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Original article

Prediabetes and mild hepatosteatosis are associated with blunted cortisol response to glucagon but not to growth hormone

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ABSTRACT

Background. – Although there is a close relationship between cortisol and growth hormone (GH) levels, glucose intolerance and hepatosteatosis, changes in GH and the hypothalamo-pituitary-adrenal (HPA) axis were not previously studied in prediabetes. The main purpose of the present study was to assess changes in GH and HPA axis and their relationship with hepatosteatosis in prediabetic patients.
Methods. – Forty prediabetic patients, with body-mass index (BMI) 25–35 kg/m^2, and 23 healthy individuals, with normal glucose tolerance and similar age and BMI, were included. The 75 g oral glucose tolerance test and glucagon stimulation test (GST) were used.
Results. – No significant differences were detected between prediabetic patients and healthy individuals in terms of insulin-like growth factor-1 (IGF-1), insulin-like growth factor-binding protein-3 (IGFBP-3), IGF-1/IGFBP3 ratio or adrenocorticotropic hormone (ACTH). GH responses to GST did not differ between groups. On the other hand, peak cortisol and area under the curve (AUC) $_{(cortisol)}$ response on GST were significantly lower in prediabetic patients. Both peak GH and AUC $_{(GH)}$ response on GST correlated negatively with waist circumference and body weight. The degree of hepatosteatosis correlated negatively with peak cortisol, GH, AUC (cortisol) and AUC (GH) response on GST.
Conclusion. – Cortisol response to GST is decreased in prediabetic patients, with relatively well conserved GH response. This suggests altered HPA axis responsiveness in prediabetes, as is known in diabetes. Thus, HPA axis changes in patients with diabetes probably start before the development of diabetes as such.

1. Introduction

Prediabetes is defined by glucose levels between normal and overtly diabetic [1]. Most diabetic individuals go through a prolonged prediabetes phase of about 10 years before overt diabetes develops [2]. To counteract peripheral insulin resistance, excessive insulin secretion occurs and euglycemia is maintained for a while. Inevitably, beta-cell function is impaired over time. Insulin resistance increases serum triglyceride levels and induces hepatic gluconeogenesis. Hepatic steatosis, which is mostly associated with insulin resistance, further aggravates hyperglycemia and insulin resistance. This vicious circle is thought to contribute to the transformation from non-alcoholic fatty liver disease (NAFLD) to non-alcoholic steatohepatitis (NASH) [3].

Growth hormone (GH) plays an important role in regulating body composition, strength, aerobic capacity and mood. Most circulating insulin-like growth factor-1 (IGF-1) originates from hepatocytes, and GH deficiency can lead to hepatosteatosis [4]. IGF-1 levels were found to be significantly lower in patients with NAFLD [5]. Although GH deficiency can lead to hepatosteatosis, the mechanism is not yet clear. Low plasma IGF-1 was associated with the development of type-2 diabetes and insulin resistance [6,7]. Previous studies showed that insulin up-regulates mRNA expression in human hepatocytes, increasing the level of total cellular hepatic GH receptors (GHRs). Therefore, insulin resistance associated with NAFLD may play a role in decreased IGF-I levels, by disrupting the insulin-induced increase in hepatic GHRs [8,9]. On the other hand, GH excess also has detrimental effects on insulin sensitivity, due to concomitant increase in free fatty acids under the lipolytic action of GH [10]. Similarly, high IGF-1 levels are associated with decreased insulin sensitivity, indicating a U-shaped association between serum IGF-1 level and insulin resistance [11]. The

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risk of glucose intolerance appears to increase in case of both deficiency and excess of GH or IGF-1, and the relationship between GH, IGF-1 and glucose intolerance seems to be divergent [12].

Clinical conditions associated with cortisol excess, such as Cushing's syndrome (CS), result in increased hepatic gluconeogenesis, which may lead to hyperglycemia and insulin resistance [13]. Apart from CS, glucose intolerance and fasting hyperglycemia were found to be associated with higher plasma cortisol levels in the morning than in normoglycemic individuals [14,15]. Low-dose adrenocorticotropic hormone (ACTH) stimulation test revealed decreased cortisol response in female diabetic subjects [16].

