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DEXAMETHASONE STRESS TEST: A PILOT CLINICAL STUDY FOR IDENTIFICATION OF INDIVIDUALS HIGHLY PRONE TO DEVELOP TYPE 2 DIABETES

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Abstract

OBJECTIVE

We examine whether "Dexamethasone Stress Test" exhibits the requisite high predictive ability to identify individuals highly prone to develop type 2 diabetes (T2DM).

METHODS

Seven years ago, we administered an oral glucose tolerance test (OGTT) to 33 individuals without T2DM and repeated the OGTT 24 h after a single oral dose of 8 mg dexamethasone (Dex); all participants had a first-degree relative with T2DM, and close to half had prediabetes. We calculated Receiver Operating Characteristic (ROC) curves for all parameters derived from the OGTT before and after Dex in individuals who subsequently developed diabetes compared to individuals who did not.

RESULTS

At seven years of follow-up, nine individuals had developed T2DM while 24 remained without diabetes. None of the OGTT-derived parameters before administration of Dex had an area under the ROC curve of > 0.8. However, 24 h after Dex, three parameters including fasting plasma insulin, Homeostatic Model Assessment- Insulin Resistance (HOMA-IR), and 2-h plasma glucose level exhibit areas under the ROC curves of 0.84, 0.86, and 0.92, respectively.

CONCLUSIONS

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The “Dexamethasone Stress Test” appears to be a good to excellent test in identifying individuals highly prone to develop T2DM.

Key words: HOMA-B, Insulinogenic index, Matsuda Index, Area under the curve (AUC) for glucose, Area under the curve (AUC) for insulin,

Abbreviations:

AUC = Area under the curve, **BMI =** Body Mass Index, **DEX =** Dexamethasone, **DEX Stress Test =** Dexamethasone Stress-Test**, HOMA-IR =** Homeostatic Model Assessment- Insulin Resistance, **IUMS =** Isfahan University of Medical Sciences, **OGTT =** oral glucose tolerance test, **NGT =** normal glucose tolerance, **PreDiab =** Prediabetes, **ROC =** Receiver Operating Characteristic, **T2DM =** Type 2 diabetes.

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Introduction

The pandemic of type 2 diabetes (T2DM) affects millions of people worldwide with the developing world having the highest incidence (1-3). The rising incidence and prevalence of T2DM is in large part due to increased dietary caloric intake and decreased physical activity (4, 5). Several patient characteristics – or risk factors - lead to greater predisposition to developing T2DM; these include having prediabetes, having a first-degree relative with T2DM, being obese or a smoker, or having hypertension or dyslipidemia (6-8). However, none of these factors either singly or in combination have exhibited the requisite high predictor value in identifying a very large fraction of people that are highly prone to develop the disease (6, 8). For example, most overweight or obese people, and many individuals with prediabetes, do not develop T2DM over the subsequent years (4, 5). Nevertheless, identification of people at very high risk to develop T2DM is of great importance in guiding our efforts and utilizing our resources that are needed for prevention of the disease.

We designed a study seven years ago to explore the predictive value of the "Dex Stress Test". We based the idea of using Dex on the well-known stimulatory effect of glucocorticoids to increase hepatic glucose production and to increase insulin resistance in peripheral tissues including the liver (9-11). In fact, several previous studies had raised the possibility that the response to exposure to glucocorticoids could potentially be used to identify persons prone to developing T2DM (12-19). What we added to the above studies and to our proposed was to challenge with a glucose load added to an acute exposure to Dex.

The current analysis is the outcome of the study that was initiated seven years ago to examine the effect of Dex on glucose homeostasis; all enrolled individuals had a first-degree relative with T2DM (20). Following an OGTT (to exclude T2DM), 43 individuals received an 8 mg oral dose of dexamethasone followed by an OGTT the next morning (20).

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We used 8 mg dose of Dex for the "Dex Stress Test" based on our earlier observations using repeated OGTTs in a group of healthy adult males and females with no family history of T2DM testing the effect of a single dose of 2, 4, and 8 mg Dex on glucose homeostasis (21). We found that, when compared to the OGTT before Dex, the 8 mg dose of Dex resulted in the greatest increment in insulin secretion and insulin resistance. Furthermore, the high excursions in glucose and insulin levels observed during the OGTT performed at 24 h after Dex were largely dissipated at 48 h (21). Based on the above, we reasoned that the glucose load given for the OGTT combined with the effects of Dex on glucose homeostasis could potentially identify at-risk individuals with a high predictive value.

