Original Article

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EFFECT OF DEXAMETHASONE ON GLUCOSE HOMEOSTASIS IN NORMAL AND PREDIABETIC SUBJECTS WITH A FIRST-DEGREE RELATIVE WITH TYPE 2 DIABETES MELLITUS

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ABSTRACT

Objective: To determine the effect of a single 8-mg orally administered dose of dexamethasone or placebo on glucose and insulin homeostasis, during an oral glucose tolerance test (OGTT) performed before and 24 hours after the administered dose.

Methods: In a randomized, double-blind, placebo-controlled study, we conducted experiments in subjects with normal glucose tolerance (NGT) or prediabetes, all of whom had at least one first-degree relative with type 2 diabetes mellitus. Measures of glucose and insulin homeostasis derived from an OGTT before and 24 hours after administration of dexamethasone or placebo were compared in 21 placebo-treated versus 23 dexamethasone-treated subjects with NGT as well as in 23 placebo-treated versus 20 dexamethasone-treated subjects with prediabetes.

Results: Before administration of dexamethasone or placebo, area under the curve (AUC) for glucose and homeostasis model assessment of insulin resistance were higher, and the Matsuda and disposition indices were lower, in the prediabetic versus the NGT group. In both NGT and prediabetic groups treated with dexamethasone, glucose and insulin values at fasting and during OGTT were increased in comparison with placebo-treated groups at 24 hours ($P = .001$). Dexamethasone treatment in both study groups increased homeostasis model assessment of insulin resistance and AUC glucose and decreased the Matsuda index ($P = .001$). No significant changes were observed in AUC insulin/AUC glucose or homeostasis model assessment of beta-cell function after dexamethasone treatment in either the NGT or the prediabetic group. The disposition index decreased and was lowest in the prediabetic group after dexamethasone treatment.

Conclusion: In a study population in which all subjects had at least one first-degree relative with type 2 diabetes mellitus, those with prediabetes were more insulin resistant and had a lower disposition index than did subjects with NGT. Subjects with prediabetes also had a pronounced decrease in disposition index when challenged with a single 8-mg orally administered dose of dexamethasone. **(Endocr Pract. 2012;18:855-863)**

Abbreviations:
AUC = area under the curve; **BMI** = body mass index; **CV** = coefficient of variation; **HOMA-B** = homeostasis model assessment of beta-cell function; **HOMA-IR** = homeostasis model assessment of insulin resistance; **IEMRC** = Isfahan Endocrine and Metabolism Research Center; **NGT** = normal glucose tolerance; **OGTT** = oral glucose tolerance test; **SE** = standard error; **T2DM** = type 2 diabetes mellitus

INTRODUCTION

The number of people with type 2 diabetes mellitus (T2DM) is predicted to increase from 135 million in 1995 to approximately 300 million by the year 2025, with the increment largely occurring in developing countries (1-3). Changes in lifestyles, including decreased physical activity and increased food consumption, have multiplied the

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prevalence of obesity globally, all leading to an expanded number of cases of insulin resistance. In genetically predisposed persons, the increase in insulin resistance results in a progressive shift of those with normal glucose tolerance (NGT) into the "prediabetic" range, many of whom will ultimately develop T2DM during the subsequent years (4-9).

In any prevention program, identification of persons who are highly likely to develop T2DM is of importance because most obese persons or subjects with "prediabetes" do not develop diabetes. Moreover, cohort studies show that not all persons with T2DM pass through a prediabetic stage (10,11).

Some investigators have suggested that persons who develop glucocorticoid-induced hyperglycemia are prone to development of T2DM (12,13). It has also been demonstrated that normal persons who are glucose tolerant under usual conditions but are at the high range of both insulin resistance and insulin secretion cannot adapt effectively to a further acute increase in insulin resistance by increasing their rate of insulin secretion to maintain euglycemia. It can be predicted that persons who cannot maintain euglycemia after acute exposure to excessive glucocorticoids may be highly susceptible to development of T2DM (14-18). In a previous study, a single orally administered dose of 2, 4, or 8 mg of dexamethasone was used as a first step toward developing a simple "stress" test for identification of persons with a predisposition for T2DM (19). In that dose-response and time course study conducted in normal healthy subjects with a normal body mass index (BMI) and no history of T2DM in a first-degree family member, it was reported that an 8-mg dose of dexamethasone resulted in small but significant increases in fasting glucose and insulin levels and large increases in 1- and 2-hour glucose and insulin levels after a 75-g oral glucose load. The effect of dexamethasone was maximal at 24 hours and largely dissipated by 48 hours after administration (19).

