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Opinion

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Increasing Adherence to the Diabetes Regimen: An Occupational Therapy Perspective

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KEYWORDS: Cultural sensitivity; Cultural competence; Health education.

Recognizing the epidemic of diabetes in the United States, the Centers for Disease Control projected that as many as one third of the population will have diabetes by 2050, without a concerted effort to change the lifestyles and habits of people diagnosed with diabetes.[1] Further, the World Health Organization (2014) announced that diabetes had become a global epidemic.

Occupational therapy has been described as a rehabilitation profession that helps a person with disease to improve their ability to function in everyday life activities or to adapt to their environmental demands, in order to continue to function to the best of their abilities.[2] The majority of occupational therapists in the United States have focused their interventions and research studies on development of the most effective ways to treat the tertiary complications of the disease such as: peripheral neuropathy, retinopathy, cardiac disease, cerebral vascular accident, and amputation. The consequences of poorly controlled or uncontrolled diabetes have devastated the health of people with diabetes by providing them with shorter life spans, poor quality of life, further disability, and increased morbidity.[3]

Having been told of their potential for debilitation, many people with diabetes may not have been able to understand and visualize their dismal futures, or had deliberately chosen not to make the necessary lifestyle changes that could maintain their quality of life for as long as possible. In addition, older adults, non-native English speakers, racial and ethnic groups with health disparities, and those with health problems have lower levels of health literacy that has led to higher morbidity and severe health risks, when compared to the normal population.[4]

Some occupational therapists researched intervention approaches that targeted secondary prevention and demonstrated improvement in diabetes adherence behaviors.[5-10] These studies provided individual and group interventions designed for Mexican-Americans with type 2 diabetes mellitus who were adherent to the recommendations for self-care from their physicians, health educators and nurses. The aim of these research studies was to provide culturally-sensitive and meaningful activity-based self-care interventions that motivated lifestyle changes that were sustainable over time.

Most health practitioners have studied issues of cultural-competency and have received training towards this end, so that their work with people from cultures other than their own could be more effective. Please notice that this author used the words cultural sensitivity in place of the more popular term of cultural competency. This was to imply that health professionals may not truly become competent, unless they have immersed themselves and lived as part of the culture that they want to understand. So, cultural-competency is the ultimate end goal. The means to that end would be everything that the practitioner would do towards achieving awareness and sensitivity to the needs of the person or people that they work with, and to modify their approach to health education accordingly.

For this reason, the *Diabetes Research-Open Journal* will feature research articles that have focused on secondary prevention of diabetes complications for subjects of any age and any type of diabetes, and provided health education interventions that were culturally-sensitive to the needs of the population or individuals studied. This would include the gamut of research from single case or single-subject research, through the highest level studies with double-blind placebo controlled trials.

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Short Communication

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Impaired Awareness of Hypoglycemia and Driving Mishaps in Patients with Type 1 Diabetes Mellitus: A Multi-center Survey in Japan

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ABSTRACT

Impaired Awareness of Hypoglycemia (IAH) is a common and serious problem in adult patients with Type 1 Diabetes Mellitus (T1DM). Driving accidents related to hypoglycemia have been previously described. The aim of this study was to determine the prevalence of driving mishaps and confirm the association between IAH and such mishaps among Japanese patients' with T1DM. Clinical data, such as the prevalence of

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hypoglycemia, IAH, and patients' behaviors to avoid driving accidents, were surveyed in 133 adult drivers with T1DM at 16 hospitals and clinics in Japan. A stepwise multiple logistic regression analysis of driving mishaps was performed. Driving mishaps were reported in 54.9% of the patients, and 15.8% reported hypoglycemia-related driving mishaps. A stepwise logistic regression analysis found that the presence of IAH (odds ratio [OR]: 5.36; 95% Confidence Interval [CI]: 1.59-18.10; P=0.01) was significantly risk factor for hypoglycemia-related driving mishaps, along with age (OR: 1.07; 95% CI: 1.01-1.13; P=0.02).Driving mishaps may be prevalent in Japanese patients with T1DM. IAH should be considered as a high risk factor for driving mishaps in this population.

KEYWORDS: Driving mishaps; Hypoglycemia; Diabetes; Insulin; Impaired awareness.

INTRODUCTION

A driver's license is essential for performing various functions in daily life, including access to medical services, in individuals with Diabetes Mellitus (DM).[1] Traffic accidents are associated with the risk of mortality[2,3] The number of deaths caused by traffic accidents in Japan was 4,863 in 2010, and the Japanese government has set a goal to reduce the annual fatality count to less than 2,500 by 2018.[4] Several studies have reported that drivers with T1DM have an increased risk of driving accidents, with a relative risk ratio of up to 2,[5,6,7] although another study did not support this.[8]

The association between hypoglycemia and traffic accidents has been discussed regarding patients with DM.[9] Patients with Type 1 DM (T1DM) often have an Impaired Awareness of Hypoglycemia (IAH).[10] Little is known about the relationship between IAH and driving mishaps among drivers with T1DM in Japan, even though the prevalence of patients with T1DM is lower in Japan compared with that in Caucasians.[10] The aim of this study, therefore, was to investigate the prevalence of hypoglycemia-related driving mishaps and confirm the association between IAH and driving mishaps among Japanese patients with T1DM.

MATERIALS AND METHODS

ETHICS

The study was approved by the ethical committee of the National Hospital Organization Kyoto Medical Center.

SUBJECTS

We recruited 133 adult drivers with T1DM at 16 hospitals and clinics located nationwide in Japan. Inclusion criteria were: 1) patients had diagnosed and insulin-treated DM, 2) patients regularly attended the hospitals and clinics surveyed, and 3) patients gave written, informed consent. Exclusion criteria were: 1) children and young patients under 20 years old, and 2) patients who were unable to answer a self-administrated questionnaire for any reason.

STUDY MEASURES

The self-administrated questionnaire was distributed and retrieved between April 2006 and October 2010. Patients completed a questionnaire to assess their awareness of hypoglycemia, which was based on the their ability to recognize hypoglycemia on the basis of symptoms, defining the answer categories "never", "seldom", and "sometimes" as impaired and "often" and "always" as normal hypoglycemia awareness.[11] Driving mishaps are defined broadly, including collisions, citations, losing control, automatic driving, someone else taking over driving, and moderate or severe hypoglycemia while driving.[12,13] Whether such accidents related hypoglycemia happened was determined by the patients with the questionnaire (hypoglycemia-related driving mishaps).

STATISTICS

Data are presented as the mean ± standard deviation or percentage. Student's t-test or chi-square test was used to compare the data between groups. A stepwise logistic regression analysis model was used to identify the related variables. The Statistical Package for the Social Sciences (SPSS 20.0, IBM Corp., New York, USA) was used for these analyses. A two-tailed p-value <0.05 was considered significant.

RESULTS

Among the 133 patients, 54.9 % (73 of 133 patients) reported at least one driving mishaps, and 15.8% of the drivers (21 of 133 patients) reported hypoglycemia-related driving mishaps, while awake. Overall, the prevalence of IAH was 37.0%. The patients who experienced driving mishaps had a higher IAH, hypoglycemic frequency, and longer diabetes duration than those who did not (Table 1). There were no significant differences in clinical characteristics, such as age, diabetes duration, and the prevalence of hypoglycemia and diabetic complications, between subjects with hypoglycemia-related accidents versus subjects without hypoglycemia-related accidents. There were no significant differences in the prevalence of measuring blood glucose before driving and carrying some sugar sources in the vehicle between groups. A stepwise logistic regression analysis found that the presence of IAH (odds ratio [OR]: 5.36; 95% confidence Interval [CI]: 1.59-18.10; P=0.01) was significantly risk factor for hypoglycemia-related driving mishaps, along with age (OR: 1.07; 95% CI: 1.01-1.13; P=0.02).

DISCUSSION

Diabetes mellitus is one of the disease conditions that may lead to traffic accidents.[5,6,7,9] The increased risk of accidents has been suggested to be associated with hypoglycemia in particular.[5,6,7,8,9] The current study showed that IAH

Variables	Drivers with mishaps (n=73)				Control (n=60)	P value (Drivers with mishaps *vs.* Control)
	All (n=73)	With hypoglycemia-related accidents (n=21)	Without hypoglycemia-related accidents (n=52)	P value		
Age, years	43.3 (11.5)	47.6 (11.6)	41.5 (11.0)	0.04	46.1 (14.4)	0.22
Male, %	41.1	52.4	36.5	0.21	48.3	0.40
Diabetes duration, years	15.3 (9.1)	17.7 (8.7)	14.4 (9.2)	0.17	9.7 (6.5)	<0.001
Continuous subcutaneous insulin infusion, %	6.8	0.0	9.6	0.14	16.7	0.75
Daily insulin dose, units	0.72(0.31)	0.82 (0.42)	0.68 (0.25)	0.10	0.63 (0.23)	0.08
Body mass index, kg/m^2	21.8 (2.5)	22.2 (2.7)	21.7 (2.5)	0.44	21.8 (2.8)	0.97
Hemoglobin A1c, %	7.9 (1.4)	7.5 (1.4)	8.1 (1.3)	0.11	7.9 (1.1)	0.96
Retinopathy, %	27.4	38.1	23.1	0.19	15.0	0.09
Nephropathy, %	17.8	19.0	17.3	0.86	13.6	0.51
Hypoglycemia, times per month	7.5 (8.7)	8.1 (7.0)	7.2 (9.3)	0.70	4.7 (5.4)	0.03
Impaired awareness of hypoglycemia, %	44.4	66.7	35.3	0.02	27.6	0.048
Measuring blood glucose before driving, %	26.4	35.0	23.1	0.30	23.7	0.73
Carrying sugar sources in the vehicle, %	67.1	81.0	61.5	0.11	64.4	0.74

Data are means (standard deviation) or number.

