Effect of Acute Psychotic Stress in Nondiabetic Subjects on β-Cell Function and Insulin Sensitivity

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OBJECTIVE — To determine the effect of acute psychotic stress on glucose homeostasis in nondiabetic subjects.

RESEARCH DESIGN AND METHODS — β-Cell function and insulin sensitivity were determined by the homeostasis model assessment in 39 nondiabetic patients with acute psychotic stress reaction admitted to a psychiatric ward. The clinical global impression (CGI) score was used to evaluate the level of psychological stress. Patients were assessed on admission, after 2 weeks, before discharge, and 6 months after discharge.

RESULTS — The mean CGI score decreased significantly with time: 5.3 ± 0.8 and 1.6 ± 0.7 on admission and predischarge, respectively ($P < 0.001$). This was associated with a significant reciprocal increase of mean β-cell function from 96.8 ± 33.2 to 134.4 ± 60% at admission and postdischarge, respectively ($P < 0.003$), and a decrease of mean insulin sensitivity from 101.7 ± 36 to 77.1 ± 34.8% ($P < 0.001$). In contrast, mean glucose and HbA_{1c} levels did not change significantly. Subgroup analysis demonstrated that patients with the highest stress score on admission (≥6) had significantly higher glucose ($P = 0.01$) and insulin levels ($P = 0.04$) than patients with lower score (<6). Furthermore, insulin sensitivity and CGI score on admission were inversely correlated ($r = -0.38$, $P < 0.02$). In these patients, no correlation was found between β-cell function or insulin sensitivity and BMI.

CONCLUSIONS — These data indicate that β-cell function and insulin sensitivity are inversely correlated with acute psychotic stress.

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The causal relation between psychological stress and the development of overt diabetes in human patients is controversial. It is commonly accepted that stress, whether physical or psychological, elicits a stereotyped kind of reaction of the "fight or flight" type (1). These reactions involve the activation of the autonomic nervous system and the release of counter-regulatory "stress hormones," namely cortisol, epinephrine, growth hormone, and glucagon, that increase glucose levels and affect glucose homeostasis (2). Several lines of evidence support the role of psychological stress in promoting the development of diabetes. Data from animal studies in a variety of diabetic prone murine strains demonstrated that environmental stress might accelerate or retard the progression of diabetes, underscoring its role in the pathogenesis of this disease (3,4). It has been repeatedly demonstrated that acute and/or chronic psychological stress results in a deterioration of metabolic control in known diabetic patients (5,6). Occurrence of new diabetes onset after an extreme stressful situation is commonly reported by human patients. Psychiatric diseases like chronic schizophrenia and major depressive disorders are associated with a higher prevalence of diabetes (7–9). Finally, several studies have shown that life events causing stress are more frequent in the period preceding the emergence of both type 1 and type 2 diabetes (10,11). Taken together, these data suggest that psychological stress may play a significant role in the development of overt diabetes. However, the lack of accepted animal and human experimental models, the extremely heterogeneous personal reaction to stress, and the difficulty to quantify psychological stress make this relation difficult to prove.

To better evaluate the relation between psychological stress and glucose control, we examined the effect of acute severe psychotic stress reaction on insulin sensitivity and β-cell function in nondiabetic patients.

RESEARCH DESIGN AND METHODS

Patients and study design

A total of 39 nondiabetic adult patients (27 men and 12 women), mean age 39 ± 10.5 years (range 19–37), who were admitted through the psychiatric emergency ward with acute psychotic stress were enrolled. The majority of these patients 33/39 (85%) had previous history of chronic psychiatric disorders such as chronic schizophrenia and residual or paranoid schizophrenia. "Acute psychotic state" is a common feature in all of these

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Abbreviations: FBG, fasting blood glucose; CGI, clinical global impression.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Demographic and clinical characteristics of the study patients on admission*

Age (years)	
Mean ± SD	39 ± 10.5
Range	19–37
Sex	
Male	27 (69.2)
Female	12 (30.8)
BMI (kg/m^2)	
Mean ± SD	26.7 ± 5.8
Range	16.0–40.1
CGI	
Mean ± SD	5.3 ± 0.8
Range	3–7
Glucose (mg/dl)*	
Mean ± SD	93.7 ± 12.0
Range	67–125
HbA_{1c} (%)†	
Mean ± SD	5.2 ± 0.27
Range	4.6–5.9
Background diseases	
Hypertension	3 (7.6)
Cardiovascular diseases	4 (10.2)
Dyslipidemia	17 (43.5)
Chronic psychiatric disorder	33 (84.6)
Family history of diabetes	19 (48.7)