The current study was designed to investigate the efficacy of the dexamethasone stress test in identifying persons who are highly predisposed to development of T2DM. We administered the dexamethasone stress test versus placebo to a group of volunteers, all of whom were deemed to be at higher risk for diabetes by virtue of having at least one first-degree relative with T2DM. Approximately half of the study participants had NGT, and the other half were classified as being prediabetic on the basis of results of an oral glucose tolerance test (OGTT); the prediabetic group consisted of persons with impaired fasting glucose, impaired glucose tolerance, or both. Study subjects in the prediabetic and normal (NGT) groups were administered an OGTT and then randomly assigned, by a double-blind method, to receive a single orally administered dose of either 8 mg of dexamethasone or placebo (in the morning), followed by an OGTT the next morning. This report summarizes some baseline demographic characteristics of the participants and results of the OGTT.

SUBJECTS AND METHODS

Study Cohort and Procedures

The current study was performed at the Isfahan Endocrine and Metabolism Research Center (IEMRC), University of Medical Sciences, Isfahan, Iran, between October 2009 and May 2010. Volunteers were 20 to 65 years old and were all first-degree relatives of patients with T2DM who were enrolled in the Isfahan Diabetes Prevention Program Study (an ongoing cohort study in the IEMRC). On the basis of the medical history of volunteers in the IEMRC, 120 potential participants with either NGT or a prediabetic state, according to the American Diabetes Association criteria (20), were invited to attend a meeting at the IEMRC, where the details of this study were explained.

Written informed consent was obtained from the volunteers who agreed to participate in the study. Then in subsequent visits, volunteers were interviewed to register their clinical characteristics (age, sex, weight, height, waist circumference, and blood pressure), their current medication history, and their past medical history. BMI was calculated as body weight in kilograms divided by the square of the height in meters. Waist circumference was measured with a tape horizontally around the abdomen at the level of the iliac crest, parallel to the floor during normal respiration (21). Blood pressure was measured with a calibrated mercury sphygmomanometer while the subjects were sitting, after 5 minutes of resting. Active peptic ulcer, active herpetic corneal ulcer, psychosis, positive pregnancy test, or current use of oral contraceptives in women and thiazide or glucocorticoid use in any person were exclusion criteria.

On the basis of inclusion and exclusion criteria, 96 persons (51 with prediabetes and 45 with NGT) were enrolled. A 75-g OGTT was performed, after an 8-hour overnight fast, during the morning of day 1. Plasma glucose and insulin concentrations were measured at 0, 30, 60, and 120 minutes, with fasting and 2-hour samples being analyzed for glucose immediately.

After completion of the OGTT on day 1, the study participants were randomly assigned to the "case" group (to take an 8-mg dexamethasone tablet) or to the control group (to take a placebo tablet). For randomization, we used a box with numbers from 1 to 100 written on pieces of paper to assign participants to case or control groups, with odd numbers for cases and even numbers for the control group. Assignments and all subsequent procedures were performed in a double-blind fashion. On exclusion of diabetes (on the basis of fasting or 2-hour glucose values) after the completion of the OGTT on day 1, participants ingested the placebo or dexamethasone tablet under direct

supervision. The OGTT was repeated on day 2, and blood samples were obtained to measure glucose and insulin levels at 0, 30, 60, and 120 minutes.

Among the 51 persons with prediabetes, 3 proved to have diabetes (according to the OGTT result on day 1), and 5 persons did not participate in the OGTT on day 2 (leaving 43 persons in the prediabetes group). Of the 45 persons with NGT, 1 person did not return for the OGTT on day 2 (leaving 44 in the NGT group).

Glucose (in mg/dL) was measured with the glucose oxidase-phenol + aminophenazone method (Pars Azmoon Company, Tehran, Iran). Glucose concentration (in mmol/L) was used in the calculation of homeostasis model assessment of insulin resistance (HOMA-IR) and homeostasis model assessment of beta-cell function (HOMA-B). The intra-assay coefficient of variation (CV) for glucose was 1.5%, and the interassay CV was 0.91%. Insulin (in μIU/mL) was measured by using a sandwich chemiluminescence immunoassay method (DiaSorin S.p.A., Vercelli, Italy). The intra-assay CV and interassay CV for insulin were 2.9% and 5.1%, respectively.