We performed an OGTT (seven years ago) in 43 individuals with NGT or with PreDiab before and 24 h after receiving the 8 mg dose of Dex (20). The present analysis is the outcome of the above study with the aim of assessing whether the "Dex Stress Test" has the requisite predicative ability to identify individuals that will develop T2DM. Of 43 persons in the original NGT plus PreDiab groups who received Dex (20 persons in the PreDiab group and 23 persons in the NGT group), we have follow-up data on 33 individuals at 7 years of follow-up; the group is comprised of 24 persons who have remained without diabetes and 9 individuals who developed T2DM. Here, we examine whether any of the parameters derived from the OGTTs performed either before or 24 h after the 8 mg dose of Dex in the 9 individuals who developed T2DM differed from values in the 24 participants who also received Dex but did not develop diabetes.

Methods

The study was initiated at (and funded by) the Isfahan Endocrine and Metabolism Research Center (IEMRC) in Isfahan University of Medical Sciences (IUMS), Iran, between October 2009 and May 2010. Ethics Committee of IUMS approved the study design and

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consent process in accordance with the Declaration of Helsinki. The full study protocol is available at IEMRC.

Baseline data of the original study group performed 7 years ago was reported previously (20). 43 individuals had an OGTT, received 8 mg Dex, and had a repeat OGTT 24 h after Dex. In the subsequent 7 years of follow-up, 5 persons each from the prediabetes and NGT groups were lost to follow-up. The current analysis is based on 33 individuals in whom we have follow-up data. Diagnosis of T2DM at seven years of follow-up was based on a repeat OGTT performed on all 33 participants according to the American Diabetes Association criteria (22). Calculation of the parameters derived from the OGTTs was described previously (20, 21). Here, we compare parameters of glucose homeostasis derived from before and after receiving Dex 7 years ago in those who did and did not develop T2DM. Receiver Operating Characteristic (ROC) curves were calculated for all the metabolic parameters derived from the OGTT performed prior to receiving Dex and at 24 h after Dex. We used the trapezoid method to calculate the area under the curve (AUC) of each ROC curve. We considered parameters with AUCs exceeding 0.80 to have a good to excellent predictive value (23) in identifying persons highly prone to develop T2DM. Unless specified, data are shown as mean ± standard error (SE) and Student's t-test was used and $p<0.05$ was considered significant.

Results

At 7 years of follow-up, data on 33 individuals (15 persons from the PreDiab and 18 from the NGT group) in the original 43 persons who had received Dex is available; 10 individuals were lost to follow-up. Nine individuals developed T2DM at follow-up; seven were from the original PreDiab and 2 from the NGT group.

Baseline characteristics of the 33 individuals who received Dex is summarized in Table 1. The predominance of females in large part reflects the unequal distribution in the

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original study (20). Individuals who developed diabetes were younger, had higher body weight, BMI, waist circumference, and systolic and diastolic blood pressure; however, only the difference in body weight was highly statistically significant between the two groups.

Table 2 summarizes glucose and insulin levels measured during the OGTT performed seven years ago in individuals currently without and those with diabetes; values are shown from both before Dex and 24 h after the 8 mg dose of Dex. Also shown (in the far right column) is the statistical significance of changes in glucose and insulin levels 24 h after Dex in individuals who did not versus those who developed T2DM. In both groups, all blood glucose and insulin levels were higher at all time-points of the OGTT after Dex in both groups. In addition, at all-time points, all values after Dex were higher in those who developed T2DM compared to those who did not. However, after Dex, only fasting glucose, 2-h glucose, and fasting insulin levels were significantly different between the two groups.

Table 3 shows parameters of insulin sensitivity and insulin resistance calculated from the results listed in Table 2 using equations detailed previously (20). Of note, HOMA-IR, HOMA-B, AUC of insulin and AUC of glucose were higher and Matsuda index was lower in both groups following Dex. Similar to Table 2, the column on the far right shows the statistical significance between parameters in individuals after Dex who did not and those who developed T2DM. Of note, highly significant differences after Dex between the two groups included increases in HOMA-IR and AUC for glucose, and a decrease in Matsuda Index consistent with greater insulin resistance in response to Dex in those who subsequently developed diabetes.