Data are *n* (%) unless otherwise indicated. *To convert glucose values to millimoles per liter, multiply by 0.0555; †upper limit <6.4%.

diseases that most commonly appears as an acute intermittent exacerbation and is usually an indication for acute hospitalization (12). All patients were well controlled before admission. Only six patients were admitted with a first episode of acute psychotic stress. Patients with depressive disorders were not included. The clinical and demographic characteristics of these patients appear in Table 1. Exclusion criteria were: *1*) presence of any endocrine or concomitant acute disease; 2) use of any medications that can affect insulin secretion or activity or cause hyperglycemia, such as atypical antipsychotic drugs, i.e., clozapine, risperidone, tricyclic antidepressants, selective serotonine reuptake inhibitors, phenothiazines, butyrophenones, β-blockers, diuretics, corticosteroids, alcohol, opiates, cyclosporine, diazoxide, or oral contraceptives; 3) Increased fasting blood glucose (FBG) (>126 mg/dl) or HbA_{1c} level (>6.4%); and 4) inability to understand and sign an informed consent after an initial evaluation by a staff psychiatrist. During hospitalization patients were treated with either phenothiazines or thioxanthenes. All patients underwent an initial routine physical, psychiatric, and laboratory evaluation including complete blood count, serum electrolytes, urinalysis, liver and kidney function, thyroid function (thyroid-stimulating hormone and FT4), FBG, and blood lipid profile. The level of psychotic stress, assessed by the CGI score, and the β-cell function and insulin sensitivity, assessed by the homeostasis model assessment (HOMA) method (see below), were evaluated in all patients four times: on admission, after 2 weeks, before discharge, and 6 months after discharge. The local ethics committee approved the study.

Laboratory evaluation

Blood (10 ml) was drawn twice, 5 min apart, after an overnight fast (12 h) from an antecubital vein, and the plasma was separated and frozen at –70°C for future determinations of insulin and glucose levels. Glucose levels were determined by the COBAS-Roche glucose analyzer, using a commercially available GDP-PAP kit (Hitachi 917 analyzer). Determination of HbA_{1c} was performed using a Hitachi 917 analyzer and a commercially available Tinaquant HbA_{1c}II kit (Roche). Insulin levels were determined by solid-phase I-125 radioimmunoassay (Coat-A Count Insulin). The sensitivity of the assay was 5 mU/l. The intra- and interassay coefficients of variation did not exceed 5–9%.

Assessment of stress

Each psychiatric interview was performed independently, by two experienced senior staff psychiatrists. During this interview the patients were asked to answer the CGI score questionnaire, which is similar to the Global Assessment Scale (GAS) and is widely used in psychiatry in clinical and research settings. It grades psychological stress on a scale of 1–7 based on the subjective impression of the interviewing psychiatrist: grade 1 indicates a self-controlled mildly agitated patient hospitalized by his own will and grade 7 indicates the most extremely ill, very agitated patient with bizarre hallucinations who is commonly subjected to a forced hospitalization (13–15).

Results of this score were not revealed to the psychiatric team until the study was completed. The ratings of the two psychiatrists were highly correlated reaching a complete agreement in 37/39 (95%) of patients.

Evaluation of β-cell function and insulin sensitivity

HOMA is a relatively simple, nonexpensive, noninvasive, and reliable method to calculate insulin sensitivity and β-cell function based on fasting insulin and glucose blood levels. The validity of this model has been established in normal control subjects and in a wide variety of diseases, including patients with psychiatric disorders (16–18). The mean values of two samples of glucose and insulin were used for calculations using HOMA-CIGMA version 2.1 software (kind gift from Dr. J.C. Levy). We have opted for the use of the full equations using the computerized program as recommend by the authors (19). Values were expressed as percent of normal values of β-cell function and insulin sensitivity derived from the original British cohort (16). Using the original computer program, the mean and SD values of both β-cell function and insulin sensitivity in the normal Israeli control subjects are comparable with those of the British cohort (O. Cohen, unpublished data)

Statistical analysis

Statistical analysis was performed using BMDP software (20). ANOVA with repeated measures–incomplete design and Pearson's correlations were used for the analysis of the data.