HOMA-IR was calculated by multiplying the fasting plasma insulin concentration (in μIU/mL) and the fasting plasma glucose concentration (in mmol/L) and then dividing by 22.5 (22). HOMA-B was the result of multiplying the number 20 and the basal insulin concentration, dividing by the basal glucose concentration, and then subtracting the constant number of 3.5 (23). The Matsuda index was calculated as 10,000 divided by the square root of the following: $(G_0 \times I_0 \times G_{120} \times I_{120})$, in which G_0 is fasting glucose, I_0 is fasting insulin, G_{120} is glucose at 120 minutes, and I_{120} is insulin at 120 minutes (from the OGTT) (24). The insulinogenic index was calculated as Δ insulin/Δ glucose from 0 to 30 minutes of the OGTT. The disposition index was calculated with use of 2 formulas: (*1*) the product of the Matsuda index and the insulinogenic index and (*2*) the Matsuda index times area under the curve (AUC) insulin/AUC glucose$_{(0 \text{ to } 120 \text{ min})}$ (19).

The trial design and consent process were approved by the Ethics Committee of Isfahan University of Medical Sciences. The study was performed in accordance with the current version of the Declaration of Helsinki.

Statistical Analysis

Statistical analyses of the data were done with use of SPSS statistical software, version 13.0 for Windows (Chicago, Illinois). Data are presented as mean (standard error [SE]). Quantitative values (age, BMI, waist circumference, and blood pressure) with normal distribution were compared between groups by the independent Student *t* test. The glucose and insulin concentrations (obtained during the 2-hour OGTT) on day 1 were compared with the same values on day 2 in each study group (NGT and prediabetic groups) by using repeated measures analysis of variance (rather than the *t* test at each time point) in order to avoid a type I error. Qualitative values with normal distribution (sex) were compared by the χ^2 test. *P* values less than or equal to .05 were considered statistically significant.

RESULTS

Comparison of NGT and Prediabetic Groups at Baseline (Day 1)

The double-blind placebo-controlled trial was completed by 87 participants (44 NGT and 43 prediabetic persons). The prediabetic group versus the NGT group, respectively, had the following mean values (SE): BMI, 30.7 (0.7) versus 29.0 (0.7) kg/m^2 (*P* = .09); waist circumference, 97.6 (1.8) versus 93.0 (1.8) cm (*P* = .1); fasting plasma glucose, 102.4 (1.3) versus 89.0 (0.7) mg/dL (*P* = .0001); and fasting plasma insulin, 9.3 (0.7) versus 7.4 (0.7) μIU/mL (*P* = .05).

Some baseline clinical characteristics of the study participants in the NGT and prediabetic groups are summarized in Table 1. There was no significant difference between the clinical characteristics of the dexamethasone-treated versus the placebo-treated participants in either the NGT or the prediabetic group on day 1 (baseline) before receiving dexamethasone or placebo.

Indices of glucose and insulin homeostasis derived from the results of OGTT at baseline performed in both study groups differed between the 2 groups. These differences included the following mean (SE) values in the prediabetic group as a whole in comparison with the NGT group, respectively (*P*<.05 for all, except for HOMA-B and AUC for insulin): higher AUC for glucose, 1,003 (22) versus 806 (14); higher AUC for insulin, 6,841 (529) versus 5,601 (5,220); higher HOMA-IR, 2.3 (0.16) versus 1.7 (0.16); and lower HOMA-B, 89.9 (8) versus 100 (8.9); Matsuda index, 11 (0.4) versus 13 (0.4); and insulinogenic index, 0.8 (0.06) versus 1.1 (0.09). With use of both methods of calculation, the disposition index was significantly lower in the entire prediabetic group versus the NGT group, respectively, at baseline—the product of the insulinogenic index and the Matsuda index as well as the product of AUC insulin/AUC glucose$_{(0 \text{ to } 120 \text{ min})}$ and the Matsuda index, respectively, yielded 8.6 (0.7) versus 14.1 (1.2) and 70.3 (4.3) versus 85.5 (5.2); *P* = .05).

Effect of Placebo and Dexamethasone in Study Participants With NGT (Day 2 Versus Day 1)

Plasma glucose and insulin levels during the OGTT in study participants in the NGT group on days 1 and 2 (before and after administration of placebo and 8 mg of dexamethasone, respectively) are shown in Figure 1 *A* and *B*. The mean (SE) fasting plasma glucose concentration increased significantly in the dexamethasone-treated group from 91.4 (8.6) to 103.0 (13.2) mg/dL (*P* = .001) and was also significantly increased at all other measured time points (30, 60, and 120 minutes during the OGTT)

on day 2 in comparison with baseline values on day 1 ($P = .001$). Similarly, the mean (SE) fasting plasma insulin level increased significantly after administration of dexamethasone from 7.9 (5.6) to 16.0 (10.3) μIU/mL ($P = .001$) and was also significantly increased at 30, 60, and 120 minutes during the OGTT on day 2 in comparison with baseline values on day 1 ($P = .001$). The glucose and insulin levels did not change in study participants with NGT who received placebo.

