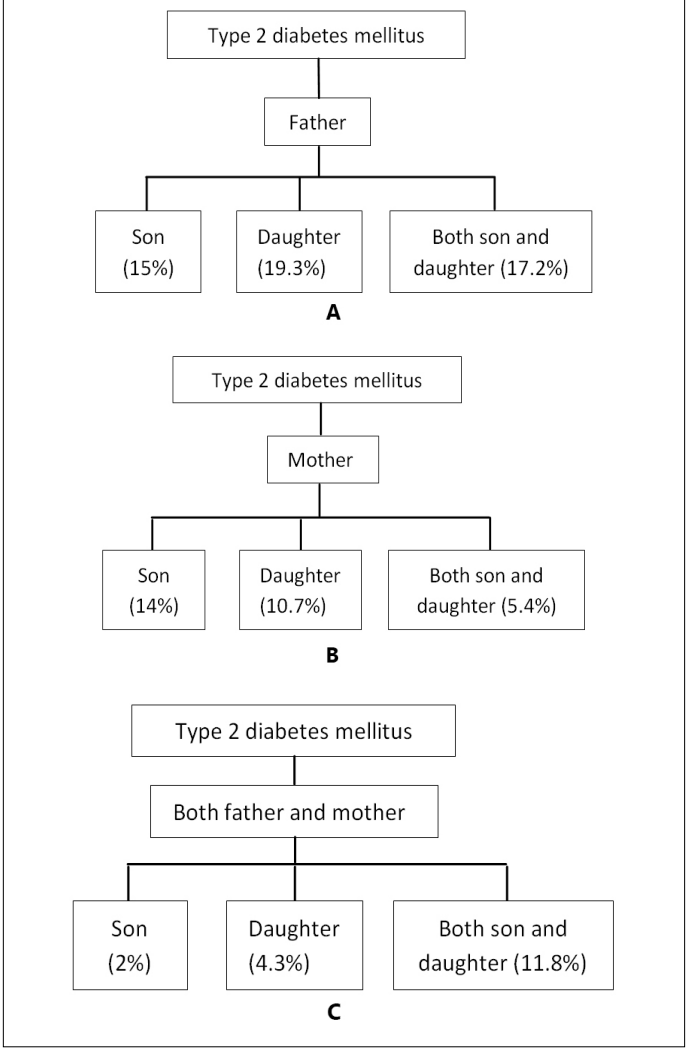
Table 1. *Age of Participants with Diabetes*

Age in years	Mean ± Standard Deviation		
	Male	Female	t-value
Age self	41.2±4.16	40.6±4.79	0.945
Age of spouse	35.4±10.22	42.7±14.22	-4.207***
Age at marriage (self)	21.5±6.99	19.2±4.87	2.698
Age at marriage of spouse	18.2±6.14	25.0±6.09	-7.870***
Age at diagnosing diabetes	36.1±5.39	35.50±5.292	0.820

***$p<0.001$

Figure 1 indicates the distribution of participants according to different inheritance pattern of families with diabetes. This result was found from the analysis of genealogy of 93 families from the present study. Three different diagrams A, B and C were shown in order to demonstrate the transmission pattern. On comparing figure 1A and 1B maximum percentage of transmission of diabetes to son, daughter and both son and daughter was found to be from the paternal side. Additionally, figure 1C represents the contribution of both maternal and paternal side in the transmission of diabetes to their children. The different inheritance patterns of the disease were displayed distinctly by genealogical representation figures 2-10.

Figure 1(A, B, C). *Distribution of Participants of 93 Families with their Inheritance Pattern*



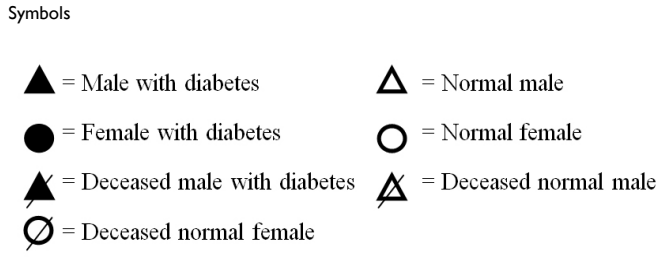


Figure 2. *Genealogical Representation of a Family Showing Father with Diabetes and Inheritance Pattern of Disease to Son*

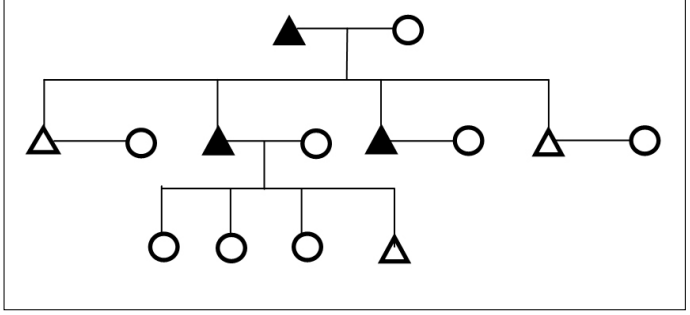


Figure 3. *Genealogical Representation of a Family Showing Mother with Diabetes and Inheritance Pattern of Disease to Son*

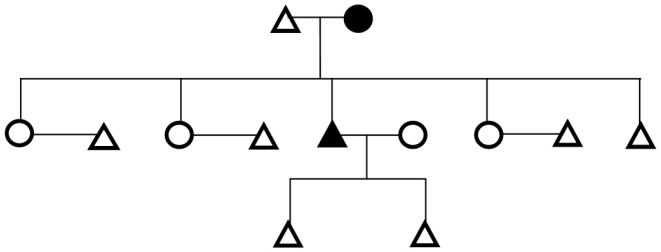


Figure 4. *Genealogical Representation of a Family Showing Both Parents with Diabetes and Inheritance Pattern of Disease to Son*

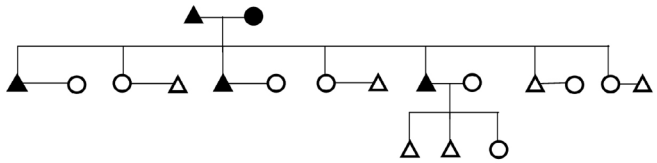


Figure 5. *Genealogical Representation of a Family Showing Father with Diabetes and Inheritance Pattern of Disease to Daughter*