Table 1: Characteristics of patients with type 1 diabetes mellitus

and older age were significantly associated with an increased risk of driving mishaps among Japanese patients with T1DM. In addition, while aging showed a significant correlation with an increased risk of accidents in this study, this likely supports the previous finding.[14] Driving mishaps appear to be prevalent in this population (although appropriate comparative statistics on the accidents are unavailable). IAH and counter-regulatory failure increase the risk of severe hypoglycemia, which links to brain dysfunction.[15,16] The mainstay for treatment of IAH is the strict avoidance of hypoglycemia.[17] A lack of awareness of hypoglycemia is a safety issue for drivers with T1DM and a challenge for health care providers. As prevention, Blood Glucose Awareness Training (BGAT) can be effective for the recognition of hypoglycemia, as shown in American and Dutch studies.[17] Leelarathna et al. reported that IAH and counter regulatory responses may be improved by a clinical strategy aimed at hypoglycemia.[18] In Japan, we also developed a BGAT training site (http://bgat.jp/index.jsp) in 2010. Further trials using such BGAT training systems are needed to reduce driving mishaps among patients with T1DM.

Unawareness of a rapid decline in the plasma glucose concentration is an additional issue to be resolved. Drivers with T1DM are obliged to check their blood glucose concentrations before driving. Actually, the prevalence of measuring blood glucose before driving was only about thirty percent in this study. Health care providers can promote the habit of patients checking their blood glucose concentrations before driving, and should strongly advise that patients do not drive until a hypoglycemic condition has been resolved in cases of low blood glucose. Also, continuous glucose monitoring might facilitate identifying and treating patients with a higher risk of hypoglycemia during driving.[19,20]

STRENGTHS AND LIMITATIONS

The strengths of the current survey include the recruitment of patients at multiple hospitals and clinics nationwide in Japan. Because patients who regularly attended medical centers were recruited, they fully responded to the questionnaire. However, this study has several limitations. First, the sample size was small and the study was cross-sectional. Second, the data on driving mishaps were from self-administered questionnaires and there were no objective measures of driving accidents. These limitations should be addressed in future research.

In conclusion, Driving mishaps appear to be prevalent in Japanese patients with T1DM. IAH should be taken into consideration as a high-risk factor for driving mishaps in this population.

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Research

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Inverse Association between Vitamin D Status and Diabetes in a Clinic Based Sample of Hispanic Adults in Puerto Rico

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ABSTRACT

Background: Vitamin D deficiency is a public health problem around the world. Diabetes has been associated with vitamin D deficiency. We aimed to examine the association between the vitamin D status and diabetes in a clinic based sample of Hispanic adults in Puerto Rico.
Methods: Demographics and laboratory test results for serum 25(OH)D, Fasting Blood Glucose (FBG), and Haemoglobin A1C (HbA1c) were extracted from medical records. Vitamin D status was classified as deficient (<12 ng/ml); inadequate (12-20 ng/ml); insufficient (21-29 ng/ml) and optimal (≥30 ng/ml) using serum 25(OH)D levels.
Results: A total of 716 records were included in the analyses. Most were females (63.3%), with mean age of 54.1±14.9 y, mean BMI 30.1±6.3 kg/m2 and mean serum 25(OH)D levels of 24.3±8.6 ng/ml. Most were classified as diabetics (41.1%). Those with diabetes had lower 25(OH)D levels compared to pre-diabetic and normal glucose status ($p<0.05$). Serum 25(OH)D levels were inversely correlated to FBG and HbA1c in the total sample and in men ($p<0.05$). After adjusting for age, gender, BMI and seasonality, there was a greater risk of diabetes, but not prediabetes, in those with serum 25(OH)D levels <30 ng/ml. This risk increased from 1.8 times in those with vitamin D insufficiency to 4.2 times in those with vitamin D deficiency (<12 ng/ml).
Conclusion: Diabetes risk significantly increased as serum 25(OH)D levels decreased in this group of Hispanic adults, underscoring the importance of routinely screening high risk individuals for vitamin D deficiency and offer supplementation to normalize serum levels.

KEYWORDS: Vitamin D status; 25(OH)D levels; Diabetes; Glucose parameters.

INTRODUCTION

Diabetes affects 25.8 million people of all ages in the United States (US), which represents 8.3% of the US population.[1] This is higher in Hispanics as evidenced by data from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL), a population-based cohort study of Hispanic and Latino adults from diverse backgrounds, in which a diabetes prevalence of 16.7% in men and 17.2% in women was reported.[2,3] Among the Hispanic groups studied in HCHS/SOL, Puerto Ricans had the highest prevalence of diabetes, particularly among women. In addition, results from the Behavioural Risk Factor Surveillance System in Puerto Rico (PR) also showed that the estimated prevalence of self-reported diabetes was >12%,[4] which is among the highest compared to other states and territories of the US. Furthermore, a study in a representative sample of adults residing in the San Juan Metropolitan Area of PR showed that

the prevalence of diabetes was even higher, with an age-standardized prevalence of pre-diabetes and diabetes, detected by Fasting Plasma Glucose (FPG) and/or HbA1c, as 25.5% and 47.4%, respectively.[5] Diabetes is considered one of the leading causes of death in US and PR;[6] therefore, this is an important health disparity to address among Puerto Ricans.

Growing evidence suggests that diabetes risk is associated with vitamin D status. A recent meta-analysis of 21 prospective studies with a total of 76,220 participants (mostly non-Hispanic Whites) with about 5,000 incident cases of diabetes found a relative risk for diabetes of 0.62 (95% CI: 0.54-0.70) when comparing the highest with the lowest levels of 25(OH)D.[7] For each 10 nmol/L increment in serum 25(OH)D levels, there was a reduction in the risk of diabetes of 4% ($p<0.01$).[7] In addition, when 25(OH)D levels were near 50 nmol/l, the risk of diabetes was significantly reduced. Another meta-analysis of 19 cross-sectional, 13 case-control, and 12 prospective studies suggested that low serum 25(OH)D levels is associated with glucose intolerance, β cell dysfunction, and insulin resistance.[8]

Vitamin D deficiency is a public health concern, with a high prevalence worldwide.[9] In the US, 32% of the population has vitamin D levels below 20 ng/mL.[10] There is also a health disparity in vitamin D status. Hispanics are at high risk of low vitamin D status.[10-15] Among 358 Hispanic-American men, the highest prevalence of vitamin D deficiency was found among those born in PR (26%), compared to those from the Dominican Republic (21%), Central America (11%), and South America (9%).[16] Recently, we found in a large sample of 2,293 adults in PR that 72% had vitamin D insufficiency (levels below 30 ng/ml) and 28% were vitamin D deficient.[17]

There is scarce information assessing the association between vitamin D status and glycemic in Hispanics. This is important to study as Hispanics have a higher prevalence of both diabetes and low vitamin D status, particularly Puerto Ricans. Therefore, to start addressing this gap in knowledge, we assessed whether there was an association between vitamin D and glycemic status in a clinic-based sample in Hispanic adults living in PR.

METHODS

The study was based on a retrospective, secondary analysis of medical records of patients attending the "Endocrinology, Diabetes and Metabolism Clinic" located in the municipality of Utuado in PR.

Participants

The study population consisted of non institutionalized individuals who attended this clinic for the first time between 2005 and 2013. A convenience sample was selected from those records meeting the following inclusion criteria: aged 21 years and older; having test results for Fasting Blood Glucose (FBG), Oral Glucose Tolerance Test (OGTT), and/or Haemoglobin A1c (HbA1c); and serum 25(OH)D levels taken within 3 weeks of each other. Patients using any type of vitamin D supplementation regimens were excluded from the study, as there was a large variation in the doses reported (from 400 to 10,000 IU/d).

Data Collection

A data collection sheet was used to extract the information from medical records, which included data on demographics, anthropometrics, blood tests results for 25(OH)D levels and glucose metabolism markers, and prescribed hypoglycemic agents, which could potentially influence vitamin D metabolism.

Demographics and other health measures

Gender and age, calculated in years at the time of the medical visit, were recorded from the medical records. Prescribed hypoglycemic agents were recorded as physician's notes with names and doses used.

Anthropometrics

Body weight (pounds) and height (inches) were measured once by the clinic staff using a physician scale (Detecto, Model 338, MO, USA) while participants were wearing street clothes but no shoes. These measurements were converted to kg and meters. Body Mass Index (BMI) was calculated as the ratio of weight (kilograms) to the square of height (meters).

Blood tests

Laboratory test results dates were recorded from the medical records as month/day/year. All blood test results were taken after an overnight fast. Results from serum 25(OH)D levels were recorded in nanograms per millilitre (ng/mL) and these were analyzed by two methods. The main method used by 97% of the samples was immunoassay and only 3% were performed with Liquid Chromatography mass spectrometry (LC-MS/MS). Due to methodological differences between these methods,[18] only blood test results analyzed by immunoassay were included. Serum 25(OH)D levels were measured by the local laboratory using a commercially available enzyme immunoassay kit (IDS 25-Hydroxy Vitamin D EIA kit). The blood tests were collected all year round and the date of the serum 25(OH)D was recorded to adjusted for seasonality. Since the half-life of 25(OH)D levels is 2-3 weeks,[18] only blood tests results measured within this period were included in the analyses.