Although there is a close relationship between cortisol, GH, glucose intolerance and hepatosteatosis, the changes in GH and hypothalamo-pituitary-adrenal (HPA) axes in prediabetes were not previously studied. The main purpose of this study was to assess changes in GH and the HPA axis and their relationship with hepatosteatosis in prediabetic patients.

2. Materials and methods

2.1. Study design and participants

The study was approved by the local review board (2016/446), and written informed consent was received from each participant. Forty prediabetic patients with glucose level < 200 mg/dl on oral glucose tolerance test (OGTT) performed in the endocrinology clinic were included. The control group comprised healthy individuals with similar age and body-mass index (BMI) and normal glucose tolerance on OGTT. Subjects with uncontrolled hypothyroidism or hyperthyroidism, diabetes, adrenal disease, history of cancer, liver disease, history of chronic tuberculosis, diagnosed depression or any other psychiatric illness, using oral contraceptives or steroids or any drugs that could affect the HPA or GH axes were excluded.

Two participants (1 in the prediabetes and 1 in the healthy group) with low IGF-1 were excluded since they had isolated GH deficiency on glucagon stimulation test (GST), confirmed on subsequent insulin tolerance test. Data of 39 prediabetic patients and 22 healthy individuals were analyzed.

2.2. Procedures

Anthropometric measurements (weight, height and waist circumference) were obtained in the morning fasting state. Liver parenchyma echogenicity was graded on hepatic ultrasound as none or grade 1, 2 or 3 hepatosteatosis [17]. Patients with diffusely increased liver echogenicity and discernible portal vein wall and diaphragm echogenicity were categorized as grade 1, those with blurred portal vein echogenicity but appreciable diaphragm echogenicity as grade 2, and those with no visualization of portal vein and diaphragm echogenicity as grade 3 [18]. Ultrasonography used a Siemens Acuson S3000 ultrasound system and 6C1 HD transducer.

OGTT with 75 g oral glucose was performed, and fasting insulin and HbA1c levels were measured. Blood sampling for cortisol, ACTH, free thyroxine (T4), thyroid stimulating hormone (TSH), GH, IGF-1 and insulin-like growth factor-binding protein-3 (IGFBP-3) was performed at 8.00–9.00 a.m. during fasting. GST was performed as following; 1 mg glucagon was applied intramuscularly and samples were taken for GH and cortisol at 0, 90, 120, 150, 180, 210 and 240 minutes.

In serum samples from patients and healthy volunteers, alanine aminotransferase (ALT) and cholesterol levels were measured in a Roche Cobas c702 autoanalyzer using appropriate commercial kits. Serum LDL-C levels were calculated with the Friedewald formula.

Table 1
Demographic and biochemical data for prediabetic patients and individuals with normal glucose tolerance.

	Prediabetes ($n = 39$)	Normal glucose tolerance ($n = 22$)	P
Age (years)	50 ± 7.6	49.4 ± 7.7	0.791
Gender: F/M (%)	23/16 (58/42%)	13/9 (59/41%)	0.930
Waist circumference (cm)	98.8 ± 8.8	96.7 ± 9.8	0.399
Height (cm)	162.2 ± 7.6	164.2 ± 9.9	0.378
Weight (kg)	79.0 ± 10.1	78.3 ± 11.5	0.813
BMI (kg/m^2)	30 (28-31.9)	28.2 (27-31.2)	0.162
FPG (mg/dL)	91 ± 9.4	82.9 ± 8.4	0.010
Triglycerides (mg/dL)	174 ± 81	128.4 ± 57.2	0.017
Total Cholesterol (mg/dL)	199 ± 41	188 ± 36.8	0.270
HDL (mg/dL)	43.4 ± 9.1	49.7 ± 10.5	0.017
LDL (mg/dL)	122 ± 36.9	112.1 ± 30.2	0.384
HbA_{1C} (%)	5.6 ± 0.4	5.7 ± 0.3	0.473
OGTT 0 h (mg/dL)	111 ± 7.3	86.9 ± 6.1	<0.001
OGTT 2 h (mg/dL)	140.1 ± 31.4	108.4 ± 17.6	<0.001
Insulin (μU/mL)	9 (6–12.8)	8.5 (6–11.7)	0.538
HOMA-IR Score	1.9 (1.5–2.7)	1.5 (1.2–2.2)	0.116