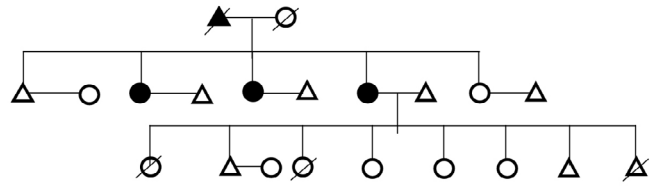


Figure 6. *Genealogical Representation of a Family Showing Mother with Diabetes and Inheritance Pattern of Disease to Son*

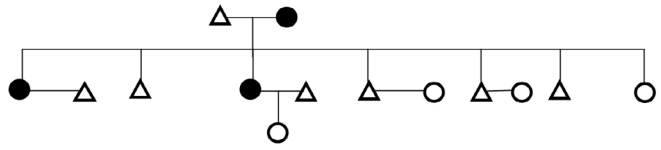


Figure 7. *Genealogical Representation of a Family Showing both Parents with Diabetes and Inheritance Pattern of Disease to Daughter*

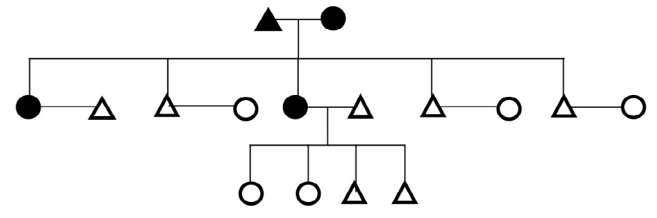


Figure 8. *Genealogical Representation of a Family Showing Mother with Diabetes and Inheritance Pattern of Disease to Both Son and Daughter*

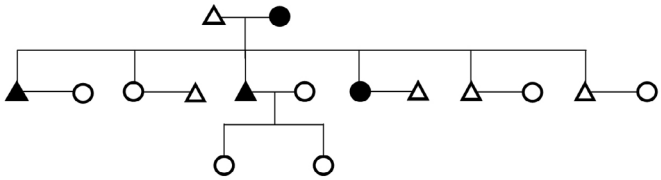


Figure 9. *Genealogical Representation of a Family Showing Father with Diabetes and Inheritance Pattern of Disease to Both Son and Daughter*

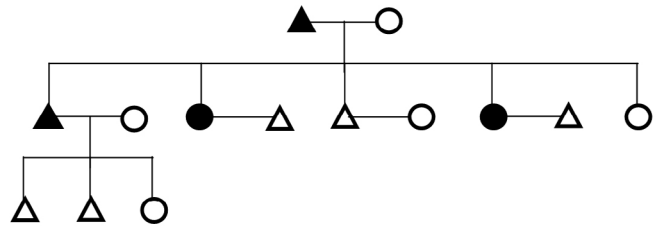
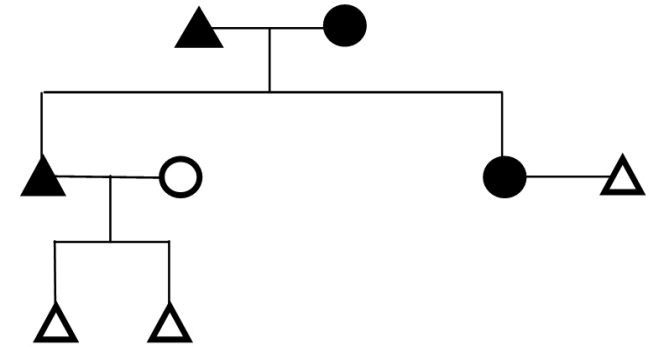


Figure 10. *Genealogical Representation of a Family Showing Parents with Diabetes and Inheritance Pattern of Disease to Both Son and Daughter*



Voluminous amount of research has been done on this major burden of the disease since many years in the past and are continuing till today among different ethnic groups of different regions for finding out the useful results that would help in decreasing the worldwide prevalence. Large numbers of people in India i.e. around 41 million have diabetes and it is expected to rise to 70 million in 2025. India being the second most populous country in the world has a wide diversity in terms of caste, religion, habitat, food habits, lifestyle, and financial status.[9]

The present study demonstrated that the mean age of self and age of spouse of the participants were older than the participants without diabetes. Mean of self-age at marriage and age at marriage of the spouse was lower among participants without diabetes as compared to the participants with diabetes. In addition to these, the mean of age at diagnosing diabetes was early among the female participants with diabetes as compared to their male counterparts. It showed consistency with the earlier study by.[10] The reason for the early onset of diabetes among the females might be

due to the lesser activity level of the body as most of the females stayed at home and after completing their household chores, they spent their leisure times on watching TV for long duration or slept during the daytime. Due to a sedentary lifestyle, early onset of diabetes among them could be explained as one of the reason.

In the present study, it was found that highest percentage of participants with diabetes of both sexes were married as compared to participants without diabetes and also showed significant differences. Some societies were found to have relationship of diabetes with single or married individuals.[11] Marriage may increase the stress level of an individual for providing for the family[12] which may further result in the reduction of activation of the neuroendocrine system. Information about diabetes in the north east region including the present study area, Manipur was very less.[13]

On tracing the genealogies of different families with diabetes in the present study, paternal transmission of the disease was found to be in the highest percentage. The transmission was not only to either son or daughter but to both sexes. It was supported by the research[6] on a randomly selected community of Framingham in which it was found that unique paternal genetic factors might transmit diabetes to children.[6] This also reported the risk of this disease to be 3.5 fold higher among offspring with only one parent with diabetes while it was 7 times higher with two parents with diabetes as compared to the offspring of parents without diabetes.

The present study suggested the contributions of the paternal role of the disease. The reason for this might be due to both father and mother genes were accountable in forming an offspring. In addition to this, those genes contributed by father might possess the factors affecting the disease before exposure to the uterine environment of the mother. In a study conducted by McCarthy et al[14] on a south Indian population in London, maternal history was more common as compared to the paternal history and it was not significant. However, the finding that excessive maternal transmission of diabetes[15] was not supported by the recent study and also by another previous study by Thorand et al.[16]

CONCLUSION

Both paternal and maternal factors might be responsible for the transmission of diabetes. The present study among the Muslims of Manipur found paternal inheritance of diabetes to be higher in percentage on tracing the genealogy of families with diabetes. This study would provide expedient information to the forthcoming researchers as well as to the common people in understanding the disease. Further, more researches are needed to be carried out among different communities of diverse regions for assessment and also to elucidate whether ethnicity plays a role or not on the transmission of diabetes.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

REFERENCES

1. Alzahrani AG, Choudhry AJ, Al Mazroa MA, Turkistani AH, Nouman GS, Memish ZA. Pattern of diseases among visitors to Mina health centers during the Hajj season, 1429 H (2008 G). *J Infect Public Health*. 2012; 5(1): 22-34. doi: 10.1016/j.jiph.2011.10.003