Although there is no universally accepted cut-offs for serum 25(OH)D levels, the Institute of Medicine (IOM)

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established that serum 25(OH)D levels above 20 ng/ml (50 nmol/l) are optimal and sufficient to maintain bone health.[19] However, the Endocrinology Society defines vitamin D deficiency as 25(OH)D levels below 20 ng/ml and adds a category for vitamin D insufficiency (levels 21-29 ng/ml; 52-72 nmol/l).[20] Furthermore, the Endocrinology Society also states that levels above 30 ng/ml (75 nmol/l) provide increased overall health benefits, such as reducing the risk of diabetes. Therefore, for the present study, vitamin D status was classified as: deficient if serum 25(OH)D levels were <12 ng/ml (30 nmol/l); inadequate if levels were 12-20 ng/ml (30-50 mmol/l); insufficient if levels were 21-29 ng/ml and optimal as levels ≥30 ng/ml.

The markers for glucose metabolism recorded were Fasting Blood Glucose (FBG), HbA1c, and 2-hour Plasma Glucose (2hPG). These were measured routinely by local laboratories; glucose levels were measured by Spectrophotometry and HbA1c by HPLC. Individuals were classified as having diabetes by using the following criteria: HbA1c ≥6.5%; FBG ≥126 mg/dl (≥7.0 mmol/l); and/or 2hPG≥200 mg/dl (≥11.1 mmol/l)[21,22] or if use of hypoglycemic agents was documented in the medical record.[23] The following criteria were used to classify pre diabetes: HbA1c 5.7-6.4%; FBG 100-125 mg/dl; or a 2hPG≥140 (≥7.8 mmol/l) and <200 mg/dl (<11.1 mmol/l).[21] Normal glucose status was defined as HbA1c <5.7%; FBG <100 mg/dl; and/or 2Hpg of <140 mg/dl (<7.8 mmol/l).[21]

This study was approved by the Institutional Review Board of the Medical Sciences Campus (MSC) of the University of Puerto Rico (UPR). In addition, the clinic director provided written authorization to access all medical records. To assure confidentiality, all data collection sheets were stored in a locked room in the Nutrition Program of the MSC UPR Graduate School of Public Health.

STATISTICAL ANALYSIS

Baseline characteristics were summarized using mean and Standard Deviation (SD) for continuous variables and frequency distributions for categorical variables. Analysis of Covariance (ANCOVA) was used to assess differences in age-adjusted mean serum 25(OH)D levels across glycemic status (normal, pre diabetes, and diabetes). Bonferroni's posthoc test was used for multiple comparisons. Pearson's correlation coefficient was used to assess the correlation of serum 25(OH)D with glucose parameters. A multinomial logistic regression model was used to assess the association between vitamin D and glycemic status after adjustment for age, gender, BMI, and season. All analyses were performed using SPSS Statistical Package (SPSS version 21.0 for Windows, 2012, SPSS Inc., Chicago, Il.). Statistical significance was set at $p<0.05$.

RESULTS

From 1,379 consecutive medical records reviewed, 716 (52%) records met the inclusion criteria. A total of 89 records reported the use of vitamin D supplements and 574 did not have the levels of serum 25(OH)D or any of the glucose measures reported or were not done within 3 weeks of each other; therefore, these were excluded from the analyses. The descriptive characteristics of the study sample are presented in table 1.

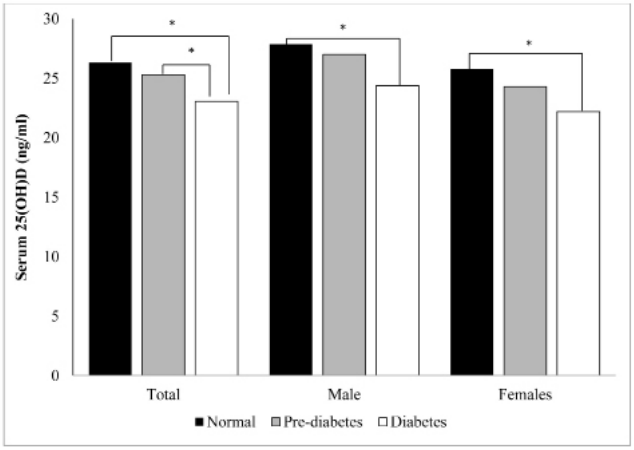
Characteristic	Total		Males		Females	
	n	mean ± SD	n	mean ± SD	n	mean ± SD
Age (y)	716	54.1 ± 14.9	263	53.8 ± 13.9	453	54.3 ± 15.4
BMI (kg/m^2)	693	30.1 ± 6.3	255	30.4 ± 5.8	438	29.8 ± 6.5
25(OH)D (ng/ml)	716	24.3 ± 8.6	263	25.5 ± 8.4	453	23.6 ± 8.6*
Vitamin D Status (%)						
Deficient (<12 ng/ml)	39	5.4	10	3.8	29	6.4
Inadequate (12-20 ng/ml)	192	26.8	63	24.0	129	28.5
Insufficiency (21-29 ng/ml)	319	44.6	120	45.6	199	43.9
Optimal (≥30 ng/ml)	166	23.2	70	26.6	96	21.2
FBG (mg/dl)	697	122.8 ± 57.7	259	132.8 ± 64.6	438	117.0 ± 52.4*
2h OGTT (mg/dl)	280	141.3 ± 68.2	100	154.1 ± 77.5	180	134.2 ± 61.5*
HbA1c	547	6.9 ± 2.0	218	7.2 ± 2.2	329	6.8 ± 1.8*
Glycemic Status (%)						
Normal	216	30.2	60	22.8	156	34.4
Pre diabetes	201	28.1	77	29.3	124	27.4
Diabetes	294	41.1	125	47.5	169	37.3
Use of hypoglycemic medications						
No	278	38.8	115	43.7	163	36.0
Yes	438	61.2	148	56.3	290	64.0

*p<0.05 compared to males by t test. † Age-adjusted means.

Table 1: Descriptive statistics of the sample (Mean ± SD† or %)

Most participants were females (63.3%) and mean age was 54.1±14.9 years. Most patients were overweight (38.8%) or obese (46.3%), had suboptimal vitamin D status (76.8%), had undiagnosed diabetes according to laboratory criteria (55.8%), and 39.1% were taking hypoglycaemic medications. Serum 25(OH)D levels and FBG were significantly higher in men compared to women (p<0.05).

Figure 1 shows the difference in mean 25(OH)D levels by glucose status. Overall, individuals classified as normal glucose status had higher 25(OH)D levels than those with diabetes (p<0.001), whereas subjects with pre-diabetes had higher 25(OH)D levels than those with diabetes (p<0.01). No significant difference was observed between subjects with normal glucose and those with pre diabetes (p=0.78). When analyzed separately by gender, those with normal glucose status had higher 25(OH)D levels than those with diabetes (p<0.001), but no significant differences were found in vitamin D levels between those with pre-diabetes and those with diabetes).



p<0.05 by ANCOVA, adjusting for age

Figure 1: Difference in 25(OH)D levels by glucose status, according to gender.

Correlations between 25(OH)D levels and glycemic parameters are shown in table 2. There was a significant inverse correlation between 25(OH)D levels and FBG (p<0.001), whereas participants with lower 25(OH)D levels had higher FBS levels in the total sample and in males. Similarly, there was a significant inverse correlation between 25(OH)D levels and HbA1c levels overall and in men (p<0.001), whereas those with lower 25(OH)D levels had with higher HbA1c levels. No correlation was seen with 2h-OGTT.

Glycemic Parameters	Total	Male	Female
FBG	– 0.10*	– 0.18*	– 0.09
2h OGTT	– 0.01	– 0.04	– 0.04
HbA1c	– 0.11*	– 0.23**	– 0.04

Table 2: Pearson's correlation† between 25(OH)D levels and glycemic parameters

In the multinomial logistic regression model, decreased serum 25(OH)D levels were associated with diabetes after adjusting for age, gender, BMI, and seasonality (Table 3). However, this was not observed with pre-diabetes status.

DISCUSSION

In the present study we found that mean serum 25(OH) D levels were significantly lower in individuals with diabetes compared to those with normal glycemic or pre diabetes. We also found a significant inverse correlation between serum

	Odds of pre diabetes (95% CI)			
25(OH)D (ng/ml)	**Crude**	**P value**	**Adjusted***	**P value**
<12 ng/ml	2.459 (0.671, 9.014)	0.174	2.140 (0.556, 8.231)	0.268
12 – 20 ng/ml	1.365 (0.725, 2.571)	0.335	1.222 (0.616, 2.424)	0.567
21 – 30 ng/ml	1.296 (0.762, 2.203)	0.338	1.392 (0.787, 2.462)	0.256
>30 ng/ml	1.00		1.00	
	Odds of diabetes (95% CI)			
25(OH)D (ng/ml)	**Crude**	**P value**	**Adjusted***	**P value**
<12 ng/ml	4.727 (1.566, 14.275)	0.006	4.195 (1.287, 13.666)	0.017
12 – 20 ng/ml	2.373 (1.419, 3.970)	0.001	2.422 (1.348, 4.354)	0.003
21 – 30 ng/ml	1.500 (0.963, 2.335)	0.073	1.773 (1.068, 2.942)	0.027
>30 ng/ml	1.00 (reference)			

*Adjusted for age, gender, BMI and seasonality.

Table 3: Multiple logistic regression of the association between 25(OH)D levels and risk of pre-diabetes and diabetes.

25(OH)D levels and glucose parameters, i.e., FBS and HbA1c, particularly in males. In addition, we found that risk of diabetes increased as levels of serum 25(OH)D levels decreased.

The inverse correlation between serum 25(OH)D levels and HbA1c found in the present study has also been reported in the US using data from the National Health and Nutrition Examination Survey in different racial/ethnic groups and in Caucasians from Italy.[24,25] Also, studies have found an inverse correlation between serum 25(OH)D levels and FBS, 2h-OGTT, and HbA1c in Caucasians in Germany and Finland ($p<0.001$).[23,26] We were unable to detect a significant negative correlation between 25(OH)D and 2 hours OGTT; this could be explained by the fact that insulin resistance was not reported in the medical records to make corrections in this variable, which is known to affect glucose metabolism.