Values derived from the OGTT data are presented in Table 2. As expected, the AUC for both glucose and insulin (0 to 120 minutes) and the value of HOMA-IR increased significantly on day 2 in study participants with NGT treated with dexamethasone in comparison with the placebo-treated NGT group (all $P = .001$); the increase in HOMA-B did not reach statistical significance. The Matsuda index decreased significantly (by approximately 50%) on day 2 ($P = .001$). There were no significant changes in the ratio of AUC for insulin/glucose, the insulinogenic index, and the disposition index on day 2 in the dexamethasone-treated NGT group in comparison with the placebo-treated NGT group. There was a nonsignificant decrease in the disposition index determined with the use of either formula for its calculation.

Effect of Placebo and Dexamethasone in Study Participants With Prediabetes (Day 2 Versus Day 1)

The mean (SE) plasma glucose and insulin levels during the OGTT in the prediabetic group on days 1 and 2 (before and after administration of placebo and 8 mg of dexamethasone, respectively) are shown in Figure 1 *C* and *D*. The mean (SE) fasting plasma glucose concentration increased significantly in the dexamethasone-treated group from 101.9 (9.2) to 121.9 (16.6) mg/dL ($P = .001$) and was also significantly increased at all other measured time points (30, 60, and 120 minutes during the OGTT) on day 2 in comparison with baseline values on day 1 ($P = .001$). Similarly, the mean (SE) fasting plasma insulin level increased significantly after administration of dexamethasone from 9.0 (4.3) to 15.7 (7.8) μIU/mL ($P = .001$) and was also significantly increased at 30 and 60 minutes during the OGTT on day 2 in comparison with values on day 1 ($P = .001$). None of the values changed in response to treatment with placebo.

Changes in values derived from the OGTT on day 2 in the prediabetic group were similar in direction to those in the NGT group. The AUC for both glucose and insulin increased as a result of dexamethasone treatment; however,

Table 1
Clinical Characteristics of Normal Glucose Tolerant and Prediabetic Study Participants on Day 1, Before Receiving Placebo or 8 mg of Dexamethasone[a]

	Normal OGTT group			Prediabetic group		
Characteristic	Placebo (n = 21)	Dexamethasone (n = 23)	*P* value	Placebo (n = 23)	Dexamethasone (n = 20)	*P* value
Age (y)	47.0 (1.4)	47.4 (1.8)	.8	46.3 (1.5)	44.8 (1.4)	.5
Sex, male:female	4:17	1:22	.17	4:19	3:17	1
Body mass index (kg/m^2)	28.3 (0.9)	29.6 (1.1)	.4	30.6 (0.9)	30.9 (1.0)	.8
Waist circumference (cm)	91.8 (2.1)	94.9 (2.9)	.4	96.8 (1.8)	98.6 (3.5)	.4
Blood pressure (mm Hg)						
Systolic	121.2 (2.7)	118.6 (2.2)	.5	116.9 (5.6)	112.2 (2.0)	.11
Diastolic	79.0 (1.8)	79.4 (1.4)	.9	77.1 (1.9)	82.5 (1.7)	.30
Fasting glucose (mg/dL)	88.0 (0.9)	90.8 (1.1)	.06	102.9 (1.8)[b]	101.9 (2.0)[c]	.7
Fasting insulin (μIU/mL)	7.0 (0.65)	7.9 (1.24)	.5	9.6 (0.96)	9.0 (0.96)	.6

Abbreviation: OGTT = oral glucose tolerance test.
[a] Values (except for sex) are shown as mean (standard error).
[b] $P<.05$ in comparison with the value in the normal OGTT group treated with placebo.
[c] $P<.05$ in comparison with the value in the normal OGTT group treated with dexamethasone.

Table 2
Derived Values From the Oral Glucose Tolerance Test Data on Days 1 and 2 in Normal Glucose Tolerant and Prediabetic Groups, Treated With Placebo or 8 mg of Orally Administered Dexamethasone[a]