2. Das M, Pal S, Ghosh A. Family history of type 2 diabetes and prevalence of metabolic syndrome in adult Asian Indians. *J Cardiovasc Dis Res*. 2012; 3(2): 104-108. doi: 10.4103/0975-3583.95362

3. Williams RR, Hunt SC, Heiss G, et al. Usefulness of cardiovascular family history data for population-based preventive medicine and medical research (the health family tree study and the NHLBI family heart study). *Am J Cardiol*. 2001; 87(2): 129-135

4. Valdez R, Yoon PW, Qureshi N, Green RF, Khoury MJ. Family history in public health practice: A genomic tool for disease prevention and health promotion. *Annu Rev Public Health*. 2010; 31: 69-87. doi: 10.1146/annurev.publhealth.012809.103621

5. Grarup N, Andersen G. Gene–environment interactions in the pathogenesis of type 2 diabetes and metabolism. *Curr Opin Clin Nutr Metab Care*. 2007; 10(4): 420-426. doi: 10.1097/MCO.0b013e3281e2c9ab

6. Meigs JB, Cupples LA, Wilson PW. Parental transmission of type 2 diabetes: The framingham offspring study. *Diabetes*. 2000; 49(12): 2201-2207.

7. Cook JT, Shields DC, Page RC, et al. Segregation analysis of NIDDM in caucasian families. *Diabetologia*. 1994; 37(12): 1231-1240. doi: 10.1007/BF00399797

8. Knowler WC, Pettitt DJ, Savage PJ, Bennett PH. Diabetes incidence in Pima Indians: Contributions of obesity and parental diabetes. *Am J Epidemiol*. 1981; 113(2): 144-156.

9. Ramachandran A, Snehalatha C. Current scenario of diabetes in India. *J Diabetes*. 2009; 1(1): 18-28. doi: 10.1111/j.1753-0407.2008.00004.x

10. Azimi-Nezhad M, Ghayour-Mobarhan MP, Parizadeh MR, et al. Prevalence of type 2 diabetes mellitus in Iran and its relationship with gender, urbanisation, education, marital status and oc-

cupation. *Singapore Med J*. 2008; 49(7): 571-576

11. Bréchon F, Czernichow P, Leroy M, Blum-Boisgard C. Chronic diseases in self-employed French workers. *J Occup Environ Med*. 2005; 47(9): 909-915

12. Ikeda A, Iso H, Toyoshima H, et al. Marital status and mortality among Japanese men and women: the Japan collaborative cohort study. *BMC Public Health*. 2007; 7(1): 73. doi: 10.1186/1471-2458-7-73

13. Shah A, Afzal M. Risk factor for diabetes in different populations of Manipur. *Biol Med (Aligarh)*. 2015; 7(2): 233. doi: 10.4172/0974-8369.1000232

14. McCarthy M, Cassell P, Tran T, et al. Evaluation of the importance of maternal history of diabetes and of mitochondrial variation in the development of NIDDM. *Diabet Med*. 1996; 13(5): 420-428. doi: 10.1002/(SICI)1096-9136(199605)13:5%3C420::AID-DIA97%3E3.0.CO;2-W

15. Thomas F, Balkau B, Vauzelle-Kervroedan F, Papoz L. Maternal effect and familial aggregation in NIDDM. The CODIAB Study: CODIAB-INSERM-ZENECA study group. *Diabetes*. 1994; 43(1): 63-67.

16. Thorand B, Liese AD, Metzger MH, Reitmeir P, Schneider A, Löwel H. Can inaccuracy of reported parental history of diabetes explain the maternal transmission hypothesis for diabetes? *Int J Epidemiol*. 2001; 30(5): 1084-1089.

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DIABETES RESEARCH
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Editorial

Rice Function for Disease Prevention and Establishment of Medical Rice Association

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When I visited Bangkok in Thailand about five years ago, I saw the label "*medical rice*" on a package of 'diabetes and health promotion' rice, and I was hopeful that the concept could be widened beyond Thailand. On December 10-12, 2014, the "*East Asia Functional Standardization of Rice Conference*" was held at Kyoto Research Park to promote the idea among related countries.

Since then, I am considering what is "*medical rice*".[1] To say 'medical rice' we need evidence from human studies. We have learned of the health effects of unpolished brown rice, *genmai* in Japanese, from Japanese history. Sagen Ishizuka (1850-1909) was a pioneer doctor in the Imperial Japanese Army who proposed the concepts of *shokuiku* (eating education) and the macrobiotic diet. He was one of the first to investigate the nutritional value of whole grains as well as kelp, radish, and *kudzu*.[2] In Kenji Miyazawa's famous poem "*Unbeaten by rain, Unbeaten by wind*", his daily intake "*With a handful brown rice a day, miso and a small amount of vegetable suffice*" was confirmed to contain all necessary daily nutrients by our recalculation.[3]

We thought that it was necessary to clarify the actual health effects of brown rice diet by a well-designed epidemiological study, so we started GENKI study (*Genmai* Evidence of Nutrition for *Kenko* (health) Innovation).[4,5] There are 1,223 participants from groups promoting a brown rice diet. Brown rice eaters show lower body mass index (BMI) in men and women at all ages. The average BMI in males was 22.0±3.2 kg/m^2 and 20.7±2.8 kg/m^2 in females. Dietary habits consisting of brown rice, rich in vegetables, and avoidance of meat seemed to support healthy life and quality of life (QoL).[4] Obese people were more likely to eat white rice and had a high risk of lifestyle-related diseases, such as diabetes and hypertension. On the contrary, brown rice eaters were less obese and had a good lifestyle with a low risk of illness. In addition, brown rice eaters showed healthy bowel movements, which suggested a good intestinal environment.[6]

Actually, brown rice eaters showed abundance of *Fermicutes* and low relative abundance of *Fusobacterium* in the intestinal microbiota at the phylum level. Abundance of microbiota at species level showed a rich *Faecalibacterium prausnitzii* (5.28%), and then *Blautia wexlerae* (3.67%), *Fusicatenibacter saccharivorans* (3.41%), *Megamonas funiformis* (3.35%), *Collinsella aerofaciens* (3.21%), and *Bacteroides vulgates* (3.12%).[6] They belong to *Fermicutes* phyla and butyrate producing bacteria. Butyrate is the preferred energy source for the colon epithelial cells, and contributes to the maintenance of the epithelial barrier functions of intestinal mucosa, and has immunomodulatory and anti-inflammatory properties.[7] *Blautiais* considered to control the intestinal immunity. Dietary fiber in brown rice seems to be the most important factor, but other ingredients could influence bacterial co-existence.[8-10] Then, *Bifidobacterium adolescentis* (2.35%) and *B. longum* (1.92%), *Bacteroides uniformis* (2.22%), *B. plebelius* (1.96%), and *B. dorei* (1.71%), and *Akkermansia muciniphila* (2.16%) were followed. Brown rice eaters, compared with the white rice eaters, showed less *Actinobacteria* (12.1 *vs.* 8.5% p=0.078) and *Fusobacterium* (1.6 *vs.* 0.018%, p=0.011). These are pathogenic in intestinal conditions.