The present study also found an increase diabetes risk as serum 25(OH)D levels decreased, which is consistent with the meta-analysis of Italian, British, Turkish, and Austrians cohort studies reported by Pittas et al.[8] Similarly, studies in individuals from southern Spain and from Greece have also found a higher incidence of diabetes in individuals with lower vitamin D status.[27,28] Furthermore, a study in Sweden found that individuals with pre diabetes and diabetes had lower vitamin D status compared to those with normal glycemia,[29] similar to results from the present study.

A possible mechanism for the relation between vitamin D status and diabetes is the presence of specific vitamin D receptors in pancreatic beta cells, which improves the function of insulin secretion.[30] A recent review suggests that vitamin D deficiency may lead to variations in insulin secretion, glucose intolerance, and diabetes, through a direct action of the vitamin D receptors activation or indirectly through calcemic hormones and also *via* inflammation.[31] Vitamin D may lower insulin resistance by its effect on phosphorus and calcium metabolism and by its effect on the regulation of the insulin receptor gene.[32]

Differences in the recommendations from the IOM and the US Endocrine Society's Practice Guidelines for the classification of vitamin D status reflect different goals and views on current evidence. Using the cut-off points established by the IOM, there are less individuals considered to have inadequate vitamin D status. The IOM levels were established with an endpoint in bone health while the Endocrine Society's cut-off points are more related to optimizing health for preventing endocrine related disorders, such as diabetes. Our results support the views of the Endocrine Society, as our study found that those with serum 25(OH)D levels >30 ng/ml had significantly lower risk of diabetes. Therefore, it is recommended that these cut-off points be used when considering the clinical management of patients with diabetes in this population of Puerto Ricans.

The present study provided the opportunity to describe the association between serum 25(OH)D levels and diabetes using a large sample of Hispanic adults in PR. The use of serum 25(OH)D as a measure of vitamin D status is an important strength because this measures total vitamin D (D2 and D3) status, which reflects vitamin D intake as well as vitamin D synthesized in the skin upon exposure to sun. However, our study has some limitations that merit discussion. First, the temporal relationship between vitamin D and glycemic status cannot be assessed in this cross sectional study. Second, this study was done at a single endocrinology clinic, thus our data are unlikely to be representative of the Puerto Rican population. Third, data on known and suspected risk factors for diabetes were not readily available (such as physical activity, family history of diabetes, central obesity, hypertension, dyslipidemia, and blood pressure), thus their potential confounding effects were not assessed. Longitudinal studies should be performed to confirm our findings in a larger and representative sample of Hispanics.

CONCLUSION

In conclusion, low vitamin D levels significantly increased the odds of diabetes in this sample of Hispanic adults in PR. Given that diabetes is one of the leading causes of death in US and PR and that Puerto Ricans have the highest prevalence of both diabetes and low vitamin D status compared to the US and other territories, it is important that health professionals regularly screen for vitamin D status and offer interventional strategies to correct vitamin D deficiency. These results may have significant public health implications for defining potential intervention and management of diabetes that may be easily implemented in the clinical setting in this high risk population.

NEW CONTRIBUTION TO THE LITERATURE

Low vitamin D status has been significantly associated with diabetes in other populations, mainly Caucasians; however, there is limited information in Hispanics, a group with a high prevalence of both diabetes and low vitamin D status. The present study confirms this association in a group of Hispanic adults in PR and adds to the available evidence for routinely screening this population for vitamin D deficiency.

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Research

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Study of the Central and Peripheral Autonomic Function in Short Evolutions Type 2 Diabetes and It's Risk Categories

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ABSTRACT

Objective: Early detection of Diabetic Autonomic Neuropathy (DAN) could help prevent serious complications and mortality associated with this condition in type 2 diabetes. We aimed to determine the prevalence of Sudomotor Autonomic Dysfunction, Cardiac Autonomic Dysfunction (SAD, CAD) in the early stages of glucose metabolism alterations, ranging from risk categories for type 2 diabetes (prediabetes) to recently established type 2 diabetes.

Research Design and Methods: It is a longitudinal, prospective and observational study (population consisting in 30 control subjects, 30 patients with increased risk for type 2 diabetes and 30 patients with type 2 diabetes ≤8 years of evolution. Study was carried out by designing a modified battery of Ewing. To study autonomic: resting Heart Rate (HR), deep inspiration, controlled breathing, 30/15, Valsalva maneuver, Sustained handgrip test (SHGT) and prolonged QTc indexes) and to study sudomotor: measurement of the Skin Conductance Response (SCR) deep inspiration, controlled breathing, standing to orthostasis, Valsalva maneuver and SHGT. The ECG and the Electrodermal response signal (EDR) was recorded while the patients execute the tests.

Results: Results were statistically analyzed by taking into account the group the patients belonged to, their anthropometric variables (directly measured) and their results from blood tests. Obtained results allowed us to determine the order in which every autonomic index passes from normal to abnormal and the corresponding nerve fibers involved.

Cardiac autonomic variables: resting HR: it is average value increases as the dysglicaemia progressed, significant differences were only found between the control and the type 2 diabetes group (p=0.041). Deep inspiration index: significant differences were only found between the increased risk group and the type 2 diabetes group (p=0.047). 42.9% of the control subjects, 39.1% of the increased risk patients and 59.3% of type 2 diabetes presented anomalous values for this index. Controlled breathing rate: significant differences were only found between the

control group and the type 2 diabetes group (p=0.008). 7.1% of the control subjects, 31.8% of the increased risk patients and 34.6% of type 2 diabetes presented anomalous values for this index. Significant differences were only found between the control group and the increased risk group (p=0.023).

Sudomotor autonomic variables: no significant differences were found between the groups for the average value of SCR, or anomalous values of SCR to the various autonomic stimuli studied. SCR-HR: we found significant correlation between the sudomotor response generated by the SHGT maneuver and the variation of the HR generated by this autonomic stimulus (p=0.036); not so for the remaining stimuli.

Conclusions: CAD appears to be the first manifestation of DAN and is already present in prediabetes and short evolution type 2 diabetes. This finding suggests an early impairment of parasympathetic fibers in disglycemic patients, and may help design preventive strategies aimed to avoid the severe complications related to this entity.

ABBREVIATIONS: DAN: Diabetic Autonomic Neuropathy; DN: Diabetic Neuropathies; AN: Autonomic Neuropathies; SAD: Sudomotor Autonomic Dysfunction; AD: Autonomic Dysfunction; EDR: Electrodermal response; SCR: Skin Conductance Response; OGI: Oral Glucose Intolerance; QSART: Quantitative Sudomotor Axon Reflex Test; HCUV: Hospital Clínico Universitario de Valladolid; OGTT: Oral Glucose Tolerance Test; BMI: Body Mass Index; BP: Blood Pressure; DM2: type 2 diabetes; QSART: Quantitative Sudomotor Axon Reflex Test; ADA: American Diabetes Association; NECP: National Cholesterol Education Program; ECG: Electrocardiogram; HOMA-IR: Model Assessment Index; HR: Heart Rate; SHGT: Sustained handgrip test; BPM: Beats per minute; CAD: Cardiac Autonomic Dysfunction; PCAD: Pathognomonic parasympathetic Cardiac Autonomic Dysfunction; SCAD: Sympathetic Cardiac Autonomic Dysfunction.

INTRODUCTION

Diabetic Autonomic Neuropathy (DAN) belongs to the group of diffuse Diabetic Neuropathies (DN), it is included in peripheral secondary Autonomic Neuropathies (AN) and carries a risk of vascular complications and sudden death, it is considered the most common AN in industrialized countries.[1]

Characterized by Sudomotor Autonomic Dysfunction (SAD) and Cardiovascular autonomic dysfunction (CVAD), DAN is the most frequent Autonomic Dysfunction (AD) with the greatest morbidity and mortality.[2]

Type 2 diabetes has a latency period estimated at 4-7 years, being in this time when the gluco-lipotoxicity on nerve fibers is just a functional and reversible damage. This damage progresses as type 2 diabetes evolves, passing through the stage of subclinical organic damage until reaching the stage of established clinical disease, where it becomes irreversible.[3]

Nerve conduction studies have shown the presence of AD in 10%-18% of patients with newly diagnosed type 2 diabetes and selective involvement of small sensitive somatic fibers in patients at increased risk for type 2 diabetes.[4,5]

These data suggest the presence of AD in stages prior to the diagnosis of type 2 diabetes, corresponding to the period of latency and increased risk for type 2 diabetes, previously known as "pre-diabetes",[6-12] making it essential to identify it through a screening test.

This study proposes to provide new ratings for AD, which apparently appears in type 2 diabetes and is possibly present in "pre-diabetes".

The controversies about the fact that the AD in diabetic patient is characterized by a SAD as first lesion continue, followed by other damages such as CVAD;[13-21] sudomotor and cardiac autonomic function have been studied in a group of patients at risk for type 2 diabetes and type 2 diabetes with short evolution, while keeping a control group.

Clinical tests for the assessment of sudomotor autonomic function include the Electrodermal response (EDR) triggered through autonomic stimulation. The phasic response is called a Skin Conductance Response (SCR), and consists of rapid changes in skin conductance level.[22]

The electrical skin conductance is related to the cholinergic sympathetic activity of the eccrine sweat glands; when sweat fills the pores, the corneum becomes more conductive. SAD hinders this activity, triggering a decrease in maximum glandular filling, reducing moisture of the skin and therefore its conductance level, which can be quantified by observing a value close to the null value[23,24] in the SCR registry.