BMI: body mass index; FPG: fasting plasma glucose; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance; OGTT: oral glucose tolerance test.

Homeostatic model assessment of insulin resistance (HOMA-IR) was calculated as [(fasting blood glucose(mg/dl) × insulin (μU/ml))/405].

Serum sex hormone binding globulin (SHBG), GH, IGF-1, IGFBP, cortisol, insulin, free T4 and TSH levels were assessed by electrochemiluminescence immunoassay (ECLIA) on the Roche Cobas c8000 series e602 module using commercial kits.

2.3. Statistical analyses

Statistical analyses used SPSS software, version 22. Normal distribution was assessed visually (histogram, probability plots) and analytically (Kolmogorov-Smirnov/Shapiro-Wilk test). Descriptive analyses were reported as median and 25–75% interquartile range (IQR) for non-normally distributed and ordinal variables. Proportions for gender and presence of metabolic syndrome were assessed by cross-tabulation and compared between groups on Chi-square test. The Mann-Whitney U test was used to compare non-normally distributed data and Student t test for normally distributed data. Pearson or Spearman correlation analysis was used according to data distribution. Multiple groups were compared on 1-way ANOVA, followed by Tukey's post-hoc test or Kruskal-Wallis test. The significance threshold was set at $P < 0.05$.

3. Results

Data of the prediabetic patients and healthy individuals with normal glucose tolerance were analyzed. Age, gender, waist circumference, height, weight and BMI were similar between the two groups (Table 1). Fasting plasma glucose (FPG), triglyceride level and 2nd hour glucose after OGTT were significantly higher and HDL-cholesterol level significantly lower in prediabetic patients. There were no significant differences in total or LDL-cholesterol, HbA1c, insulin, HOMA-IR score, IGF-1, IGFBP-3, IGF-1/IGFBP3 ratio, ACTH, SHBG or TSH (Table 1).

Basal and peak GH and $AUC_{(GH)}$ responses to GST did not differ between the two groups ($P = 0.401$, $P = 0.213$, $P = 0.081$, respectively) (Fig. 1). Basal cortisol did not significantly differ ($P = 0.620$), while peak cortisol and $AUC_{(cortisol)}$ responses to GST were lower in prediabetic patients ($P = 0.001$ and $P = 0.025$, respectively) (Fig. 1). 35 prediabetic patients (90%) and 13 subjects with normal glucose tolerance (59%) had mild hepatosteatosis (grade 1–2) on ultrasonography ($P = 0.01$). No patients showed grade 3 hepatosteatosis.