We determined the AUC of Receiver Operating Characteristic (ROC) curves for all values measured at baseline before Dex and 24 h after Dex to evaluate their predictive strength in identifying individuals at high risk for developing T2DM (Table 4). AUC of ROCs above 0.8 is considered to have a good to excellent predictive value (23). AUCs measured

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before Dex ranged from 0.53 to 0.78. After Dex, there was no systematic trend for the AUCs to increase or decrease, although many increased. However, AUC of three parameters increased and became greater than 0.80, including areas under ROC curves for fasting insulin (0.84), HOMA-IR (0.86), and 2-h glucose (0.92). Figure 1 shows the sensitivity and specificity of these three parameters using two different "cut-points" for each ROC graph.

Discussion

Identification of individuals prone to develop T2DM with requisite high predictive ability has been difficult (6-8, 24). The results of this study show that the homeostasis parameters derived from the OGTT performed before Dex all had AUCs of ROC curves ≤ 0.78 (0.53-0.78) with some having AUCs between 0.70 and 0.78 signifying modest to moderate predictive value. However, three parameters measured 24 h after an 8 mg dose of Dex appear to be good to excellent predictors of development of T2DM in subsequent years. The known increase in insulin resistance after Dex (9-11), added to the glucose load of the OGTT appears to bring about the largest change in many parameters of glucose homeostasis. The most predictive parameters with AUCs of greater than 0.80 after Dex were fasting insulin, HOMA-IR, and 2-h glucose level during the OGTT. It is worth noting that two of these three parameters (fasting insulin level and HOMA-IR) require only a fasting blood sample, and hence lend themselves to a less complex and perhaps a more useful and practical screening test.

Our results are in general agreement with previous studies. Durck *et al* performed OGTTs on normoglycemic individuals with a first-degree relative with T2DM before and after treatment with 2 mg Dex twice a day for four days (25). They noted that fasting and 2-h glucose values and HOMA-IR measured at baseline were the best predictors of dysglycemia at 10 years; of note, four individuals from the original group of 20 had developed diabetes

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during the 10 years. Other investigators have reported that sensitivity of beta-cells to glucose and whole-body insulin sensitivity (26), and first-phase insulin release in response to glucose (27) are good markers of future development of T2DM over the course of five and 25 years, respectively. Finally, Hanley *et al* reported that beta-cell function and whole-body insulin resistance derived from IVGTT were good predictors of T2DM over a five-year period (28), and Ferrannini *et al*, using OGTT, found fasting and 2-h glucose were independent predictors of risk for development of T2DM over a seven year period (29). The present study extends these observations by supplying ROC curves with sensitivity and specificity values.

The present study has some limitations. First, this was a relatively small pilot study performed as proof of concept. Hence, the "Dex Stress Test" requires validation in large population-based studies in different ethnic groups. Second, we used an 8 mg dose of Dex and it is possible that a somewhat higher dose (e.g.12 mg) would have resulted in higher discrimination. Third, the study had enrolled significantly more females than males, which may have skewed the results. Finally, the observed rate of conversion to T2DM in this study (with 9 out of 33 individuals over seven years) is lower than some previous reports (30-32); the reasons for this finding are not known but might reflect differences in ethnic background.

Conclusions

We conclude that the "Dex Stress Test" appears to be a good to excellent predictive test for identifying persons that are highly prone to develop T2DM. Once validated in a large population-based study, the test would have great utility in focusing our resources and efforts for prevention of diabetes on those individuals that are highly prone to develop the disease.

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Conflict of interest:

Drs. Taheri, Aminorroaya, and Amini have no duality to disclose. Dr. Ismail-Beigi has received research grants from NIH and Novo-Nordisk, is a consultant to Sanofi, BAYER, and COVANCE, and has shares in Thermalin Diabetes; there is no conflict with this study.