Its inclusion in our study is also based on the suggestion made by several authors that in individuals with Oral Glucose Intolerance (OGI), a decrease in nerve conduction is found thus presenting an added risk of distal small fiber neuropathy.[6-10] Not to mention the association found between the OGI and the Quantitative Sudomotor Axon Reflex Test (QSART), which seems to support the theory that the OGI can affect the function of the autonomic small nerve fibers, and be the prelude of diabetic polyneuropathy[11] dysfunction.

Despite EDR having been recently proposed as an indicator in the evaluation of the diabetic foot,[24,25] there are few publications on SAD diagnosis in patients with type 2 diabetes using SCR;[26] and no studies in subjects with increased risk for type 2 diabetes can be found in literature.

In this context, we designed a prospective study aimed to determine the prevalence and types of autonomic neuropathy in patients at different stages of the natural history of type 2 diabetes: ranging from risk categories for type 2 diabetes to recently

establish.

RESEARCH DESIGN AND METHODS

It is a longitudinal, prospective and observational study designed at the beginning of 2009, carried out within the scope of the "Servicio de Medicina Interna del Hospital Clínico Universitario de Valladolid" (HCUV), with the collaboration of CARTIF´s Biomedical Engineering Division.

The ethical committee of the HCUV approved the designed experimental protocol.

Patient Selection

We included patients aged between 25 and 75 years diagnosed with type 2 diabetes of ≤8 years of evolution or its risk categories increased. Were excluded long-standing or severe complications, those who presented polyneuropathy or dysautonomia, acute heart disease, heart rhythm disorders and / or take medications that may modify.

All members expressed their approval of the study by signing the informed consent.

Criteria

The study population consists in 30 control subjects, 30 patients with increased risk for type 2 diabetes and 30 patients with type 2 diabetes ≤8 years of evolution, selected according to ADA's 2009 diagnostic.[1,27]

With the exception of those patients already diagnosed with type 2 diabetes, patients underwent an Oral Glucose Tolerance Test (OGTT). The group to which each of the patients belonged was established based on its results and those from previous blood analysis.

Anthropometric Variables Studied were

Age, sex, height, weight, Body Mass Index (BMI), waist and neck perimeter.

Epidemiologic Variables

Epidermiologic variables were collected from the information provided by the participant.

Smoking: consumption: <5 packages/year =1 (light consumption); 5-15 packages/year =2 (moderate); and >15 packages/year = 3 (serious).

Alcoholic beverages: zero consumption = 0; 1 cup/day =1; 2 cups/day =2; and ≥3 glasses/day =3.

Physical Activity

Physical activity was determined based on daily walk at a pace that would prevent fluid talking while walking and the weekly day's physical exercise. A person was considered to exercise if walking lasted more than 1 hour and if it was executed more than twice a week.

Clinic Variables

Hypertension: was established based on the measurements of Blood Pressure (BP) and data recorded in the clinical history. The recommendations of the 2007 guide of the European Society of hypertension and the European Society of Cardiology state that, BP ≥140/90 mm Hg must be considered hypertension. For patients with DM2, hypertension is diagnosed if BP ≥130/80 mm Hg according to the ADA in 2009.[1]

Dyslipidaemia: was used the criteria of The Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) from the National Cholesterol Education Program (NCEP), to determinate the lipids plasma concentration.

Ischemic heart disease was established on the basis of data provided by patients, data found in the clinical history and through the ECG measured in this study.

Cardiovascular family history was established by the presence of a family history of hypertension, hypercholesterolemia and hypertriglyceridemia.

Biological Variables

Two analytical determinations of each of the biochemical variables of interest were requested for our study in order to obtain the mean of the recorded values. Blood and urine tests were carried out under basal conditions and performed two days prior to study entry.

Hyperinsulinemia was defined as basal levels of insulinemia ≥16 mU/L.

Insulin Resistance (IR) was quantified with the Homeostatic model assessment index (HOMA-IR): multiplying the mean basal insulinemia (mU/L) and basal glycaemia (mg/dl), divided by 405. Border value for the Spanish population was set at HOMA-IR ≥3,8.[28]

HbA1c: normal v <7%.

HDL-c: values were considered abnormal below 40 mg/dl in men and 50 mg/dl in women according to the American Heart Association.

Micro-albuminuria: correlation albumin/creatinine of early morning urine samples was determined. Anomalous values were considered ≥30 mg/gr.

Uric acid: anomalous values were considered above 7 mg/dl in males and 6 mg/dl in women.

Homocysteinemia: anomalous values considered above 15 µmol/L.

Evaluation of Autonomic Function

Two sensors with isotonic conductive gel were placed on the fingertips of the second and third fingers of the non-dominant hand for the registration of the responses associated with distal innervation of the median nerve (SCR).[24] Similarly, standard electrodes needed to capture a conventional ECG comprising six bipolar derivations and three unipolar leads (V3, V4 and V5-V6) were placed.

Once all electrodes were placed, the SCR signal was monitored until its stabilization.

A BioPac MP 150 System® with a sampling frequency of 1 kHz was used for the registration of the SCR and the ECG.

For the detection of events in the ECG, a proprietary algorithm was developed in Matlab 7®, it automatically searches for events by using a modification of the algorithm proposed by Martínez.[29] This generates a log that is stored in digital format and was forwarded to CARTIF´s Biomedical Engineering Division for reading and interpretation.

After waiting twenty minutes at rest and maintaining a periodic breathing, Heart Rate (HR) was recorded and we then proceeded to the execution of the autonomic testing battery, based on DAN's statement.[30]

Afterwards, the variables were analyzed and diagnosis of CAD was established if ≥2 indexes with anomalous value were found.[31-33]

The studied cardiac autonomic variables: were resting HR, deep inspiration, controlled breathing, 30/15, Valsalva maneuver, Sustained handgrip test (SHGT) and prolonged QTc indexes.[30]

Resting HR: the average value the HR during the last 5 minutes of the 20 that the subject remains at rest and prior to the start of the battery. It was accounted in Beats per minute (BPM): normal values: ≤90, borderline: 91-99, anomalous: ≥100.

Deep inspiration index: difference between maximum HR during deep inspiration and the minimum HR within fifteen seconds. It is a value in BPM: normal values: ≥15, borderline: 11-14, anomalous: ≤10.

Controlled breathing rate: difference between the average of the HR during inspiration and average HR during exhalation registered during the controlled breathing maneuver. It is a value in BPM: normal values: ≥15, borderline: 11-14, anomalous: ≤10.

30/15 index: ratio between the 30th RR interval and the 15th RR 30s after standing up from rest to orthostasis. Normal values: ≥1.04, border: 1.01-1.03, anomalous: ≤1.00.

Valsalva index: ratio between the maximum RR interval registered within 45 seconds after the Valsalva maneuver and the minimum RR interval during the 15 seconds of the maneuver. Normal values: ≥1.21, border: 1.11-1.20, anomalous: ≤1.10.

SHGT index: we decided to determine the HR rather than the diastolic ABP during isometric, sustained muscle contraction; we then calculated the difference between the achieved maximum HR during this maneuver and the mean HR prior to the maneuver. We established the anomalous value as ≤12 bpm, on the basis of prior studies.[34-37]

Prolonged QTc interval: we proceeded to measure QT intervals during the ten minutes that the patient remained in dorsal decubitus. Martinez's algorithm was used to measure the position of the QRS complex.[29] Farina´s DWT algorithm was used for the correct measurement of the end of the T wave.[38-40] These QT intervals were corrected using Bazett's formula[41] to get the corrected QT interval (QTc) and finally, we calculated the average QTc in miliseconds for each patient: normal between 300-440 ms in men and 300-450 ms in women, borderline: 440-470 ms in men and 450-480 ms in women, abnormal: greater than 470 ms in men and 480 ms in women.

Sudomotor Autonomic Indexes

Measurement of the SCR is associated to a specific stimulus; each response is different in each repetition of the stimulus. We used the second response to a given stimulus for having the best amplitude for the maneuver before habituation to the stimuli occurred.

The following maneuvers can be associated with a SRC: deep inspiration controlled breathing, standing to orthostasis, Valsalva maneuver and SHGT; but the measurement of the SCR associated with the standing to orthostasis had to be discarded due to the electromyographic noise generated during postural change.

Statistical Analysis

A descriptive analysis of all collected variables was made. Quantitative variables are presented with their mean and standard deviation. The qualitative variables are exposed according to the distribution of frequencies. The association between qualitative variables of the three study groups was analyzed us-

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ing the Pearson's Chi-square test. In the event the number of cells with expected value <5 would be higher than 20, Fisher's exact test was used. The Pearson correlation coefficient was used to analyze the relationship between the SCR and the HR in various autonomic stimuli. The comparison of quantitative values was made through Student's t-test or Mann-Whitney's test in the case of two groups. Anova or Kruskal-Wallis H test were used when the number of groups was greater than 2. Test applied afterwards include Fisher's Least Significant Difference and Dunnett's test.

P-values <0.05 have been considered as statistically significant.

Data were analyzed using SPSS version 18.0 for Windows.

RESULTS

Anthropometric Variables: See Table 1

The overall prevalence of obesity was the 30.0% of the population plus a 44.4% of overweight (74.4% with BMI 25 Kg/$m^{2)}$. P-value (p=0.047) was found to be statistically significant between groups. We did not find statistical significance for the rest of the studied variables.