RESULTS

Psychotic stress

Evaluation of the psychotic stress was done in all patients on admission, 2 weeks afterward, before discharge, and 6 months after discharge. The mean CGI score, which was 5.3 ± 0.8 on admission, decreased gradually and significantly during hospitalization, reaching a nadir of 1.6 ± 0.7 before discharge ($P < 0.001$). Six months later there was a slight nonsignificant increase of the CGI score to a mean of 2.9 ± 1.5 (Table 2). No correlation was found between the level of the psychotic stress and other demographic and clinical characteristics of these patients, including sex and age (data not shown). These data indicate that patients admitted to a psychiatric ward with acute psychotic stress demonstrate a rapid improvement within a time frame of several weeks.

Table 2—*Psychotic stress level and glucose homeostasis during and after hospitalization*

	Admission	2 weeks	Discharge	6 months	*P**
CGI	5.3 ± 0.8†	2.7 ± 0.8	1.6 ± 0.7†	2.9 ± 1.5	<0.001
HbA_{1c} (%)‡	5.2 ± 0.27	5.2 ± 0.2	5.3 ± 0.3	5.3 ± 0.2	NS
Glucose (mg/dl)§	93.7 ± 12	94.7 ± 11.3	96.5 ± 22.3	90.6 ± 15.4	NS
Insulin (mU/l)	8.7 ± 4.9	11.6 ± 7.3	18.1 ± 28.5	13.2 ± 11.1	NS
β-Cell function (%)	96.8 ± 33.2‖	110 ± 35.9	118.8 ± 54.5	134.4 ± 60‖	<0.02
Insulin sensitivity (%)	101.7 ± 36†	84.6 ± 39.3	87.4 ± 41.2	77.1 ± 34.8†	<0.001

Data are means ± SD. *Resulting from ANOVA with repeated measures using all four time points; †$P < 0.001$ post hoc analysis resulting from ANOVA with repeated measures; ‡upper limit <6.4%; ‖$P < 0.003$ post hoc analysis resulting from ANOVA with repeated measures; §to convert glucose values to millimoles per liter, multiply by 0.0555.

Fasting glucose and insulin levels

To examine the effect of acute psychotic stress on glucose homeostasis, we initially determined glucose and insulin levels. Table 2 demonstrates that the mean FBG, which was within normal range on admission, i.e., 93.7 ± 12.0 mg/dl, did not change significantly throughout the study. Elevation of FBG in the diabetic range >126 mg/dl was not observed in any of these patients. The mean insulin level was 8.7 ± 4.9 mU/l on admission with no significant change on later determinations. However, a subgroup analysis according to mean stress levels showed that patients with the highest CGI score (≥6) on admission had significantly higher glucose and insulin levels than patients with lower CGI scores. The mean FBG was 98.9 ± 11.0 mg/dl in patients with a CGI score ≥6 compared with 89.8 ± 11.4 mg/dl in patients with a CGI <6 ($P < 0.01$). The insulin level was 10.6 ± 6.4 mU/l in patients with the highest scores compared with 7.4 ± 2.8 mU/l in patients with the lowest scores ($P < 0.04$) (Fig. 1). We also found a positive correlation between CGI score and insulin and FBG on admission ($r = 0.37$, $P = 0.021$ and $r = 0.47$, $P = 0.003$, respectively). Multivariate analysis did not demonstrate any significant relation between these parameters and the demographic and clinical characteristics of these patients, including age, sex, and background diseases. These data demonstrate that FBG and insulin levels are directly related to the level of psychotic stress in acutely ill patients.