	Normal OGTT group			Prediabetic group		
Characteristic	Placebo (n = 21)	Dexamethasone (n = 23)	*P* value	Placebo (n = 23)	Dexamethasone (n = 20)	*P* value
AUC (glucose)						
Day 1	798 (21)	813 (20)	.6	982 (29)[b]	1,027 (33)[c]	.3
Day 2	807 (34)	1,056 (43)	.001	966 (33)[b]	1,254 (41)[c]	.001
AUC (insulin)						
Day 1	5,403 (771)	5,790 (725)	.7	6,584 (703)	7,122 (812)	.6
Day 2	6,133 (617)	10,606 (1,534)	.001	6,721 (665)	9,431 (913)	.01
AUC (insulin/glucose)						
Day 1	6.6 (0.8)	7.0 (0.7)	.7	6.6 (0.6)	7.0 (0.8)	.7
Day 2	7.6 (0.7)	9.7 (1.0)	.1	7.0 (0.6)	7.7 (0.8)	.5
HOMA-IR						
Day 1	1.5 (0.1)	1.7 (0.3)	.4	2.4 (0.2)[b]	2.2 (0.2)	.5
Day 2	1.8 (0.2)	4.3 (0.7)	.001	2.7 (0.3)[b]	4.7 (0.7)	.001
HOMA-B						
Day 1	99.8 (8.4)	101.0 (15.8)	.9	86.4 (9.3)	93.8 (14.6)	.6
Day 2	113.5 (9.9)	146.1 (18.1)	.1	115.5 (15.9)	102.3 (11.1)	.5
Matsuda index						
Day 1	13.6 (0.7)	13.1 (0.7)	.5	10.8 (0.5)[b]	11.3 (0.5)	.5
Day 2	10.4 (0.7)	6.9 (0.5)	.001	8.1 (0.3)[b]	6.2 (0.4)	.001
Insulinogenic index						
Day 1	1.0 (0.1)	1.2 (0.1)	.3	0.8 (0.1)	0.8 (0.1)[c]	.6
Day 2	0.9 (0.3)	1.5 (0.2)	.1	0.9 (0.2)	0.8 (0.1)[c]	.8
Disposition index						
Day 1[d]	13.1 (1.3)	15.1 (1.9)	.7	8.7 (1.0)[b]	8.5 (1.0)[c]	.4
Day 2[d]	10.5 (2.0)	10.4 (1.8)	.7	7.2 (1.4)	5.3 (0.9)[c]	.3
Day 1[e]	83.1 (6.8)	87.8 (8.0)	.4	67.3 (4.4)[b]	73.6 (7.6)	.5
Day 2[e]	73.0 (5.1)	63.3 (4.9)	.9	55.9 (5.0)	48.3 (5.9)[c]	.3

Abbreviations: AUC = area under the curve; HOMA-B = homeostasis model assessment of beta-cell function; HOMA-IR = homeostasis model assessment of insulin resistance; OGTT = oral glucose tolerance test.
[a] Values are shown as mean (standard error).
[b] $P<.05$ in comparison with the value in the normal OGTT group treated with placebo.
[c] $P<.05$ in comparison with the value in the normal OGTT group treated with dexamethasone.
[d] Disposition index calculated as the product of the insulinogenic index and the Matsuda index.
[e] Disposition index calculated as the product of AUC insulin/AUC glucose (0-120 minutes) and the Matsuda index.

the increase in AUC of insulin was modest (in comparison with that in the NGT group) and was not significant (Table 2). HOMA-IR increased and the Matsuda index decreased significantly (P = .001) on day 2 in the dexamethasone-treated group in comparison with the placebo-treated group. There were no significant changes in HOMA-B and the insulinogenic index, whereas the disposition index was significantly reduced in the dexamethasone-treated group on day 2 in comparison with the value in the dexamethasone-treated NGT group.

Comparison of Effect of Dexamethasone at 24 Hours in Study Participants With NGT Versus Prediabetes

Changes in derived variables of the OGTTs performed on day 1 versus day 2 in participants treated with dexamethasone show that AUCs for both glucose and insulin increased in participants with NGT (n = 23) as well as in those with prediabetes (n = 20). The increment in AUC for insulin in the prediabetic group (2,309) was less than that in the NGT group (4,816). Treatment with dexamethasone caused a significant increase in HOMA-IR and a significant decrease in the Matsuda index in both the NGT and prediabetic groups; however, there was no differential effect. HOMA-B increased by 45.1 and 8.5 units in the NGT and prediabetic groups, respectively. The disposition index was significantly lower in the prediabetic group in comparison with the NGT group on day 1 before administration of dexamethasone with use of either method of calculation. The disposition index decreased in both groups on day 2 after administration of dexamethasone, with the final mean value (SE) being significantly lower in the prediabetic group in comparison with the NGT group—5.3 (0.9) versus 10.4 (1.8) with use of the insulinogenic index and 48.3 (5.9) versus 63.3 (4.9) with use of the AUC insulin/AUC glucose$_{(0\text{ to }120\text{ min})}$ in the calculation; P<.001 for both.