Epidemiologic and Biochemical Variables: Described in Tables 1 and 2

Statistical significance was found between the control and the type 2 diabetes group, both for the levels of HDL-c

	CONTROL	INCREASED RISK FOR TYPE 2 DIABETES	TYPE 2 DIABETES	
	Mean±SD (Minimum-maximum)	**Mean**±SD (Minimum-maximum)	**Mean**±SD (Minimum-maximum)	**p-value**
Age (years)	**47.4**±7.30 (31-61)	**53.7**±13.2 (27-75)	**56.4**±8.4 (28-67)	0.075
Male	**49.4**±7.4 (40-61)	**48.5**±13.3 (27-74)	**54.9**±10.6 (28-67)	-
Female	**46.6**±7.2 (31-58)	**59.6**±10.8 (43-75)	**58.4**±5.2 (47-66)	-
Height (meters)	**1.60**±0.10 (1.50-1.90)	**1.60**±0.10 (1.50-1.90)	**1.60**±0.10 (1.40-1.80)	0.992
Weight (kg)	**76.7**±27.4 (49.5-170.0)	**77.6**±18.8 (46.0-128.0)	**81.1**±17.7 (54.0-142.5)	0.733
BMI (kg/m^2)	**28.1**±7.3 (21.1-53.7)	**28.3**±4.9 (17.1-39.6)	**29.7**±4.4 (23.8-43.8)	0.510
Waist (cm)	**92.2**±16.8 (70.0-140.0)	**96.4**±12.0 (70.0-125.5)	**99.1**±11.5 (87.5-120.5)	0.169
Neck(cm)	**35.9**±4.8 (30.5-46.0)	**35.7**±3.9 (30.0 - 44.5)	**36.6**±3.3 (30.5 - 43.0)	0.785
Basal Insulin (mU/L)	**9.7**±7.8 (3.0-39.0)	**11.0**±5.0 (4.0-24.0)	**12.6**±9.9 (4.0-47.0)	0.389
HOMA-IR (mU/mmol)	**2.2**±1.8 (0.6-9.2)	**2.8**±1.2 (1.1-6.0)	**4.5**±3.4 (1.1-13.8)	**0.014+**
HbA1c (%)	**5.7**±0.3 (5.0-6.0)	**6.0** ± 0.3 (5.6 - 6.3)	**7.0** ± 1.1 (5.5 - 10.0)	**<0.001#**
Total cholesterol	**216.3**±41.1 (125.0-308.0)	**215.9**±36.9 (163.0-353.0)	**213.4**±31.7 (150.0-289.0)	0.946

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HDL-c (mg/dl)		**56.4**±17.5 (33.0-117.0)		**50.3**±13.4 (33.0-90.0)		**45.5**±15.8 (6.0-70.0)		**0.033+**
HDL-c male (md/dl)		**44.3**±13.8 (33.0-71.0)		**44.0**±8.8 (33.0-62.0)		**39.6**±15.7 (6.0-67.0)		-
HDL-c female (mg/dl)		**61.5**±16.6 (43.0-117.0)		**57.6**±14.2 (39.0-99.0)		**51.9**±13.7 (25.0-70.0)		-
LDL-c (mg/dl)		**137.6**±40.1 (61.2 - 228.8)		**139.2**±31.8 (66.0-226.0)		**130.0**±29.6 (73.8-201.4)		0.548
Triglycerides (mg/dl)		**112.1**±62.4 (45.0-334.0)		**131.2**±80.0 (57.0-413.0)		**192.1**±155.0 (51.0-781.0)		**0.041+**
µalbuminuria (mg/gr)		**5.0**±6.8 (2.9-19.6)		**3.3**±0.7 (2.9-5.6)		**7.3**±14.7 (2.9-447.0)		0.158
Uric acid (mg/dl)		**4.4**±1.4 (2.1-8.0)		**5.0**±0.9 (3.4-7.5)		**5.4**±1.5 (2.9-8.4)		**0.028+**
Homocistein (µmoles/l)		**9.3**±2.8 (5.0-18.0)		**9.6**±1.5 (7.0-12.0)		**10.8**±5.2 (7.0-33.0)		0.241
		n	**%**	**n**	**%**	**n**	**%**	**p-valor**
BMI (kg/m2)	**Normal**	13	43.3	7	23.3	3	10.0	**0.047***
	Overweight	12	40.0	15	50.0	13	43.3	
	Obesity	5	16.6	8	26.6	14	46.6	

* : control - increased risk - type 2 diabetes + : control - type 2 diabetes # : increased risk - type 2 diabetes

Table 1: Anthropometric and biochemical variables results.

(p=0.033), triglycerides (p=0.041), uric acid (p=0.028), hypertension, hypercholesterolemia and hypertriglyceridemia (p= 0.001) as well as for ischemic heart disease (p=0.005) and the HOMA-IR (p=0.014). The highest average value of HOMA-IR corresponded to the type 2 diabetes group.

No significant differences were found for the rest of the variables studied.

Cardiac Autonomic Variables: See Table 3

Resting HR: it is average value increases as the dysglicaemia progressed, significant differences were only found between the control and the type 2 diabetes group (p=0.041).

Deep inspiration index: significant differences were only found between the increased risk group and the type 2 diabetes group (p=0.047).

Controlled breathing rate: a progressive decrease of its average value was observed as dysglicaemia progressed, significant differences were only found between the control group and the type 2 diabetes group (p=0.008). Significant differences were only found between the control group and the increased risk group (p=0.023).

No significant differences were found in the rest of the indices studied.

Diagnosis of CAD: all patients who showed more than 2 indexes with anomalous were diagnosed with CAD, and therefore 30.2% of the control group; 42.9% of the increased risk group

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		CONTROL		INCREASED RISK FOR TYPE 2 DIABETES		TYPE 2 DIABETES		
		Mean±SD (Minimum-maximum)		**Mean**±SD (Minimum-maximum)		**Mean**±SD (Minimum-maximum)		**p-value**
Snuff consumption		**1.3**±0.9 (0-3)		**1.5**±1.3 (0-3)		**1.8**±1.2 (0-3)		0.138
Alcohol consumption (a)		**1.7**±1.0 (0-3)		**1.7**±0.9 (0-3)		**2.4**±0.6 (0-3)		0.204
		n	**%**	**n**	**%**	**n**	**%**	**p-value**
Smoking	**No**	12	40.0	9	30	10	33.3	
	Ex-smoker	6	20.0	14	46.6	10	33.3	0.247
	Yes	12	40.0	7	23.3	10	33.3	
Drinking	**No**	24	80.0	21	70.0	20	66.6	
	Ex-alcoholic	2	6.6	5	16.6	3	10.0	0.551
	Yes	4	13.3	4	13.3	7	23.3	
Daily walking	**<1 hour**	14	46.6	12	40.0	10	33.3	0.492
	≥1 hour	16	53.3	18	60.0	20	66.6	
Weekly exercise	**<2 days**	18	60.0	16	53.3	20	66.6	
	≥2 days	12	40.0	14	46.6	10	33.3	0.623
Hypertension		3	10.0	7	23.3	15	50.0	**0.001**
Hypertension family history		16	53.3	11	36.6	19	63.3	0.319
High cholesterol		8	26.6	11	36.6	23	76.6	**0.001**
High cholesterol family history		15	50.0	15	50.0	15	50.0	0.959
High triglycerides		3	10.0	6	20.0	15	50.0	**0.001**
High triglycerides family history		6	20.0	6	20.0	9	30.0	0.718
Ischemic cardiopathy		1	3.3	6	20.0	10	33.3	**0.005**
Ischemic cardiopathy family history		17	56.6	13	43.3	13	43.3	0.246

(a) Non consumption: 0; 1 glass wine/day: 1; 2 glasses wine/day: 2; ≥3 glasses wine/day: 3

Table 2: Clinical-epidemiologic variable results.

and 58.7% of the type 2 diabetes group, with a p-value =0.064.

Sudomotor Autonomic Variables: See Table 3

SCR-HR: we found significant correlation between the sudomotor response generated by the SHGT maneuver and the variation of the HR generated by this autonomic stimulus (p=0.036) (Figure 1); not so for the remaining stimuli.

No significant differences were found in the rest of the indices studied

CONCLUSIONS

The Type 2 Diabetes and Its Neuropathic Effect

Early detection of autonomic diabetic neuropathy could help prevent serious complications and mortality associated with this condition in type 2 diabetes patients. We aimed to determine the prevalence of Sudomotor Autonomic Dysfunction and Cardiac Autonomic Dysfunction (SAD, CAD) in the early stages of glucose metabolism alterations, ranging from risk categories for type 2 diabetes (prediabetes) to recently established type 2 diabetes.

The last adaptation on the classification of DN and data revealed by recent studies[4-11,42] suggest the presence of AD in the stages prior to the diagnosis of type 2 diabetes, which justifies our study.

