The effect of serum cortisol on the prediabetes stage under normal and stress state.

Ali Abdulraheem Jabbar, Maysaa jalal majeed *

Department of Biochemistry, College of Medicine, University of Baghdad, Baghdad, Iraq

*Corresponding author : ali_poet@yahoo.com.

Abstract

Introduction Prediabetes is a disorder described as having above normal blood glucose levels but below the specified diabetes threshold. It is considered a dangerous condition, with a high likelihood of developing diabetes. Stress appears to be an significant consideration for the risk of prediabetes. Cortisol is a glucocorticoid that is the product of a long and complex endocrine reaction chain resulting from stress. It is formed by the zone fasciculate of the adrenal cortex in the adrenal gland in many animals. It is formed in lesser amounts in other tissues.

Material and method case study was conducted during the period from October 2019 to January 2020. It consisted of 60 men; 30 were prediabetes subject (27 persons under normal state, 7 persons under stress state) and 30 healthy men.

Result serum cortisol significant in normal and stress state with differences mean in both conition.

Conclusion the level of serum cortisol in prediabetes subject supports the hypothesis that cortisol will effect to prediabetes but this is too early to consider serum cortisol as an influential and major cause of prediabetes.

Key words; prediabetes, serum cortisol, stress hormone, stress with glucose level
Introduction

Prediabetes is a disorder described as having above normal blood glucose levels but below the specified diabetes threshold. It is considered a dangerous condition, with a high likelihood of developing diabetes. Observational evidence indicates a connection between prediabetes and diabetes complications such as nephropathy, small fiber neuropathy, early retinopathy and macrovascular disease risk[1].

Daily follow-up services and lack of knowledge of the symptoms of the disease may be the explanation for the rate of complications increase. While the manifestations of the disease begin in the early stages of the disease, the pre-stage called prediabetes is before it is known as a full blown disorder[2]. The World Health Organization (WHO) has defined prediabetes as a state of intermediate hyperglycemia which is laboratory diagnosed with the help of two specific parameters:

- **Impaired Fasting Glucose**
  also defined as fasting plasma glucose of 6.1-6.9 mmol/L (110 to 125 mg/dL).

- **Impaired Glucose tolerance**
  defined as 2 h plasma glucose of 7.8-11.0 mmol/L (140-200 mg/dL) after ingestion of 75 g of oral glucose load[3].

At the other hand, the American Diabetes Association (ADA) recommends the same cut-off value for impaired glucose tolerance (140-200 mg / dL) but a lower cut-off value for impaired fasting glucose (100-125 mg / dL). Hemoglobin A1c (HbA1c) with a prediabetes diagnosis range of 5.7 to 6.4 per cent[4]. This is what was mainly adopted in this study, as it gives an indication for a longer period of time than the instantaneous stage that the fasting sugar level provides us with, which can be inaccurate in terms of the person’s commitment to the abundance required to fast an increase or decrease. Prediabetes takes priority over the development of type II diabetes. Prediabetes, is associated with elevated levels of plasma insulin (hyperinsulinemia). It happens as a compensatory reaction of the pancreatic beta cells to decrease the responsiveness of target tissues to the metabolic effects of insulin, a disorder known as prediabetes insulin resistance. This is due to the derangement of the liver's glucostatic function as the major cause of hyperglycemia, the liver contains 6-phosphatase glucose which regulates glucose entry into circulation. Insulin
stimulates glycogen synthesis and inhibits the production of hepatic glucose. When plasma glucose is high, the secretion of insulin is usually increased, and hepatic glucogenesis is reduced. Glucagon can help with hyperglycemia as it induces gluconeogenesis. Declining insulin sensitivity impairs the use and storage of carbohydrates, raises blood glucose and induces a compensatory rise in insulin secretion. Insulin resistance development and impaired glucose metabolism is typically a gradual process, beginning with excess weight gain and obesity. Most of the insulin resistance seems to be caused by insulin signaling pathways abnormalities that link receptor activation with multiple cellular effects[5][6]. A comparison of insulin mechanism in healthy and resistance state show in (figure 1), Prolonged insulin resistance is not necessary even for increased insulin levels to maintain normal glucose control. Consequently, mild hyperglycemia occurs in the early stages of the disease after consumption of carbohydrates, In later stages of prediabetes, the pancreatic beta cells become "exhausted" and cannot produce enough insulin to prevent hyperglycemia, particularly after the individual ingests a meal rich in carbohydrates.