So, brown rice could be considered to be typical medical rice by contributing to healthy life.[1] Organic brown rice contains many functional ingredients, such as γ-aminobutyric acid (GABA), γ- oryzanol, ferulic acids with high antioxidant function, in addition to the dietary fiber. The wax-free brown rice is made to improve palatability by scraping the surface wax layer from rice grain. Wax free brown rice contains almost all nutrients of brown rice.

Dietary fibers remained the same as in brown rice, although water-soluble fiber seemed to be more easily dissolved than insoluble dietary fiber during boiling.

From wax-free brown rice a low protein brown rice has been produced.[11-13] The protein in rice is stored in two different types of compartments. The major proteins are prolamin and glutelin. Prolamin is the alcohol soluble protein that remained after salt extraction of globulin. Glutelin is the dilute-acid or dilute-alkaline soluble protein after prolamin extraction. Most of the prolamin is present at the periphery in whole rice grains, so prolamin could be easily removed by the enzymatic digestion on polished white rice, but it has been difficult to remove from brown rice directly. Removal of the wax layer made it possible to immerse the enzyme solution beneath the bran layer. Removal of rice protein yielded low protein brown rice (LPBR) which is beneficial for chronic kidney disease patients.[11]

Medical rice for chronic kidney disease (CKD) should contain enough energy source and low protein, as well as low potassium and phosphate. Reduction of these minerals is a great benefit for CKD patients, because hyperkalemia and hyperphosphatemia are often difficult to avoid when eating meat.[14] Distinct mechanisms of low protein diet for CKD patients are identified, such as improvement of hyperphosphatemia and hyperkalemia, decrease in urinary protein, improvement of subjective symptoms, prevention of complication, and good control even after the introduction of hemodialysis for better survival. Protein overload promotes glomerular hyper-infiltration which causes prefibrotic effects. Recently, the therapy of CKD targeted at reducing hyperfiltration within the glomerular capillaries by using the angiotensin converting enzyme inhibitor or angiotensin receptor blocker to dilate the glomerular arterioles.[15] Other classes of diabetes medications, such as glucagon-like peptide-1 (GLP-1) agonists, peptidase-4 (DPP-4) inhibitors and sodium-glucose co-transporter 2 (SGLT2) inhibitors, are also thought to slow the progression of diabetic nephropathy. However, the dietary therapy is far more cost-effective.[16] High protein diets acutely elevate the glomerular filtration rate, and substitution of low protein brown rice for bread or western foods could delay the progression toward end-stage renal disease.

Looking at the degree of achievement of Japanese rice researches, breeding and production of brand rice, large embryo rice, etc., were developed, and bran-grind (BG) rinse-free rice and wax-free brown rice were elaborated by the rice processing.[17] As Japan becomes a super-aging society, medical expenses are expected to increase by US$ 600 billion in the next ten years and may lead to economic collapse. To this end, we must change to an idea that prevention of illness by dietary lifestyle is superior to the idea that treatment of diseases is only possible by drug therapy.[18]

Basic research on rice function is usually conducted in the university's agronomics and agrochemical department, testing stations and corporate research institutes, and animal experiments are also conducted on functional substances, but knowledge may not be shared among various institutes. Long-term large-scale intervention studies have not been conducted for epidemiological purposes in which humans are at the center of control, and human clinical studies are insufficiently carried out only for the application of supplements.

Integration of these knowledges under the recently established Medical Rice Association by researchers, rice-processing industries, farmers and consumers could produce great energy for building a healthy society.[19] Researchers, farmers, and distributors in Japan were able to establish the association with the purpose of constructing and computerizing the evidence of the fragmentary research, and disseminating it widely to the society. With the cooperation of producers and consumers, standardization of medical rice should enable disease prevention with diet-based evidence for health. Within the association, there will be a research grant committee and a function evaluation committee, and we hope to foster young researchers in this field.

Rice is the main staple food for approximately 70 percent of the world's population, mainly living in ten areas of the Asia-Pacific region. In many countries, rice contributes to overall better health by supplying dietary energy, protein and fat. It accounts for more than 50% of the diet in Bangladesh, Myanmar, Lao People's Democratic Republic, Vietnam and Indonesia.[13] The high prevalence of diabetes among polished white rice eaters has become well-known. Rice with high amylase with a low glycemic index (GI) may be used to prevent diabetes, and high GABA containing large germ rice could contribute to mental health. In this regard, the nutritional aspects of brown rice should be re-evaluated, and further development should produce wonderful medical rice.[20,21]

REFERENCES

1. Watanabe S, Hirakawa A, Nishijima C, et al. Food as medicine: The new concept of "Medical Rice". *Adv Food Technol Nutr Sci Open J.* 2016; 2(2): 38-50. doi: 10.17140/AFTNSOJ-2-129

2. Watanabe S. Pionieer of nutritional science: Sagen Ishizuka. *Clin Funct Nutriol.* 2011; 3(2): 60.

3. Watanabe S. Kenji shoku. *Clin Funct Nutriol.* 2011; 3(2): 60.

4. Watanabe S, Mizuno S, Hirakawa A. Effects of brown rice on obesity: GENKI study I (Cross sectional epidemiological study). *J Obes Chronic Dis.* 2018; 2(1): 12-19. doi: 10. 17756/jocd. 2018-013

5. Watanabe S, Hirakawa A, Mizuno S. Dietary life habits of obese people and brown rice eaters among GENKI study. *Clinical and Functional Nutriology.* 2018; 10 (2): 79-86.