Given that there is still no consensus on the use of cer-

	CONTROL		INCREASED RISK FOR TYPE 2 DIABETES		TYPE 2 DIABETES		
	Mean±SD (Minimum-maximum)	**Mean at 95%** (inferior limit-superior limit)	**Mean**±SD (Minimum-maximum)	**Mean at 95%** (inferior limit-superior limit)	**Mean**±SD (Minimum-maximum)	**Mean at 95%** (inferior limit-superior limit)	**p-value**
Resting HR (bpm)	**69.10**±11.72 (46.12-92.88)	(64.55-73.64)	**73.95**±12.72 (51.11-112.7)	(68.31-79.59)	**77.62**±12.14 (49.88-98.04)	(72.72-82.53)	**0.041+**
Deep inspiration index (bpm)	**14.00**±8.97 (1.30-35.77)	(10.52-17.47)	**16.61**±11.85 (4.31-54.07)	(11.49-21.74)	**10.05**±6.81 (1.61-25.91)	(7.36-12.75)	**0.047#**
Controlled breathing index (bpm)	**23.14**±8.85 (4.29-41.00)	(19.71-26.57)	**19.01**±11.07 (3.78-48.04)	(14.10-23.92)	**14.97 ±** 8.12 (2.98 - 28.07)	(11.69-18.25)	**0.008+**
Valsalva index	**1.54**±0.37 (0.88-2.33)	(1.40-1.68)	**1.56**±0.35 (1.13-2.52)	(1.42-1.70)	**1.50**±0.46 (1.03-2.94)	(1.32-1.68)	0.874
30/15 index	**1.20**±0.16 (1.00-1.63)	(1.13-1.26)	**1.17**±0.15 (1.00-1.62)	(1.10-1.24)	**1.15**±0.07 (1.03-1.31)	(1.12-1.17)	0.315
SHGT index (bpm)	**7.58**±6.58 (10.22-23.08)	(5.02-10.13)	**9.78**±5.92 (2.54-24.09)	(7.15-12.40)	**10.51**±6.57 (0.00-33.41)	(7.85-13.16)	0.223
QTc (ms)	**370**±30 (300-420)	(360-390)	**380**±30 (340-460)	(370-400)	**380 ±** 30 (330-430)	(370-390)	0.721
SCR (deep inspiration)	**0.30±0.25 (0.00-1.06)**	(0.20-0.39)	**0.24±0.17 (0.00-0.67)**	(0.16-0.31)	**0.30±0.24 (0.04-1.16)**	(0.21-0.39)	0.533
SCR (controlled breathing)	**0.18±0.19 (0.00-0.85)**	(0.10-0.25)	**0.14±0.12 (0.00-0.48)**	(0.09-0.19)	**0.19 ±0.13 (0.00-0.56)**	(0.14-0.25)	0.475
SCR (Valsalva maneuver)	**0.23±0.23 (0.00-1.23)**	(0.14-0.32)	**0.23±0.16 (0.00-0.61)**	(0.16-0.29)	**0.32±0.31 (0.00-1.21)**	(0.20-0.45)	0.258
SCR (SHGT maneuver)	**0.20**±0.15 (0.00-0.65)	(0.14-0.26)	**0.18**±0.11 (0.05-0.40)	(0.13-0.23)	**0.21**±0.15 (0.00-0.69)	(0.15-0.28)	0.734

+: control - type 2 diabetes #: increased risk - type2 diabetes

Table 3: Autonomic variable results.

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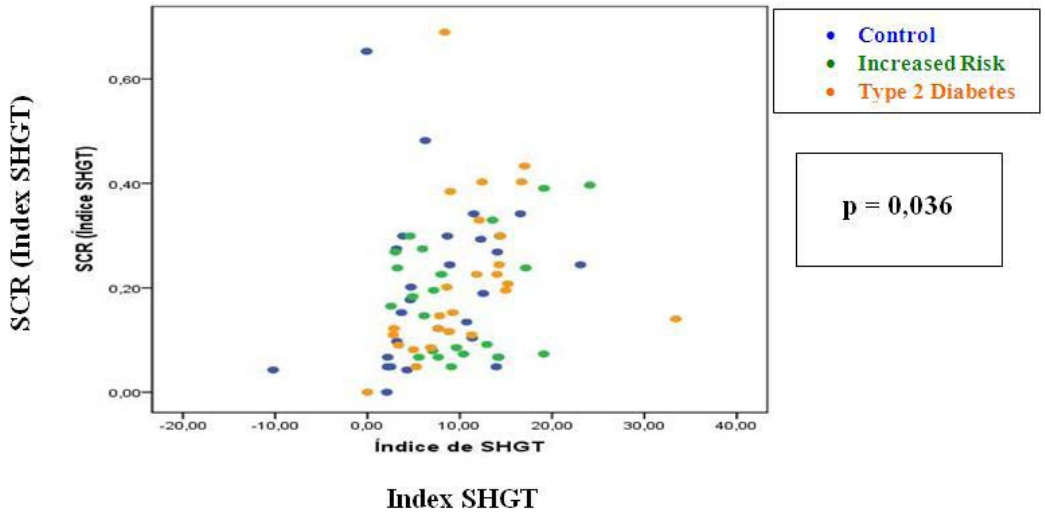

Figure 1: Relationship between the sudomotor response generated by the SHGT maneuver and the variation of the HR generated by this autonomic stimulus.

tain standardized methodology, autonomic tests battery proposed by Ewing et al. continue to be the gold standard for the diagnosis of CVAD.[31] This situation led to its use as a base from which we developed the battery of autonomic tests for our study, which was completed following the guidelines provided by the ADA in its statement about for the diagnosis of CVAD.[30]

The Cardiac Autonomic Variables and Diagnosis of CAD

Before an autonomic stimulus, the loss of variation in the HR is considered a Pathognomonic parasympathetic CAD (PCAD) marker; while the registration of a fixed HR is an accurate indicator of PCAD and Sympathetic CAD (SCAD).[32] Regarding the deep inspiration index, the statistical significance found for the average value between the type 2 diabetes and increased risk for type 2 diabetes and the average value of the type 2 diabetes group, approach to the abnormality, this reflects a trend towards PCAD. Detection of anomalous values for the 30/15 index in the increased risk group indicates the presence of PCAD.

Given the important influence that the respiratory rate has on the variation of the HR, being its modulation almost in it is entirely of vagal origin; finding anomalous values to the autonomic stimulation of controlled breathing reflect the existence of a functional compromise of the Parasympathetic Nervous System (PNS).

It is known that during SHGT there is a rise in HR, and we would expect this rise to decrease as dysglicaemia progresses, being that HR is particularly sensitive to the dysfunction of sympathetic fibers from the right stellate ganglion.[34-37] Not having registered null values for the various indexes, together with results from the HR's response during SHGT, the integrity of the responsible for the regulation of the heart's chronotropism sympathetic component can be established, at least in the increased risk group. However, the fact finding participants with abnormal values for the Valsalva index in the type 2 diabetes group, speak in favour of a possible SCAD accompanying the PCAD already present in this group.

Finally, the absence of participants with prolonged QTc, reveals the integrity of left stellate ganglion sympathetic fibers. However, there may be fiber injury without being reflected in QTc prolongation. The heart acts as a syncytium and requires global damage of the sympathetic component to be observed in QTc.

The idea of using the controlled breathing index as a screening test is strengthened. It is the first component of the CAD related to altered dysglicaemia,[33] after this first altered index, the following would be: deep inspiration, 30/15 index and Valsalva index in order to establish the diagnosis of CAD based on the presence of ≥ 2 abnormal indexes, as proposed by the ADA and the AAN.[31]

The fact of finding control subjects with ≥ 2 abnormal indexes for CAD, speaks in favour of other reasons beyond dysglicaemia; although it could also be participants with "hidden pre-diabetes" not shown in the requested analytical determinations.

The Sudomotor Autonomic Variables and Diagnosis of SAD

For the study of the sympathetic component at peripheral level we used the SCR since the eccrine sweat glands present at the fingertips react weakly to heat but intensely to autonomic stimuli and reflect only the nerve activity of cholinergic

postganglionic sympathetic fibers of the median nerve.

Since no significant differences among the studied groups were found for any of the sudomotor responses generated by different autonomic stimuli; no presence of SAD can be detected.

The presence of a low percentage of patients in every group with null SCR values, can be related to a source of SAD outside the dysglicaemia despite the preventive measures taken before the study: hand washing, abundant use of isotonic conductive gel, recording the signal in the non-dominant hand to avoid neural mechanical wear of the nerve; without forgetting that the detection of the SCR in the chosen fingertips, reflects SAD in relation to a single nerve and distal level.

The Presence of Autonomic Dysfunction

Considering parasympathetic preganglionic fibers, results from this study demonstrate the presence of PCAD, both in the group of patients with increased risk and in the type 2 diabetes group.

Regarding the right stellate ganglion's sympathetic fibers, abnormal results found with the Valsalva maneuver show a possible SCAD in the group of patients with short evolution type 2 diabetes; while the group of patients with increased risk we found no proof of SCAD.

Concerning left stellate ganglion sympathetic fibers, the non-presence of patients with prolonged QTc interval shows the integrity of the fibers.

SAD secondary to dysglicaemia cannot be detected in connection to cholinergic postganglionic sympathetic fibers.

Signs make us suspect that SAD is not the first autonomic injury and therefore does not precedes the PCAD already present in patients with increased risk for type2 diabetes, and followed by a possible SCAD in the group of patients with short evolution type 2 diabetes.

In conclusion, signs indicating autonomic neuropathy are already present in patients at risk for type 2 diabetes, being its prevalence higher in patients with recently diagnosed type 2 diabetes. Whereas diabetic patient's exhibit signs suggesting parasympathetic and sympathetic involvement, prediabetic subjects show only cardiac autonomic dysfunction, which supports the notion, that parasympathetic fiber are the ones initially affected by dysglicemia-related glycolipotoxicity. These findings may contribute to optimise preventive strategies aimed to early detect autonomic neuropathy in dysglicemic patients, even before they become diabetics.

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F.J.P.B., P.V.R.F. and E.G.S. were responsible to develop the article, M.I.F.G., J.F.A. and J.P.T. Contributed to the data analysis and writing the comments of the manuscript and M.F.M.M. the statistical analysis

CONFLICTS OF INTERESTS

The authors declare not to have potential conflicts of interest.