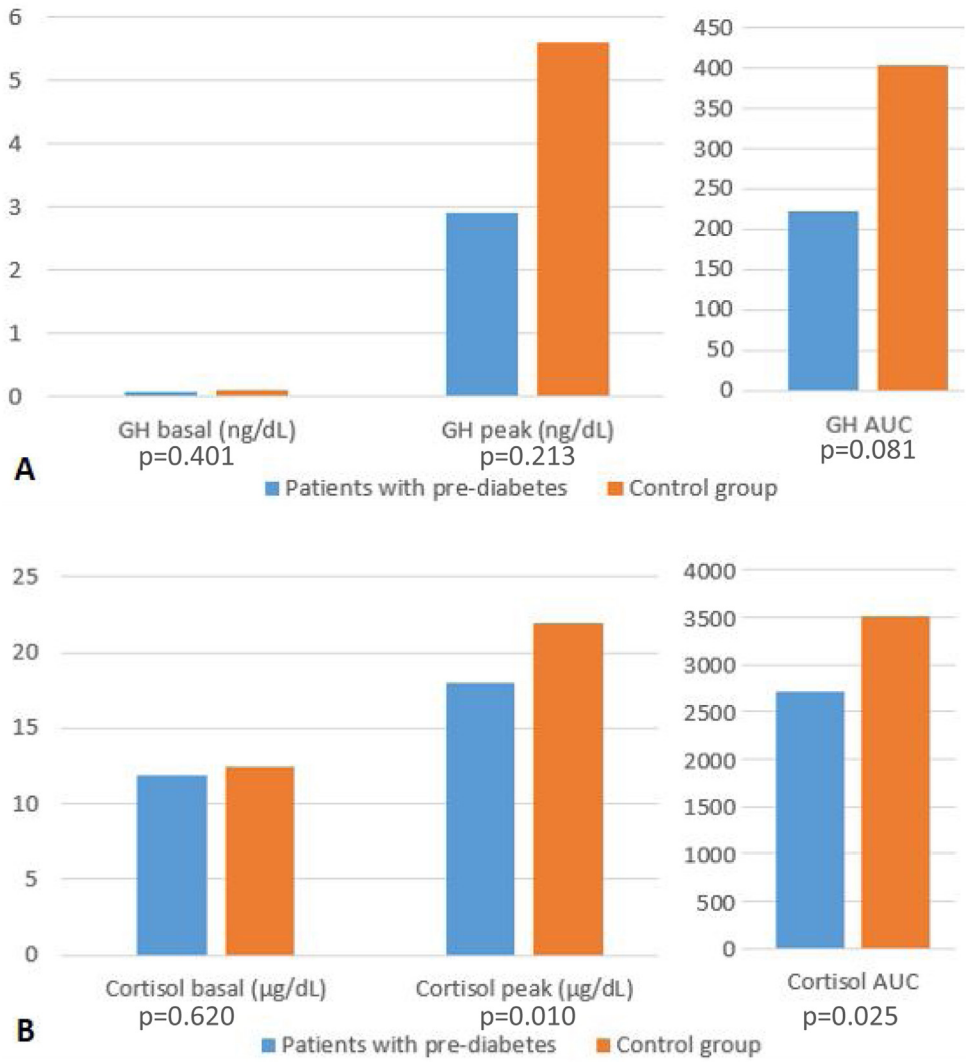

Fig. 1. Comparison of basal, peak and AUC values of growth hormone (A) and cortisol (B) during glucagon stimulation test between prediabetic patients and controls.

Peak cortisol and AUC (cortisol) responses to GST remained significantly lower in (59%) after controlling for BMI and presence of hepatosteatosis ($P = 0.033$ and $P = 0.025$, respectively).

Regardless of prediabetes status, IGF-1 did not correlate with age, HOMA-IR score or glucose level. Both peak GH and AUC (GH) responses to GST correlated negatively with waist circumference (rho: −0.257, $P < 0.05$ and rho: −0.270, $P < 0.05$, respectively). Basal and peak GH and AUC (GH) responses to GST correlated negatively with body weight (rho −0.254, −0.419, −0.438 and $P < 0.05$, < 0.01, < 0.01 respectively). Peak GH and AUC (GH) responses to GST were lower in obese (BMI > 30 kg/m^2) than overweight subjects (BMI 25–30 kg/m^2) (median (range) 2.30 (0.11–30.4) and 6.0 (0.41–20.20), $P = 0.029$; 179.4 (13.5–793.7) and 383.7 (16.4–1707.0), $P = 0.021$, respectively), and there was no difference in basal GH, basal or peak cortisol or AUC (cortisol) response to GST. There was no correlation between body weight and IGF-1.