6. Hirakawa A, Aoe S, Watanabe S, et al. The nested study on the intestinal microbiota in genki study with special reference to the effect of brown rice. *Eating J Obes Chronic Dis.* 2019; 3(1): 1-13. doi: 10.17756/jocd.2019-022

7. Duncan SH, Russell WR, Quartieri A, et al. Wheat bran promotes enrichment within the human colonic microbiota of butyrate-producing bacteria that release ferulic acid. *Environ Microbiol.* 2016; 18(7): 2214-2225. doi: 10.1111/1462-2920.13158

8. Shimabukuro M, Higa M, Kinjo R, et al. Effects of the brown rice diet on visceral obesity and endothelial function: the BRAVO study. *Br J Nutr.* 2014; 111(2): 310-320. doi: 10.1017/S0007114513002432

9. Tang G, Wang D, Long J, Yang F, Si L. Meta-analysis of the association between whole grain intake and coronary heart disease risk. *Am J Cardiol.* 2015; 115(5): 625-629. doi: 10.1016/j.amjcard.2014.12.015

10. Masuzaki H, Kozuka C, Okamoto S, Yonamine M, Tanaka H, Shimabukuro M. Brown rice-specific γ-oryzanol as a promising prophylactic avenue to protect against diabetes mellitus and obesity in humans. *J Diabetes Investig.* 2019; 10(1): 18-25. doi: 10.1111/jdi.12892

11. Watanabe S, Hirakawa A, Takei N, Beppu S, Hashimoto H, et al. Medical rice: A new wax-free brown rice and its protein reduced rice. *Adv Food Technol Nutr Sci Open J.* 2018; 4(1): 10-16. doi: 10.17140/AFTNSOJ-4-147

12. Takei N., et al. Low-protein rice (LPR) product: Processing method and product safety. *Adv Food Technol Nutr Sci Open J.* 2017; 3(1): 33-41. doi: 10.17140/AFTNSOJ-3-142

13. Takei N, Kodama S, Hirakawa A, Mizuno S, Saika K, Watanabe S. Medical rice: Brown rice for health and low protein rice for preventing CKD. *EC Nutrition.* 2019; 14(2): 142-150.

14. Watanabe S. Low-protein diet for the prevention of renal failure. *Proc Jpn Acad Ser B Phys Biol Sci.* 2017; 93(1): 1-9. doi: 10.2183/pjab.93.001

15. Palatini P. Glomerular hyperfiltration: A marker of early renal damage in pre-diabetes and pre-hypertension. *Nephrol Dial Transplant.* 2012; 27(5): 1708-1714. doi: 10.1093/ndt/gfs037

16. Chen XM, Huang C, Pollock CA. Current opinion in the treatment of diabetic nephropathy. *Nephrol Open J.* 2015; 1(2): 20-24. doi: 10.17140/NPOJ-1-104

17. Saika K, Watanabe S. Producing rinse-free rice by the bran-grind method: A way to stop environmental pollution from rice industry waste water. *Adv Food Tech Nutr Sci Open J.* 2017; 3(1): 45-50. doi: 10.17140/AFTNSOJ-3-144

18. Mohan V, Spiegelman D, Sudha V, et al. Effect of brown rice, white rice, and brown rice with legumes on blood glucose and insulin responses in overweight Asian Indians: A randomized control trial. *Diabetes Technol Ther.* 2014; 16(5): 317-325. doi: 10.1089/dia.2013.0259

19. Nakamura S, Satoh H, Ohtsubo K. Palatable and bio-functional wheat/rice bread from pre-germinated brown rice of superhard cultivar, EM10. *Biosci Biotechnol Biochem.* 2010; 74(6): 1164-1172. doi: 10.1271/bbb.90850

20. Hudson EA, Dinh PA, Kokubun T, Simmonds MS, Gescher AC. Characterization of potentially chemopreventive phenols in extracts of brown rice that inhibit the growth of human breast and colon cancer cells. *Cancer Epidemiol Biomarkers Prev.* 2000; 9(11): 1163-1170.

21. Tungtrakul P. Innovative rice products in Thailand. Proceedings of the East Asia Conference on Standardization of Rice Function. Kyoto, Japan. 2013: 61-62.

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Editorial

Latent Autoimmune Diabetes in Adults (LADA) in Recent Clinical Practice

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Diabetic patients have been increasing and this tendency has become a medical and social problem worldwide.[1] There are some types of diabetes, in which the prevalence of type 2 diabetes mellitus (T2DM) has been higher without requiring insulin treatment. On the other hand, type 1 diabetes mellitus (T1DM) has acute onset due to virus infection. Under such circumstances, there is a disease that has been clinically important in recent years. It is Latent autoimmune diabetes in adults (LADA).

As to LADA, there are both clinical and immunological characteristics between T2DM and T1DM. The genesis of T1DM has been the autoimmune destruction of islet β-cells in the pancreas. There are some major anti-islet autoantibodies, such as glutamic acid decarboxylase autoantibody (GADA), and T1DM shows a high prevalence of GADA.[2,3]

When positive GADA is observed in the patient with T2DM, the patient does not require insulin treatment during the early stage, but the patient may become insulin-dependent status within a few years. This subtype of diabetes has been called LADA mainly in Europe and North American region.[4] In contrast, in Japan and the Asian region, it has been called slowly progressive insulin-dependent (type 1) diabetes mellitus (SPIDDM),[5] and/or LADA.[6]

The characteristic point of LADA would be a conceptual phenotype that exists between conventional T1DM and T2DM. Recently, there has been some clinical issues and challenges for LADA.[7] They include the prevention of progressive β-cell failure by dipeptidyl peptidase-4 (DPP-4) inhibitors, Glucagon-like peptide-1 (GLP-1) analogs, metformin, and insulin.[8] Furthermore, there was an investigation of islet cells and exocrine pancreatic tissues in the pancreas for LADA which were positive for GADAs and islet cell antibody (ICA).[9]

LADA is characterized for its rather less intensive autoimmune situation and its broad clinical features.[10] Patients with LADA are initially insulin independent at early stages and can be checked by examination of islet-cell autoantibodies. Then, it is rather difficult to diagnose LADA in the usual clinical setting. Probably, there are lots of cases of LADA which would exist in the large group of T2DM with higher misdiagnosis rate.

As a matter of fact, the screening test for ICAs would be necessary for the patients with newly diagnosed as T2DM. Unless this exam of antibodies is performed, a gradual decrease in the ability of insulin secretion may be found later after years.[10] Consequently, LADA may show slower decreased pancreas function compared with that of T1DM. Furthermore, patients with LADA can prepare the pathophysiological changes in advance a few years later, with the adequate therapeutic approach of diabetic treatment.