The plot of the insulinogenic index as a function of the Matsuda index (the product being the disposition index) before and after administration of dexamethasone in both NGT and prediabetic groups is shown in Figure 2. The theoretical hyperbolic curves depicting the disposition indices before dexamethasone treatment are also shown for both study groups. Treatment of the NGT group with dexamethasone resulted in a leftward (more insulin resistant) and, to a relatively lesser degree, an upward shift (more insulin secretion) of the coordinates to a position close to the hypothetical curve for the prediabetic group before administration of dexamethasone. The final coordinates of the NGT group after dexamethasone treatment corresponded to an increase in the mean (SE) fasting blood glucose level from 90 (4) to 102 (8) mg/dL and an increase in the mean (SE) 2-hour postprandial glucose value from 111 (15) to 136 (20) mg/dL, signifying that approximately half of the group fulfilled the criteria for prediabetes after administration of dexamethasone. Treatment of the prediabetic group caused a left shift in the Matsuda index with no

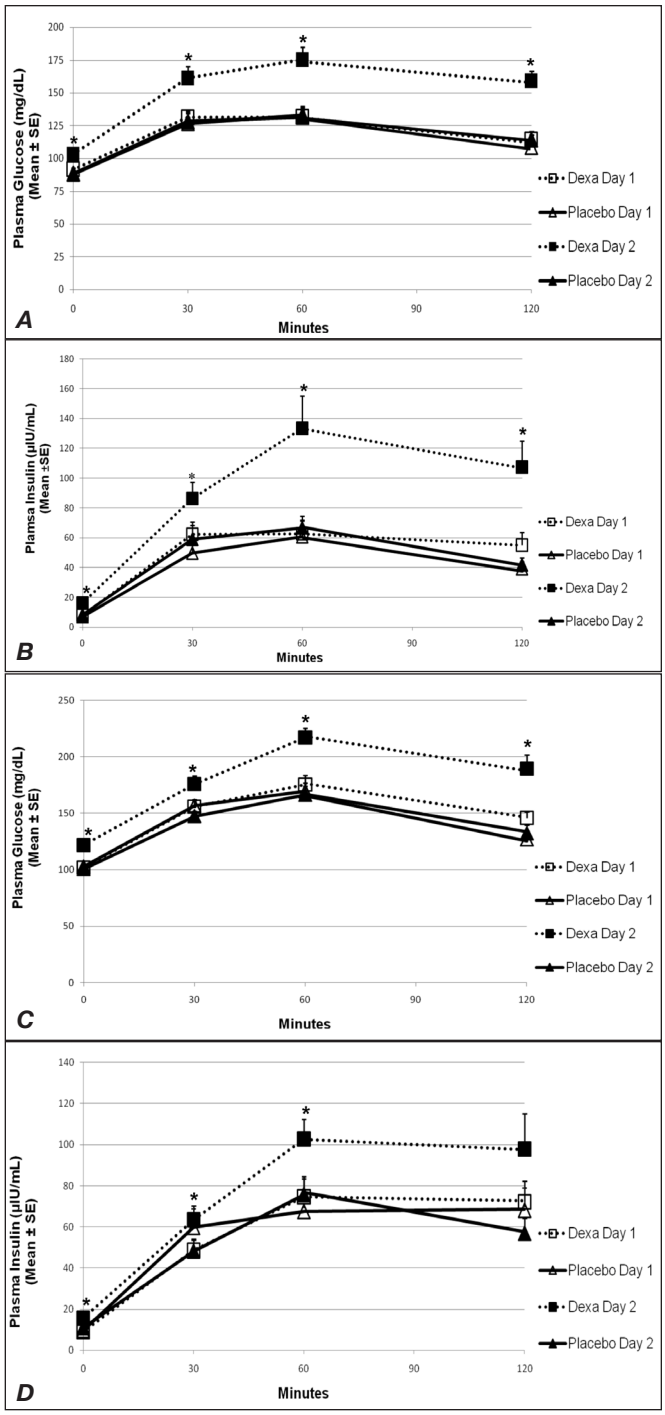

Fig. 1. *A*, Plasma glucose values during oral glucose tolerance test (OGTT) performed in study participants with normal glucose tolerance (NGT) on day 1 (baseline) and day 2, after administration of placebo and 8 mg of dexamethasone. *Denotes P<.05. *B*, Plasma insulin values during OGTT performed in study participants with NGT on day 1 (baseline) and day 2, after administration of placebo and 8 mg of dexamethasone. *Denotes P<.05. *C*, Plasma glucose values during OGTT performed in study participants with prediabetes on day 1 (baseline) and day 2, after administration of placebo and 8 mg of dexamethasone. *Denotes P<.05. *D*, Plasma insulin values during OGTT performed in study participants with prediabetes on day 1 (baseline) and day 2, after administration of placebo and 8 mg of dexamethasone. *Denotes P<.05. *Dexa* = dexamethasone; *SE* = standard error.