Basal GH levels were significantly higher in participants without hepatosteatosis than those with grade 1 ($P = 0.049$) or grade 2 ($P = 0.046$), while mean basal cortisol levels were similar on post-hoc analysis. Peak serum GH and cortisol did not differ between subjects without hepatosteatosis and those with grade 1 hepatosteatosis ($P = 0.067$ and $P = 0.051$, respectively), but were significantly higher than in those with grade 2 hepatosteatosis ($P = 0.011$ and $P = 0.001$, respectively). The AUC (GH) value was higher in the group without hepatosteatosis than in subjects with grade 1 ($P = 0.013$) or grade 2 ($P = 0.002$). The AUC (cortisol) value did not differ between subjects without hepatosteatosis and those with grade 1 hepatosteatosis ($P = 0.588$), but was significantly higher than in those with grade 2 hepatosteatosis ($P = 0.004$).

4. Discussion

In the present study, prediabetes was associated with a blunted cortisol response to GST and relatively well-conserved GH response. Prediabetic patients showed more frequent (90% vs. 59%) and higher-grade hepatosteatosis than subjects with normal glucose tolerance, despite the similarity in age and BMI between the two groups.

It is well known that increased BMI and waist circumference are risk factors for prediabetes [19,20]. NAFLD developed in 45.4% and diabetes in 8% of 6240 prediabetic patients at 5 years' follow-up, and diabetes developed more frequently in those with NAFLD [21].

In the present study, prediabetic patients had similar IGF-1 levels and GH responses to GST compared to subjects with normal glucose tolerance, and there were no correlations between IGF-1 and glucose levels. In a recent study, IGF-1 levels were found to be similar in diabetic and healthy subjects [16].

Previous studies reported dysregulated GH metabolism in NAFLD. Hepatic IGF-1 expression, but not GHR, was lower in patients with NASH than in simple hepatosteatosis [22]. In patients with HIV and NAFLD, hepatic IGF-1 mRNA was decreased [23]. Other studies reported a negative association between NAFLD severity and serum IGF-1 and GH [24,25]. Thus, the changes in GH metabolism may be due more to hepatosteatosis than prediabetes per se. We attributed the tendency for lower GH levels in the present study to the presence of hepatosteatosis in prediabetic patients.

We did not find a significant difference in HbA1c between prediabetic patients and subjects with normal glucose tolerance. Recently, in a study of 946 individuals, HbA_{1C} and OGTT were not in full concordance in the diagnosis of prediabetes and diabetes in obese and overweight individuals [26].

Both clinical and experimental studies indicate increased cortisol levels in diabetes, related to the duration and complications of the disease [27–29]. Diabetes is associated with a flattened circadian cortisol curve, with higher cortisol levels in the evening and at night, and disturbed cortisol response to stress and recovery from stress [30,31]. Furthermore, cortisol suppression by dexamethasone is also abolished in diabetes in the absence of Cushing's syndrome, and poorly-controlled diabetes is among the etiologic factors of pseudo-Cushing syndrome [32]. In a retrospective analysis of 884 obese patients, hypercortisolism (defined by elevated urinary free cortisol (UFC) and non-suppression on dexamethasone suppression test (DST)) was more frequent in case of impaired glucose homeostasis, including very early stages; however, there was no such relationship for the other components of the metabolic syndrome: waist circumference, hypertension or atherogenic dyslipidemia [33]. In a study by Hepsen et al., morbidly obese individuals were divided into 3 groups: normal glucose tolerance, prediabetes and type-2 diabetes. Plasma cortisol levels after DST were highest in diabetics followed by prediabetics and lowest in normal glucose tolerance. High plasma cortisol response to DST was reported to be an independent risk factor for type-2 diabetes in obese subjects [34]. Moreover, Leibowitz et al. reported a 3.3% prevalence of subclinical Cushing's syndrome in obese patients with poorly controlled type-2 diabetes; screening for Cushing's syndrome should be considered in these patients [35]. The stress response is also altered in diabetic patients, making them more prone to depression [36]. Patients with type-2 diabetes who presented to an emergency department with severe hypoglycemia showed impaired cortisol response in 20% of cases, impaired GH response in 73%, and impairment of both in 7%. Advanced age and higher BMI were independently associated with abnormal GH response [37].