LADA has been characterized for the presence of specific autoantibodies for the islet cells. It includes GADA and IA-2 antibodies.[11] This type is often diagnosed as T2DM at an early stage, but a few years later its diabetic status will develop to the degree similar to T1DM. This situation has been as rather popular in adulthood as in childhood.[11] Thus, there is a possibility of misdiagnosis between T2DM and LADA just after the diagnosis of diabetes. These patients are defined as LADA which has been one of the subtypes of autoimmune diabetes.[12] Its specific points would be more heterogeneous than T1DM in a young person and slower changes to β-cell failure for years with necessary treatment of insulin.[13]

From the guidelines of the Immunology of Diabetes Society (IDS), a patient with LADA has been defined by i) adult age of onset usually more than 30-years, ii) insulin independence at

onset for at least 6-months, iii) positive results for islet-cell autoantibodies.[13] In contrast, there have much discussion and controversy concerning the definition of LADA. It is rather difficult to show clear diagnostic guidelines at present. Consequently, the various situation of LADA includes heterogeneous matters in phenotypic, immunological and genetic features. These phenomena probably come from the variability of autoimmunity, insulin resistance and pancreatic β-cell impairment rate.[14]

In clinical practice, LADA has been sometimes unnoticed among patients with T2DM. Its incidence may be supposed to be about 5-10% of misdiagnosis rate.[11] Actually, it is recommended to order the measurement of the blood C-peptide value and autoantibody examination such as GADA in the patients with newly diagnosed as T2DM. It is necessary to make confirmation the diagnosis whether there is the possibility of LADA or not.[15] It is indeed that it cost some expense for the detecting GADA antibody, but it is crucial to be checked at the early stages of diagnosis. Obtaining the data for GADA antibody, prevention for β-cells failure and other clinical diabetic disorder for the future can be prepared in advance.[16]

According to the study on GADA in 32 patients with LADA, 59% of them showed positive results for the measurement of GADA-ELISA method.[17] Patients with positive ELISA had significantly lower insulin secretion, suggesting the presence of more cytotoxic GAD epitopes. Consequently, measuring the value of GADA may predict the ability of insulin secretion in patients with LADA.

In the action LADA study, the majority of subjects showed positive for GADA, while only 24.1% of subjects were positive for at least two autoantibody types.[18] There are some controversies concerning the pathogenesis of LADA, which has not been clarified yet. A recent study revealed a significant association between Islet cell antigen 512 (IA-2) positivity and increased body mass index (BMI).[19] It may suggest two possibilities in obese or lean subjects for LADA. One is persisting low-grade inflammation with genetic susceptibility to T2DM in obese people, and another is specific immunological involvement with genetic susceptibility to T1DM in lean people.[16]

Formerly, T1DM has been thought of as a childhood disease. In the last decade, however, about 30% of T1DM cases have been diagnosed after 30-years-old by statistical investigations.[15] Thus, T1DM onset in adults becomes an important matter at present. From various studies, the incidence rate of adult-onset autoimmune diabetes has been different in countries and ethnicity. It is rather higher in North Europe than American, Latino, and Asia.[12,20] The prevalence of LADA has been reported as follows: 2.6% in the United Arab Emirates, 3.2% in India, 4.4%-5.3% in Korea, 5.7% in China, 7.0-14.0% in North Europe.[20,21] In these studies, however, there have been various differences in study design, method, and criteria, where we have to compare the data of incidence and prevalence from a different area in the world.

In summary, LADA has been recently found in various areas. When the patient is diagnosed as LADA, autoantibodies and the clinical course should be carefully monitored. The pathogenesis for LADA has been gradually elucidated and the development of future research is expected.

REFERENCES

1. Kowall B, Rathmann W, Bongaerts B, et al. Incidence rates of type 2 diabetes in people with impaired fasting glucose (ADA *vs.* WHO Criteria) and impaired glucose tolerance: Results from an older population (KORA S4/F4/FF4 Study). *Diabetes Care*. 2019; 42(2): e18-e20. doi: 10.2337/dc18-1473

2. Kawasaki E, Nakamura K, Kuriya G, et al. Differences in the humoral autoreactivity to zinc transporter 8 between childhood- and adult-onset type 1 diabetes in Japanese patients. *Clin Immunol*. 2011; 138(2): 146-153. doi: 10.1016/j.clim.2010.10.007

3. Wenzlau JM, Juhl K, Yu L, et al. The cation efflux transporter ZnT8 (Slc30A8) is a major autoantigen in human type 1 diabetes. *Proc Natl Acad Sci U S A*. 2007; 104(43): 17040-17045. doi: 10.1073/pnas.0705894104

4. Zhou Z, Xiang Y, Ji L, et al. Frequency, immunogenetics, and clinical characteristics of latent autoimmune diabetes in China (LADA China study): A nationwide, multicenter, clinic-based cross-sectional study. *Diabetes*. 2013; 62(2): 543-550 doi: 10.2337/db12-0207

5. Kobayashi T, Tamemoto K, Nakanishi K, et al. Immunogenetic and clinical characterization of slowly progressive IDDM. *Diabetes Care*. 1993; 16(5): 780-788.

6. Buzzetti R, Di Pietro S, Giaccari A, et al. High titer of autoantibodies to GAD identifies a specific phenotype of adult-onset autoimmune diabetes. *Diabetes Care* 2007; 30(4): 932-938. doi: 10.2337/dc06-1696

7. Leslie RD, Palmer J, Schloot NC, et al. Diabetes at the crossroads: Relevance of disease classification to pathophysiology and treatment. *Diabetologia*. 2016; 59(1): 13-20. doi: 10.1007/s00125-015-3789-z

8. Awata T, Shimada A, Maruyama T, et al. Possible long-term efficacy of sitagliptin, a dipeptidyl peptidase-4 inhibitor, for slowly progressive type 1 diabetes (SPIDDM) in the stage of non–insulin-dependency: An open-label randomized controlled pilot trial (SPAN-S). *Diabetes Ther*. 2017; 8(5):1123-1134. doi: 10.1007/s13300-017-0299-7

9. Aida K, Fukui T, Jimbo E, et al. Distinct Inflammatory Changes of the pancreas of slowly progressive insulin-dependent (Type 1) diabetes. *Pancreas*. 2018; 47(9): 1101-1109. doi: 10.1097/MPA.0000000000001144

10. Pieralice S, Pozzilli P. Latent autoimmune diabetes in adults: A

review on clinical implications and management. *Diabetes Metab J.* 2018; 42(6): 451-464. doi: 10.4093%2Fdmj.2018.0190

11. Mishra R, Hodge KM, Cousminer DL, Leslie RD, Grant SFA. A global perspective of latent autoimmune diabetes in adults. *Trends Endocrinol Metab.* 2018; 29(9): 638-650. doi: 10.1016/j.tem.2018.07.001