β-Cell function and insulin sensitivity

To further evaluate the effect of acute psychotic stress on glucose control in our patients, we used the HOMA model to determine β-cell function and insulin sensitivity. Mean β-cell function was the lowest on admission (96.8 ± 33.2%) and increased significantly throughout the study to a level of 134.4 ± 60% after discharge ($P < 0.003$). In contrast, mean in-

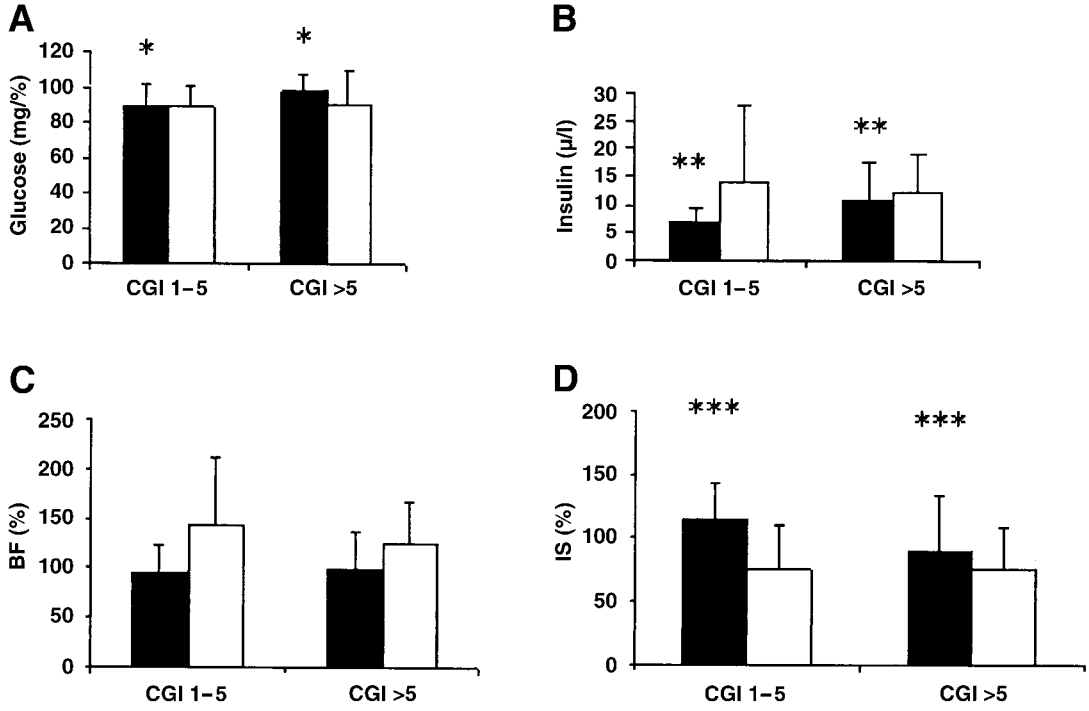

Figure 1—*FBG, insulin levels, β-cell function, and insulin sensitivity according to high and low CGI score on admission. Patients were divided into high (>5) and low (1–5) CGI groups according to CGI on admission. Data represent mean group values ± SD of FBG* (A)*, insulin* (B)*, β-cell function* (C)*, and insulin sensitivity* (D) *on admission and after discharge.* ■*, admission;* □*, 6 months.* *P < *0.01,* **P < *0.004,* ***P < *0.02.*