appreciable increase in the insulinogenic index. The final coordinates of the prediabetic group after dexamethasone treatment corresponded to an increase in the mean (SE) fasting blood glucose level from 96 (10) to 122 (17) mg/dL and an increase in the mean (SE) 2-hour postprandial glucose value from 159 (38) to 189 (54) mg/dL, suggesting that somewhat less than half of the group met the criteria for diabetes after dexamethasone treatment.

DISCUSSION

In a dose-response and time-course study conducted in healthy persons with a normal BMI and negative family history for T2DM, it was reported that a single 8-mg orally administered dose of dexamethasone resulted in significant increases in plasma glucose and insulin levels, both during fasting and during an OGTT conducted at 24 hours; the changes were associated with an approximate 25% decrease in the disposition index (19). The objective of the current study was to determine the effect of a single 8-mg orally administered dose of dexamethasone on glucose homeostasis at 24 hours in persons who have a predisposition to development of T2DM by virtue of having one or more first-degree relatives affected with the disease. The study was conducted with use of a double-blind placebo-controlled design. We compared the response of the entire group of study participants with prediabetes (n = 43) with the response of those who had NGT (n = 44) to placebo or 8 mg of dexamethasone.

Participants enrolled in this study were, on average, overweight with a BMI of 29.0 kg/m^2 (NGT group) or obese with a BMI of 30.7 kg/m^2 (prediabetic group). Predictably, members of the prediabetic group had higher fasting plasma glucose levels and slightly higher plasma insulin levels at baseline in comparison with those in the NGT group. In addition, on the basis of HOMA-IR as well as the Matsuda index, the prediabetic persons were more insulin resistant (or less insulin sensitive) than those with NGT. Although all participants in this study had a first-degree relative with T2DM, genetic, environmental, and metabolic factors such as higher adiposity and exposure to higher glucose levels might have a role in the increased insulin resistance in the prediabetic group (25).

The inclusion of a positive family history of T2DM as an enrollment criterion may have also had a role in minimizing differential responses of NGT and prediabetic persons to dexamethasone treatment.

Differences in Response to Dexamethasone

Despite the fact that this study was designed on the basis of all participants having at least one first-degree family member with T2DM, some critical differences in the response to dexamethasone treatment are apparent between those with NGT and those with prediabetes. Most important is the set of findings singling out decreased insulin secretory response to an acute increase in insulin resistance induced by dexamethasone in the prediabetic group. Included in these findings is the lack of a