12. Maddaloni E, Lessan N, Al Tikriti A, Buzzetti R, Pozzilli P, Barakat MT. Latent autoimmune diabetes in adults in the United Arab Emirates: Clinical features and factors related to insulin-requirement. *PLoS One.* 2015; 10(8): e0131837. doi: 10.1371/journal.pone.0131837

13. American Diabetes Association. 2. Classification and diagnosis of diabetes. *Diabetes Care.* 2015; 38(1): S8-S16. doi: 10.2337/dc15-S005

14. Hernandez M, Mollo A, Marsal JR, et al. Insulin secretion in patients with latent autoimmune diabetes (LADA): Half way between type 1 and type 2 diabetes: Action LADA 9. *BMC Endocr Disord.* 2015; 15: 1. doi: 10.1186/1472-6823-15-1

15. Park Y, Wintergerst KA, Zhou Z. Clinical heterogeneity of type 1 diabetes (T1D) found in Asia. *Diabetes Metab Res Rev.* 2017; 33(7). doi: 10.1002/dmrr.2907

16. Buzzetti R, Zampetti S, Maddaloni E. Adult-onset autoimmune diabetes: Current knowledge and implications for management. *Nat Rev Endocrinol.* 2017; 13(11): 674-686. doi: 10.1038/nrendo.2017.99

17. Takagi S, Miura J, Hoshina S, Uchigata Y, Babzono T. Association of anti-GAD antibody positivity measured by RIA and ELISA with clinical characteristics in patients with type 1 diabetes. *Diabetes.* 2018; 67(1). doi: 10.2337/db18-1700-P

18. Hawa MI, Kolb H, Schloot N, et al. Adult-onset autoimmune diabetes in Europe is prevalent with a broad clinical phenotype: Action LADA 7. *Diabetes Care.* 2013; 36(4): 908-913. doi: 10.2337/dc12-0931

19. Buzzetti R, Spoletini M, Zampetti S, et al. Tyrosine phosphatase-related islet antigen 2(256-760) autoantibodies, the only marker of islet autoimmunity that increases by increasing the degree of BMI in obese subjects with type 2 diabetes. *Diabetes Care.* 2015; 38(3): 513-520. doi: 10.2337/dc14-1638

20. Rawshani A, Landin-Olsson M, Svensson AM, et al. The incidence of diabetes among 0-34 year olds in Sweden: New data and better methods. *Diabetologia.* 2014; 57(7): 1375-1381. doi: 10.1007/s00125-014-3225-9

21. Sachan A, Zaidi G, Sahu RP, Agrawal S, Colman PG, Bhatia E. Low prevalence of latent autoimmune diabetes in adults in northern India. *Diabet Med.* 2015; 32(6): 810-813. doi: 10.1111/dme.12644

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Case Report

Effect of Music Therapy as an Adjunct in Management of Diabetic Foot Ulcer

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ABSTRACT

Diabetes mellitus is a chronic debilitating metabolic disorder which, when it involves the foot, is one of the most dreaded complications associated with increased morbidity and mortality. Various treatment modalities are used for the treatment of diabetic ulcer. Better wound care and control of blood sugar levels helps in preventing amputation and limb loss. Here we discuss a case of diabetic foot ulcer in which music therapy was used as an adjunct modality of treatment.

Keywords
Music therapy; Diabetic foot ulcer; Wound healing.

INTRODUCTION

India is the world capital for diabetes mellitus. Diabetic foot ulcers (DFU) are the most costly and devastating complication of diabetes mellitus which affects 15% diabetic patients in their lifetime.[1] Early effective management can reduce the severity of complications such as preventable amputations and reduce the mortality.More than 50% of non-traumatic lower-extremity amputations are related to diabetic foot ulcer infections and 85% of all lower-extremity amputations in patients with diabetes are preceded by an ulcer; up to 70% of diabetic patients with a DFU-related amputation die within 5 years of their amputation.[2] Together with achieving strict glycemic control, thorough wound debridement in combination with other modalities of treatment such as advanced-dressings, off loading technique, Negative pressure wound therapy are an integral part of diabetic ulcer management.[1] Music therapy is one of the adjunct modality of therapy that has shown promise in relieving pain and helped in emotional and physical healing and wellbeing of the patient. In addition music permits the patient to be involved in the treatment; music can be adapted to each individuals need and can be used to distract the patient during painful procedures and experiences with the hope that they will experience decreased levels of pain. Here we describe a case of diabetic ulcer in the management of which music therapy was used as an adjunct.

CASE PRESENTATION

This study was conducted in the Department of Plastic Surgery in a tertiary care hospital during February to March 2019. An informed consent was taken from the subject under study who was a 38-year-old male, manual laborer, recently detected with diabetes mellitus who presented with ulcer over right foot of 2 months duration (Figure 1). At presentation the wound was infected and the patient had very poor glycemic control, his HbA1c being 11.8. Wound debridement was done and antibiotics were started according to culture sensitivity. In the course of the treatment, strict glycemic control was achieved with the use of insulin and oral hypoglycemic agents. Wound bed preparation was done with multiple surgical debridements (Figure 2). In addition to this, music therapy was used as an adjunct treatment.Patient was made to listen to mu-

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sic of his own choice daily for a period of 10 minutes, three times a day. His usual preferences were Tamil cinematic music and Carnatic music (Figures 3 and 4). Patient was also made to listen to music during dressing and wound debridement sessions. Debridement and dressings were carried out in operation theatre under local anesthesia and music of patients liking was played in a portable music device connected to patient's earphone. Debridement and dressings were done every 3rd day according to unit protocol, with and without music therapy alternatively. Data was collected after every debridement and dressing change both when music therapy was used and without using music therapy. Patients pulse rate and blood pressure were recorded after every dressing change with or without music therapy. The mean values of pulse rate and blood pressure were recorded and mean standard deviation was calculated.