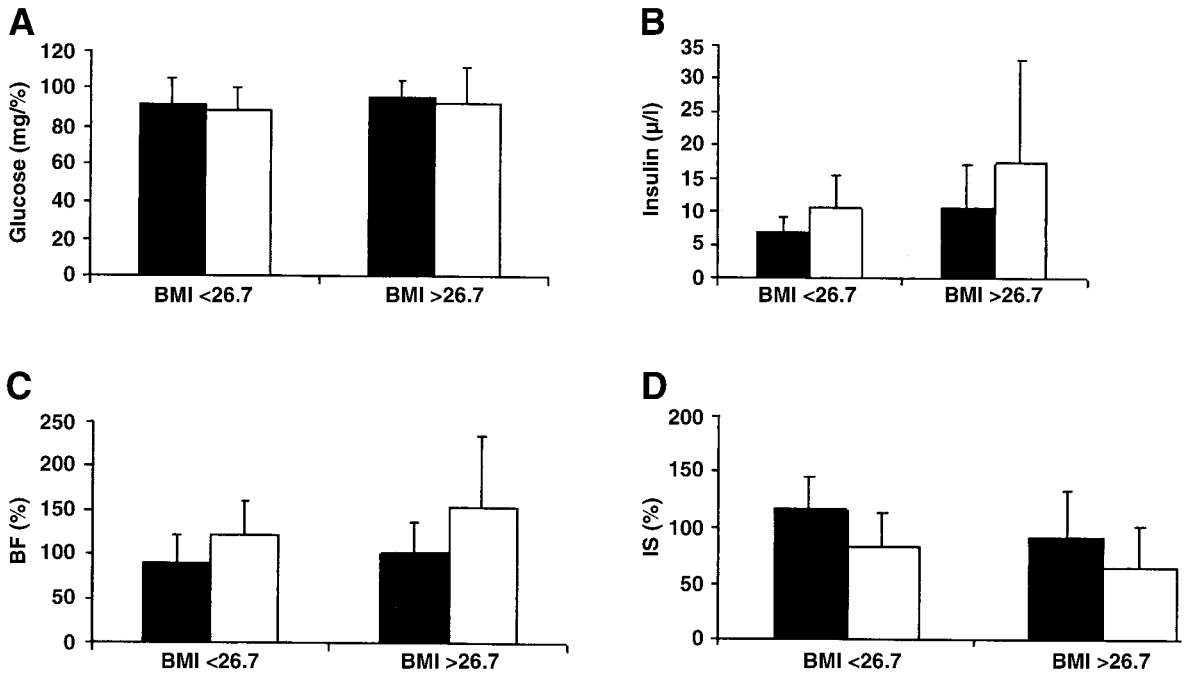

Figure 2—*FBG, insulin levels, β-cell function, and insulin sensitivity according to high and low BMI. Patients were divided into high (>26.7 kg/m^2) and low (<26.7) BMI groups according to BMI on admission. Data represent mean group values ± SD of FBG* (A)*, insulin* (B)*, β-cell function* (C)*, and insulin sensitivity* (D) *on admission and after discharge.* ■*, admission;* □*, 6 months.*

sulin sensitivity was the highest on admission (101.7 ± 36%) and decreased significantly to a level of 77.1 ± 34.8% after discharge ($P < 0.001$) (Table 2). Analysis according to CGI score on admission demonstrated that insulin sensitivity was inversely correlated to the psychotic stress: 90.7 ± 41.8 and 109.7 ± 29.6% for high and low CGI score patients, respectively ($P < 0.02$) (Fig. 1). No significant difference was observed between the low– and high–CGI score patients in β-cell function on admission (96.7 ± 37.0 and 97.0 ± 31.0%, respectively). Taken together, these data demonstrate that acute psychotic stress temporarily suppresses β-cell function and increases insulin sensitivity and that patients with extreme stress behave differently from patients with lower stress, demonstrating a decrease of insulin sensitivity.

Analysis according to BMI

BMI inversely affects the insulin sensitivity of nondiabetic individuals (21). Therefore, we analyzed our patients according to their mean BMI (26.7 kg/m^2) and subdivided them to high- and low-BMI groups. As shown in Fig. 2, FBG levels on admission and after discharge were comparable in the two groups (95.5 ± 9.4 and 91.6 ± 13.8 mg/dl and 89.1 ± 12.2 and 92.4 ± 18.9 mg/dl for high and low BMI, respectively). High BMI was associated with increased admission and postdischarge insulin levels (10.6 ± 6.5 and 17.4 ± 15.6 mU/l as compared with low BMI at 6.9 ± 2.3 and 10.4 ± 4.9 mU/l), but this difference was not significant. The mean β-cell function was increased and insulin sensitivity decreased in the high BMI group at admission and postdischarge compared with the low-BMI group, but these differences did not reach statistical significance. No correlation was found between BMI and CGI throughout the study, and the BMI did not change appreciably between admission and postdischarge (data not shown). These data indicate that the observed effects of psychotic stress on glucose control in our patients were independent of BMI.