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Role in the Study:

Dr. Taheri performed the study under supervision of Drs. Amini and Aminorroaya. Dr. Ismail-Beigi reviewed the data and wrote the first draft. All authors have had input into the manuscript and agree with the submitted version.

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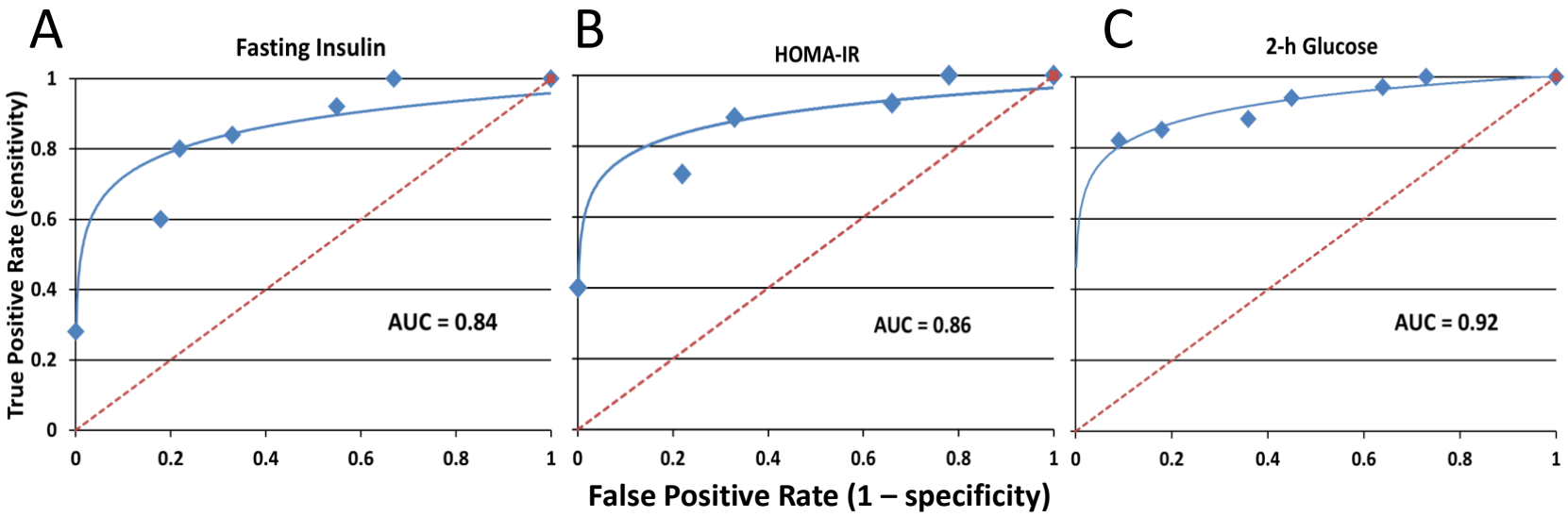

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> 15	60%	88%
> 20	84%	67%

	Sens.	Spec.
> 4	72%	88%
> 5	88%	67%

	Sens.	Spec.
> 190	85%	88%
> 200	88%	74%

Figure 1. ROC curves for Fasting Insulin concentration (µIU/mL), HOMA-IR [(mg * µIU) ÷ (dl * ml)], and 2-h Glucose (mg/dl), derived from an OGTT performed 24 h after 8 mg of Dex. ROC curves are shown for the three parameters and the AUC for each curve is shown in each figure. Sensitivities and specificities at different cut-points are shown below each panel.

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Table 1. Characteristics of individuals at baseline who did not and those who did develop type 2 diabetes during follow-up.

Characteristic	No Diabetes (n=24)	Diabetes (n=9)	*P*
Male/Female	1/23	1/8	-
Age (years)	46.7±6.4	43.3±7.3	0.20
Height (cm)	156.8±6.0	159.4±5.8	0.27
Weight (kg)	71.1±8.5	98.0±1.4	0.003
BMI (kg/m^2)	29.6±5.6	31.3±5.6	0.45
Waist (cm)	93.2±12.5	105.1±22.1	0.06
Systolic BP (mm Hg)	117.0±10.7	125.0±7.0	0.05
Diastolic BP (mm Hg)	78.3±8.4	84.4±4.6	0.05

Mean ± SD

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Table 2. Derived values from OGTTs performed at baseline before and after receiving 8 mg dexamethasone in individuals who did and those who did not develop type 2 diabetes at 7 years of follow-up.