Although there are a number of studies of the effects of diabetes on the HPA axis, most reporting chronic hypercortisolemia, decreased stress responsiveness and disturbed circadian rhythm, data on prediabetes are very limited. Cortisol secretion, although normal, was suggested to be inappropriately high given the enhanced central and peripheral sensitivity to glucocorticoids in patients with diabetes and prediabetes [38]; however, there were only 5 prediabetic subjects in that study. Previously, prediabetes was found to be associated with higher 10–12 a.m. salivary cortisol levels than in healthy subjects, but lower than in diabetic patients [39]. In a very recent study on a prediabetic rat model, plasma corticosterone levels were elevated despite similar ACTH levels in the non-stressful state in prediabetes. In the stressed condition, the rodents showed decreased ACTH and corticosterone levels. The changes were attributed to the preceding chronic cortisol elevation. The expression of hippocampal glucocorticoid and mineralocorticoid receptors was increased in the stressed prediabetic rats. It was suggested that mineralocorticoid receptor elevation decreased corticotropin-releasing hormone (CRH) inhibition, which was thought to be responsible from the altered behavior under stress [40].

In the present study, patients with prediabetes had similar basal cortisol levels but lower cortisol responses to GST compared to subjects with normal glucose tolerance. This was the first study to show a blunted cortisol response to GST in prediabetes. Prediabetes itself may be responsible for this blunted cortisol response, supporting the findings of the above-mentioned study in prediabetic rats [40]. Our results may shed light on how impaired glucose metabolism causes disturbances in the HPA axis not only in severe states but also in prediabetes.

The effect of obesity may be another factor affecting cortisol response to the GST, but we recently showed that obesity was not associated with decreased HPA axis response to the GST in healthy people, unlike GH [41]. Furthermore, BMI and weight were similar between groups in the present study.

Higher fasting glucose levels and presumably higher nocturnal hyperglucagonemia may be factors leading to reduced responsiveness to glucagon, changing the glycemic fluctuations. Nocturnal hyperglucagonemia was suggested to be responsible for increased glucose levels during the night and morning in diabetic subjects [42]. Obesity and insulin resistance resulted in higher glucagon levels during both hypoglycemic and hyperglycemic clamp, with associated alterations in autonomic nervous system response [33]. Unfortunately, we did not measure fasting glucagon levels or glucose responses during GST. Other stimulation tests may be required to eliminate the effects of variations in glucagon level and tissue response to glucagon in patients with prediabetes. Another study limitation was that we used ultrasonography for the evaluation of hepatosteatosis. Being less sensitive, this may have underestimated the presence of hepatosteatosis, especially in the control group, as 90% of prediabetic patients were already diagnosed with either grade 1 or 2 steatosis.

5. Conclusion

Cortisol response to GST is decreased in prediabetic patients, with relatively well-conserved GH response. These data suggest reduced HPA axis responsiveness in prediabetes, as seen in diabetes. Thus, the changes in the HPA axis in diabetic patients probably start before the development of diabetes.

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Authors' contribution

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Ozlem Deveci, Kamil Deveci, Zuleyha Karaca, Fatih Tanriverdi, Aysa Hacıoğlu, Kursad Unluhizarci and Fahrettin Kelestimur. The first draft of the manuscript was written by Ozlem Deveci and Zuleyha Karaca and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval

This study was approved by Local Ethics Committee (approval number: 2016/446).

The study was approved by Erciyes University Medical School Ethics Committee (approval number: 2016/446) and was performed in accordance with the ethical standards as laid down in

the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Consent

Informed consent was obtained from all individual participants included in the study.

Disclosure of interest

The authors declare that they have no competing interest.

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