CONCLUSIONS — Our data demonstrate for the first time that acute psychotic stress is significantly correlated to glucose homeostasis in nondiabetic patients. Glucose and insulin levels were higher and insulin sensitivity was lower among patients with the uppermost stress (CGI >6) on admission. In addition, the mean β-cell function of all patients, which was the lowest on admission, increased gradually during hospitalization in parallel to the decrease of the psychotic stress. These findings indicate that acute psychotic stress has adverse effects on glucose control in psychiatric nondiabetic patients. In contrast, the mean insulin sensitivity of the study group was directly correlated with psychotic stress, reaching its peak on admission and decreasing afterward. This suggests that acute psychotic stress may result in opposite effects on blood glucose levels that ultimately remain within normal limits. Nevertheless, it should be kept in mind that our data represent mean values of glucose, insulin, and the resulting β-cell function and insulin sensitivity of the patients studied. Thus, it is conceivable that these opposing effects of stress on glucose control may be ultimately unbalanced and result in overt diabetes in individual patients, particularly in those with latent subclinical disease and higher stress scores.

The prevalence of type 2 diabetes is increased in patients suffering from major psychiatric disorders. The most prominent single feature of these patients underlying the increased diabetes prevalence is probably the associated eating disorder resulting frequently in obesity (7–9). In addition, several medications commonly used to treat these patients,

such as clozapine, have been implicated in their increased prevalence of diabetes, either directly by reducing insulin sensitivity at the cellular level or indirectly by modifying eating habits and/or physical activity (18,22,23). These data raise the question whether the changes in β-cell function and insulin sensitivity in our patients are due to changes in BMI (21) or to the use of atypical antipsychotic or antidepressant drugs. This explanation is unlikely for two main reasons: first, patients treated with atypical antipsychotic or antidepressant medications have been excluded from our study, and these drugs were not administered during hospitalization. Second, the mean BMI of our patients was not changed during the study period, and no correlation was found between BMI, stress score or the various parameters of glucose control. Nevertheless, the mean BMI of our patients (26.7 ± 5.8) was higher than normal. This, associated with a prevalent positive family history for diabetes or diabetes-associated conditions such cardiovascular diseases or dyslipidemia in the majority of the patients, indicates high risk for diabetes. The higher mean BMI may also explain why after discharge and upon return to a balanced mental state, their β-cell function and insulin sensitivity remained abnormal.

The effects of intermittent or continuous chronic psychological stress, i.e., weeks or months in duration rather than hours, on glucose control and incidence of type 2 diabetes remain controversial. This is due to the lack of accepted experimental human models, the extremely heterogeneous personal reaction to stress, and the difficulty to quantify psychological stress. The recently published Hoorn study (11) demonstrated an association between antecedent events of chronic psychological stress and increased incidence of type 2 diabetes. However, being a cross-sectional retrospective study based on a patient self-reported questionnaire, it could not establish a causative role for stress in promoting diabetes. Seematter et al. (24) demonstrated that short-term psychological stress of several hours induced by mental exercise resulted in a blunted increase in insulin sensitivity in obese nondiabetic individuals. Again, due to its short duration and use of external stress, this study could not establish the effect of long-standing endogenous psychological stress on glucose homeostasis. In contrast, our study provides for the first time prospective and relatively long-term human data, establishing the deleterious effect of acute and ongoing endogenous psychotic stress on glucose homeostasis in nondiabetic subjects. Our data also provide a plausible explanation to the increased incidence of diabetic ketoacidosis reported in schizophrenic patients treated with atypical antipsychotic drugs who develop type 2 diabetes (21,25,26). The combined effect of these drugs and the decreased insulin sensitivity observed in patients with extreme stress, together with the suppressed β-cell function may result in an acute derangement of glucose control and the ensuing ketoacidosis.

The interpretation of our data should be made with caution, however, because of several limitations. We studied patients with several risk factors for diabetes including elevated BMI, positive family history of diabetes, and chronic psychiatric background. Moreover, these patients were subjected to an extreme rather than "ordinary" psychological stress necessitating a referral to an emergency psychiatric ward. Finally, during hospitalization our study patients were treated with different dosages of phenothiazines or thioxanthenes, which may have a metabolic impact (27). The heterogeneous therapeutic regimens and the limited sample size did not allow us to determine the effect of these drugs on the study parameters. Nevertheless, in view of the relatively minor effect of these drugs on glucose metabolism, we believe that these therapies did not significantly affect our results.

In conclusion, our study demonstrates that severe acute psychotic stress may adversely affect glucose control in nondiabetic patients. Longer follow-up studies with a larger number of normal control subjects free of predisposing risk factors for diabetes are necessary to clarify the correlation between various forms and modalities of psychological stress and aberration of glucose control and the development of type 1 or type 2 diabetes.

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