	No DIABETES (n = 24)			DIABETES (n = 9)			
Derived Values	**Before Dex**	**After Dex**	***P***	**Before Dex**	**After Dex**	***P***	***P**** **After Dex**
Fasting glucose (mg/dl)	94.9±1.7	107.7±3.4	0.01	102.4±2.8	120.7±5.4	0.002	0.05
Glucose 30 min (mg/dl)	133.1±4.8	163.9±8	0.01	152.8±0.9	180.3±7.5	0.002	0.3
Glucose 60 min(mg/dl)	138.9±6.2	190.5±11.1	0.01	186.3±13.8	216±13.5	0.03	0.2
Glucose 120 min (mg/dl)	121±4.9	158.1±7.6	0.01	146±8.6	216.6±19.4	0.002	0.002
Fasting Insulin (µIU/mL)	6.5±0.53	12.7±8.5	0.01	9±1	19.9±3.3‡	0.005	0.002
Insulin 30 min (µIU/mL)	42.8±5.3	71.8±8.5	0.01	55.4±11.9	84.9±18.4	0.07	0.5
Insulin 60 min (µIU/mL)	53.1±6.5	100.9 ±11.6	0.01	81±13.9	111.7±21.1	0.04	0.7
Insulin 120 min (µIU/mL)	44.9±5.5	89.4±14.2	0.01	73.9±13.7	127.3±36.5	0.08	0.26

Values are means ± SE. ‡ denotes that n = 8 for this measure.
P values reflect the difference before and after Dex in each group.
*P** values reflect the difference after Dex between the two groups

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Table 3. Derived values from the results of OGTTs shown in Table 2 in participants who did and those who did not develop diabetes at 7 years of follow-up.

	No DIABETES (n = 24)			DIABETES (n= 9)			
Derived Values	**Before Dex**	**After Dex**	***P***	**Before Dex**	**After Dex€**	***P***	***P**** **After Dex**
HOMA-IR	1.5 ±0.13	3.4±0.35	0.01	2.3±0.26	6.1 ±1.1	0.007	0.002
HOMA-B	76.9 ±6.7	115.6 ±13.1	0.01	86.2±14.6	125 ±20.4	0.004	0.4
Matsuda Index	13.5 ±0.53	7.2 ±0.35	0.01	10.9 ±0.77	5.4±0.5	0.001	0.006
Insulinogenic Index	0.97±0.12	1.1±0.18	0.18	0.85±0.24	1 ±0.34	0.3	0.7
Disposition Index1	13.2±1.8	8.2.±1.29	0.03	8.5±2	6±2	0.12	0.3
Disposition Index2	81.7 ±3.2	84.5 ±3.1	0.4	92.8±5.9	98.9 ±7.7	0.22	0.01
AUC-Glucose	850 ±28	1103 ±47	0.01	1049 ±58	1302 ±69	0.001	0.03
AUC-Insulin	5123±542	9569±1023	0.01	6614±874	10055±1607	0.03	0.32

Values are mean ± SE. €n = 8, except for AUC Glucose where n=9.
P values reflect the difference before and after Dex in each group.
*P** values reflect the difference after Dex between the two groups

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Table 4. AUC of ROC curves calculated before Dex and 24 h after Dex in individuals who developed T2DM compared to those who did not.

AUC of ROC Curves		
Parameters	**Before Dex**	**After Dex**
Fasting Glucose	0.63	0.76
Glucose, 30 min	0.68	0.76
Glucose, 60 min	0.78	0.62
Glucose, 120 min	0.68	***0.92***
Fasting Insulin	0.65	***0.84***
Insulin, 30 min	0.60	0.58
Insulin, 60 min	0.72	0.60
Insulin, 120 min	0.64	0.61
HOMA-IR	0.76	***0.86***
HOMA-B	0.54	0.60
Matsuda	0.55	0.77
Insulinogenic Index	0.53	0.52
Disposition Index1	0.62	0.55
Disposition Index2	0.60	0.78
AUC Glucose	0.78	0.78
AUC Insulin	0.71	0.65

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