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Short Communication

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Reduced Sampling Schedules for Calculation of an Insulin Sensitivity Index from the Liquid Meal Tolerance Test

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ABSTRACT

Background: The objective of this study was to evaluate the performance of the Matsuda index of insulin sensitivity (MISI) calculated using reduced sampling schedules.
Methods: Relationships between MISI values from a Liquid Meal Tolerance Test (LMTT) and insulin sensitivity (S_I) derived from an intravenous glucose tolerance test were assessed in 24 overweight/obese subjects (67% women) without diabetes.
Results: Significant correlations were found between S_I and 1) MISI calculated from 0, 30, 60, 90, and 120 min ($r=0.776$, $p<0.0001$); 2) MISI calculated from 0, 60, and 120 min ($r=0.815$, $p<0.0001$); and 3) MISI calculated from and 0 and 120 min ($r=0.848$, $p<0.0001$).
Conclusion: MISI from LMTTs calculated using reduced sampling schedules (0, 60, 120 min or 0, 120 min) may be useful, lower cost options for assessment of insulin sensitivity in population studies and large clinical trials.

KEYWORDS: Type 2 diabetes mellitus; Insulin resistance; Insulin sensitivity; Glucose tolerence test.

INTRODUCTION

The Matsuda composite index of insulin sensitivity (MISI) has been widely used as a measure of whole body insulin sensitivity in clinical and epidemiological research. Recently, reduced sampling schedules for calculation of the MISI from an Oral Glucose Tolerance Test (OGTT) have been shown to produce values that correlate well with insulin sensitivity measured by the euglycemic clamp method.[1] However, a mixed meal represents a more physiologic stimulus than an oral glucose load. Because insulin resistant states are associated not only with disturbances in carbohydrate metabolism, but also with disturbances in postprandial lipid and hormonal responses, a mixed meal stimulus allows assessment of additional variables of potential interest such as postprandial triglyceride, incretin and appetite regulation hormone responses. These variables change minimally in response to a glucose-only stimulus. Additionally, a liquid meal allows for simpler standardization across research sites, particularly research sites in different countries, where it may be difficult to obtain standard products for a solid meal test.[2,3] Therefore, the objective of this study was to evaluate the performance of the MISI derived from Liquid Meal Tolerance Test (LMTT) data, calculated using reduced sampling schedules, compared with the insulin sensitivity index (S_I) derived from minimal model analysis of data from an insulin-modified Intravenous glucose tolerance test (IVGTT) in overweight and obese subjects.

SUBJECTS AND METHODS

These data were collected as part of a previously published validation study in overweight and obese men and women without diabetes, the details of which have been described previously.[4] Briefly, subjects included men and women with waist circumference ≥102 cm and

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≥89 cm, respectively, and a body mass index <35.0 kg/m^2. Exclusion criteria included body mass index ≥35.0 kg/m^2; abnormal laboratory values of clinical importance, history of clinically important endocrine, cardiovascular, renal, pulmonary, hepatic, biliary, or gastrointestinal disease; recent history of cancer, major trauma or surgery, or a current infection. Subjects with habits that might confound the results (e.g., alcohol or substance abuse, extreme dietary or exercise habits) or using systemic medications known to influence carbohydrate metabolism were also excluded.

For the insulin-modified IVGTT, 300 mg/kg body weight intravenous glucose (50% dextrose solution) was administered over approximately 1.5 min at t=0 min. At t=20 min, intravenous regular human insulin (0.03 U/kg, diluted to 10 mL with normal saline) was administered over approximately 1 min. Blood samples were collected at the following pre- and post-glucose infusion time points: t=-10, -5, 3, 5, 7, 10, 12, 14, 16, 19, 22, 25, 30, 40, 50, 60, 75, 90, 120, 150, and 180 min. Plasma glucose and insulin values were entered into the Minmod Millennium program (Version 6.02; RN Bergman, USC, Los Angeles, CA, USA) for determination of S_I.[5]

For the LMTT, subjects consumed within 10 minutes, two 8 oz servings of a liquid meal (Ensure®, Abbott Nutrition, Columbus, OH, USA) providing a total of 500 kcal, 84 g carbohydrate, 12 g fat and 18 g protein. Blood samples were obtained from an indwelling intravenous catheter for analysis of plasma glucose and insulin concentrations at t=-1, 30, 60, 90, and 120 min, where t=0 min was the start of the LMTT. The MISI was calculated as $10{,}000/(G_0 \times I_0 \times G_m \times I_m)^{0.5}$ where G_0 and I_0 were pre-meal values for Glucose (G) and Insulin (I) and Gm and Im were mean post-meal values using all sample time-points as well as subsets of the available samples.[6] The strengths of the relationships between MISI values from the LMTT and S_I from the IVGTT were assessed using linear regression analysis and Pearson correlation coefficients.

RESULTS

Participants included primarily non-Hispanic white (83%) generally healthy men (n=8) and women (n=16) with a mean (±SEM) age 48.9±2.0 years, BMI 30.8±0.6 kg/m^2 and waist circumference 104.3±1.6 cm. On the day of the IVGTT, fasting glucose was 5.5±0.1 mmol/L, insulin was 57.0±7.8 pmol/L, and S_I was 6.57±1.15 (10^{-5} × pmol / L^{-1} × min^{-1}). MISI from an LMTT on a separate day was 19.1±2.4 (pmol/L^{-1} × mmol / L^{-1}). Glucose and insulin responses to the LMTT are presented in Figure 1. All possible combinations of pre-LMTT (t=0 min) and post-LMTT sampling time points were assessed. Pearson correlation coefficients between S_I and MISI were as follows: 0, 30, 60, 90, and 120 min (full schedule), r=0.776 (p<0.0001), MISI=8.3+2.7 (S_I); 0, 60, and 120 min, r=0.815 (p<0.0001), MISI=7.7+3.3 (S_I); and 0 and 120 min, r=0.848 (p<0.0001), MISI=10.6+3.2 (S_I).

CONCLUSIONS

Because impaired insulin sensitivity has a central role in the pathogenesis of type 2 diabetes mellitus and metabolic disturbances that increase risk for atherosclerotic disease, simple and cost-effective techniques for assessing insulin sensitivity are of value for use in clinical and population studies. Results from previous studies indicate that the MISI calculated from OGTT, LMTT, or mixed solid meal tolerance tests correlate well with measures of insulin sensitivity derived from IVGTT minimal model and euglycemic clamp data.[1,4,7-10]

The present results are in agreement with those from DeFronzo and Matsuda,[1] who reported that calculation of the MISI from an OGTT using reduced sampling schedules produced values that correlated well with insulin sensitivity measured by the euglycemic clamp method. It should be noted that results calculated using different sampling schedules are not numerically interchangeable.[1] In their study and in the present investigation, the relationship was strengthened somewhat by exclusion of the 30 min value, and the strongest association was present when only the pre-load and 120 min values were used. The standard deviation of the 30 min insulin concentration was more than two-fold higher than that for the 120 min value (Figure 1). Even after excluding one very insulin resistant subject, the standard deviation of the 30 min insulin concentration remained approximately one-third higher than the 120 min

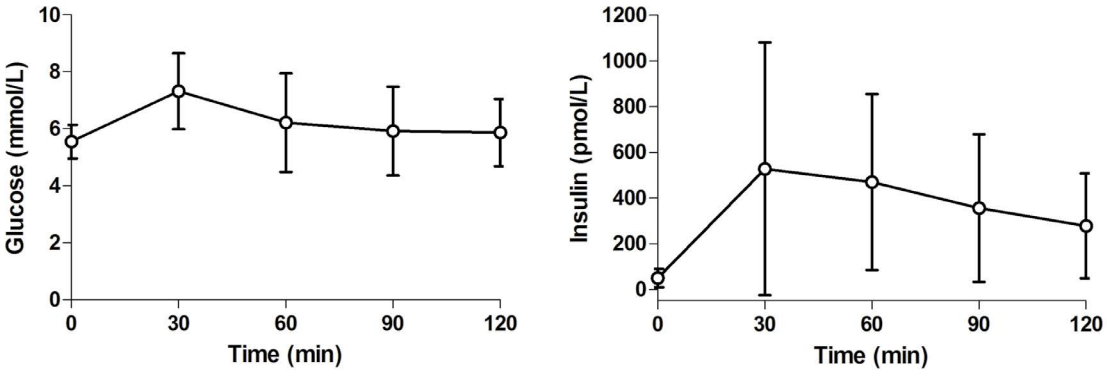

Figure 1: Glucose and insulin responses to a liquid meal tolerance test (LMTT). Data Presented as mean±standard deviation.

value. Thus, exclusion of the 30 min value may reduce variability, enhancing the precision of the point estimate for the MISI. In addition, differences in the relative contributions of hepatic and peripheral insulin sensitivities might have an impact on the strength of the relationship between MISI and other measures of insulin sensitivity. Abdul-Ghani et al.[11] found that glucose values during the first 30 min of an OGTT were closely related to hepatic insulin sensitivity, whereas values later in the test correlated more strongly with skeletal muscle insulin sensitivity.

Because this was a sub-study[4] to a clinical trial[12] that specifically selected overweight and obese subjects with increased waist circumference, generalization of these results may be limited. Replication of these results in a wider range of subjects, including those with normal glucose tolerance and various manifestations of pre-diabetes is needed. It would also be of interest in future research to compare the performance of the MISI calculated from the OGTT and LMTT to directly evaluate the influence of the type of carbohydrate load employed on the performance of the MISI.

In summary, the primary findings from this analysis suggest MISI values obtained from reduced sampling schedules (0, 60, 120 min and 0, 120 min) may be useful for application in population studies and large clinical trials.

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KCM was responsible for the study concept and design and reviewed and edited the manuscript; CMC prepared the manuscript; KK and AL were study physicians who collected data and were involved in the design of the trial and interpretation of results; ALS performed all statistical analyses; MRD and TMR wrote the manuscript for the original validation study and reviewed and edited the present manuscript.

AUTHOR DISCLOSURE STATEMENT

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