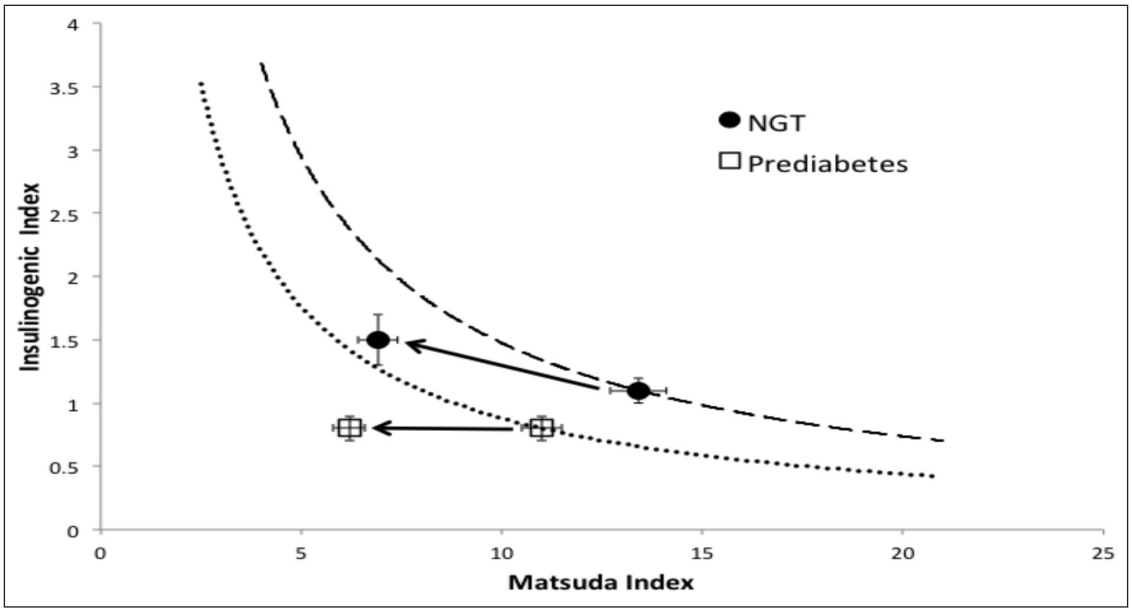

Fig. 2. Disposition index, calculated by using the insulinogenic index and the Matsuda index. Changes in the insulinogenic index and the Matsuda index in subjects with normal glucose tolerance (*NGT*) and those with prediabetes before and 24 hours after treatment with 8 mg of dexamethasone. Theoretical hyperbolic curves are also drawn for the NGT and prediabetic groups before treatment with dexamethasone. Plotted values are means; error bars represent standard error.

significant increase in HOMA-B in the prediabetic group at 24 hours in response to dexamethasone, despite a similar degree of insulin resistance in the 2 groups estimated by HOMA-IR and the Matsuda index after administration of dexamethasone.

In addition, and of critical importance in this comparative analysis, are the findings related to the disposition index, a variable that is considered one of the "gold standard" measures of beta-cell function (26). The disposition index was significantly lower by approximately 20% to 30% (depending on the method of calculation) in the prediabetic group in comparison with the NGT group before exposure to dexamethasone, a finding that corresponds to previous reports (27,28). Exposure to dexamethasone reduced the disposition index in both study groups, with the absolute value of the index in the prediabetic group reaching approximately one-third to one-half of the value in the NGT group before treatment with dexamethasone. Hence, an important hallmark of glucose metabolism in persons with prediabetes in comparison with those who have NGT is their relative inability to increase insulin secretion to compensate for an induced higher degree of insulin resistance. This premise is depicted in Figure 2, where insulin sensitivity is shown to decrease in conjunction with a relatively smaller increase in the insulinogenic index in the NGT group or with no change in the insulinogenic index in the prediabetic group in response to treatment with dexamethasone. One can surmise that dexamethasone appears to have converted the situation in the NGT group to approximate that in the prediabetic group before treatment with dexamethasone and that the hormone has converted a large number of persons with prediabetes to having diabetes within 24 hours.

A significantly smaller nonequivalence between increased insulin resistance versus insulin secretion was observed in the response of healthy persons with normal BMI to 8 mg of dexamethasone (19). A study by Henriksen et al (29) demonstrated that dexamethasone-induced insulin resistance uncovers beta-cell dysfunction in relatives of patients with non-insulin-dependent diabetes mellitus in comparison with control subjects who were not relatives of such patients. This raises the possibility that the disposition index itself, or perhaps some other variable of glucose homeostasis, may prove to be a highly useful measure in developing the "dexamethasone stress test" as a specific and sensitive screening procedure for identifying persons susceptible to development of T2DM with requisite specificity and sensitivity. Measurement of incretins (glucagon-like peptide-1 and gastric inhibitory polypeptide), however, may provide insights into the natural history of the evolution of prediabetes to T2DM.

Study Strengths and Limitations

Strengths of our study include that it was conducted in a randomized double-blind fashion. The requirement for having a positive family history of T2DM, however, also partially limited the differentiation of the response between those with NGT and those with prediabetes. Use of calculated indices of insulin sensitivity and secretion, rather than an insulin clamp test as the standard method, was another limitation of our study. A weakness is the extent to which the results can be generalized to other populations, inasmuch as the phenotype of T2DM, and presumably prediabetes, appears to differ among various ethnic groups. Finally, our study would have been strengthened if a control group of participants with normal BMI and no family history of T2DM had been included. Because the reported part of our investigation was a cross-sectional study, it is unclear which subset of prediabetic subjects are at the highest risk for developing diabetes mellitus. In the longitudinal part of our study, we will conduct a follow-up of these subjects to determine which of them will eventually develop diabetes and to clarify whether a post-dexamethasone OGTT is more sensitive than a routine OGTT in identification of persons at risk.

CONCLUSION

Among subjects with a first-degree relative with T2DM, those with prediabetes are more insulin resistant and manifest lower beta-cell function, as assessed by the disposition index, in comparison with persons who have NGT. In addition, prediabetic persons show a notable suppression of increasing insulin secretion in response to an acute increase in insulin resistance, resulting in a decrease in their disposition index when challenged with a single 8-mg dose of dexamethasone.

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DISCLOSURE

The authors have no multiplicity of interest to disclose.

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