Figure 1. *Diabetic Foot Ulcer at Presentation*

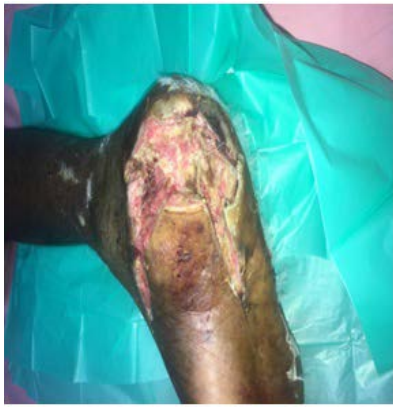

Figure 2. *After Wound Bed Preparation*

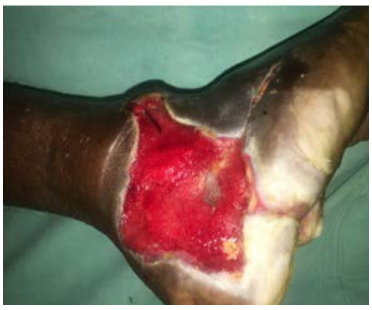

Figure 3. *After Reconstruction with SSG*

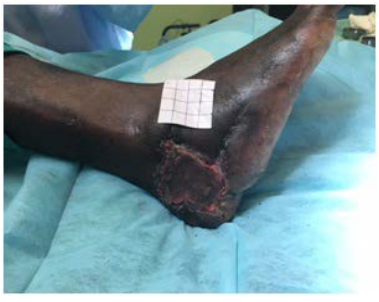

Figure 4. *Session of Music Therapy*

Feedback was collected from the patient regarding how he felt when he listened to the music, whether it helped him in decreasing his pain and alleviating stress and anxiety, whether it helped in easing his discomfort during dressing and debridement sessions.

Wound bed preparation was done for a period of 3 weeks, music therapy was continued all throughout and split thickness skin grafting at the wound site was done.The study was conducted on descriptive basis and only descriptive analysis was done.

RESULTS

Music therapy was found to play an effective role as an adjunct in diabetic wound management. It helped in relieving anxiety and stress associated with wound debridement and dressings. Slight decrease in blood pressure and pulse rate was noted when debridement and dressings were done with music therapy (Tables 1 and 2).

Table 1. *Assessment of Parameters without Music Therapy*

	Week 1 (Debridement 1)	Week 2 (Debridement 1)	Week 3 (Debridement 1)
Pulse Rate (Mean (Standard Deviation)) (bpm)	109.2 (+/- 2)	107.4+/-4	107.4+/-4
Mean Systolic Blood Pressure (Mean+/-SD) (mmHg)	114.8+/-3	114.2+/-3	112.2+/-2
Mean Diastolic Blood Pressure (Mean+/-SD) (mmHg)	84.8+/-5	87.4+/-6	82.2+/-4

Table 2. *Assessment of Parameters with Music Therapy*

	Week 1 (Debridement 2)	Week 2 (Debridement 2)	Week 3 (Debridement 2)
Pulse Rate (Mean (Standard Deviation)) (bpm)	101.4+/-2	91.4+/-6	87.7+/-6
Mean Systolic Blood Pressure (Mean Standard Deviation) (mmHg)	102.8+/-3	103.4+/-3	111.4+/-3
Mean Diastolic Blood Pressure(Mean Standard Deviation) (mmHg)	79+/-2	79.4+/-4	78+/-4

DISCUSSION

Diabetic Foot Ulcers (DFUs) cause morbidity and frequent visit to healthcare professionals and may lead to lower extremity amputation.[3] A multimodality approach is recommended to address potential underlying problems. Proper clinical examination and shoe gear, gait, orthopaedic, neurologic, and vascular exams are also recommended. Appropriate offloading and continuing diabetes education are also an important aspect included in the treatment for all DFUs.[4]

Music therapy has been used as an adjuvant for healing and symptom management. Listening to music affects multiple physiological parameters including autonomic nervous system.[5] Bradt et al[6] reviewed the evidence for music therapy with cancer patients and concluded that music therapy may have beneficial effects on anxiety, pain, quality of life, heart rate (HR), respiration rate (RR), and blood pressure (BP) in cancer patients.[6] Acute stress can activate the immune system and cause inflammation through the complement cascade.[7] On the other hand, chronic stress can impair immune function and delay wound healing.[8] It is important that when people are in a state of healing their immune systems are functioning optimally. Therefore, environmental stress should be kept to a minimum.[5]

Music therapy also helps in building better interpersonal communication between patient and healthcare workers. As a preliminary work, the authors of this study have designed and carried out this study to find out the role of music therapy as an adjunct in the management of diabetic foot ulcers. Based on feedback from patient and positive outcome, author feels that there is a positive association between the effects of music therapy as an adjunct in management of DFUs. There are limitations in the present study as it's a single centre study performed on one subject with no control, comparison, randomisation and statistical analysis. The music used was of the subjects liking which may not be appropriate for another person. The type of music and its various aspects such as pitch, rhythm, dynamics, etc. were not studied in detail.

CONCLUSION

This is a preliminary study to find the effect of music therapy as an adjunct treatment in the management of diabetic foot ulcers. A positive effect was found but a large multi-centric double-blind, control study with statistical analysis is recommended to substantiate the result of this study.

CONSENT

The authors have received written informed consent from the patient.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

REFERENCES

1. Yazdanpanah L, Nasiri M, Adarvishi S. Literature review on management of diabetic foot ulcer. *World J diabetes*. 2015; 6(1): 37-53. doi: 10.4239/wjd.v6.i1.37

2. Mavrogenis AF, Megaloikonomus PD, Antoniadou T, et al. Current concepts for the evaluation and management of diabetic foot ulcers. *EFFORT Open Rev*. 2018; 3(9): 513-525. doi: 10.1302/2058-5241.3.180010

3. Lipsky BA, Berendt AR, Deery HG, et al. Diagnosis and treatment of diabetic foot infections. *Plast Reconstr Surg*. 2006; 117(7 Suppl): 212S-238S. doi: 10.1097/01.prs.0000222737.09322.77

4. Blume P, Wu S. Updating the diabetic foot treatment algorithm: Recommendations on treatment using advanced medicine and therapies. *Wounds*. 2018; 30(2): 29-35.

5. Chiasson AM, Baldwin AL, Mclaughlin C, Cook P, Sethi G. The effect of live spontaneous harp music on patients in the intensive care unit. *Evidence-Based Complementary and Alternative Medicine*. 2013; 2013(22). doi: 10.1155/2013/428731

6. Bradt J, Dileo C, Magill L, Teague A. Music interventions for improvinpsychological and physical outcomes in cancer-patients. *Cochrane Database Syst Rev*. 2016; (8): CD006911. doi: 10.1002/14651858.CD006911.pub3

7. Bruser C, Winter S, Leonhardt S. Unsupervised heart rate variability estimation from ballistocardiograms. *International Journal of Bioelectromagnetism*. 2013; 15(1): 1-6.

8. Umetani K, Singer DH, McCraty R, Atkinson M. Twenty-four hour time domain heart rate variability and heart rate: relations to age and gender over nine decades. *J Am Coll Cardiol*. 1998; 31(3): 593-601. doi: 10.1016/S0735-1097(97)00554-8