Stress appears to be a significant consideration for the risk of prediabetes, as shown by a prospective cohort study showing that perceived permanent stress resulted in an increase in prediabetes risk of 45% (relative to those who reported no stress), even after adjustment for traditional risk factors like socio-economic status[7]. An analysis of psychosocial predictors for prediabetes also identified depression, general emotional stress, anxiety, sleep problems and aggression as main risk factors[8] Stressful conditions activate the hypothalamic-pituitary-adrenal (HPA) axis to produce cortisol (the primary hormone responsible for the physiological stress
response), which induces resistance to hepatic insulin and decreases insulin secretion[8]. Chronic overpressure may also have a detrimental effect on control of the HPA axis. Dysregulation of the HPA axis is problematic in that it is heavily involved in prediabetes growth, possibly due to increased visceral adiposity[9], Furthermore, stress may also increase the risk of prediabetes by altering food intake habits, in particular by raising the cravings and consumption of foods in fat and sugar, thus raising the response of postprandial insulin and the risk of obesity[10]. Cortisol is a glucocorticoid that is the product of a long and complex endocrine reaction chain resulting from stress[11]. Is formed by the zone fasciculate of the adrenal cortex in the adrenal gland in many animals[12]. It is formed in lesser amounts in other tissues[13]. This is released with a diurnal cycle and its release in reaction to stress and low blood glucose concentration raises blood sugar through gluconeogenesis, suppresses the immune system and improves fat, protein and carbohydrate metabolism[14]. This also limits bone development[15].

**Material and method**

This case study was done at the National Center for teaching laboratories in Medical City of Baghdad / Iraq during the period from October 2019 to January 2020. It consisted of 60 men; 30 were prediabetes subject (27 persons under normal state, 7 persons under stress state) and 30 healthy men. Blood sample was taken from the blood vein in a fasting state for two groups. Blood samples will be taken after overnight fasting state (8-12 hr.) in serum-separating tube (vacationer gel tube) and (EDTA tube) for Glycated haemoglobin (HbA1c). The vacationer tube blood sample allows to clot for 30 minutes, centrifuged at 3000 rpm. The fasting serum glucose and lipid, HbA1c and a.m serum cortisol were measured in the same day of blood collection. Fasting serum glucose, HbA1c, serum cortisol Measurements was implemented at the National Center for teaching laboratories in Medical City of Baghdad. For serum glucose, fasting using Siemens Dimension RxL Max clinical chemistry system. HbA1c high-performance liquid chromatography (HPLC) Technique, Serum cortisol determination by Siemens IMMULITE 2000 systems. **Statistical analysis** ; analysis of data by using statistical program spss 21 for all parameters to mean, standard deviation (SD). For Sensitivity, specificity, area under curve and cut-off point use ROC analysis.
**Result**

significant difference (p ≤ 0.05) which was found among and between groups for serum Glucose and glycated hemoglobin (HBA1C). Finding Clearfield by (table1)

| Studied parameters | Studied groups           | mean ± SD          | F-Test sig |
|--------------------|--------------------------|--------------------|------------|
| Serum glucose (mg/dl) | Healthy subject          | 92.31 ± 7.80       | p ≤ 0.05   |
|                    | Prediabetes subject      | 108.17 ± 20.73     | S          |
| HBA1C %            | Healthy subject          | 5.15 ± 0.32        | p ≤ 0.05   |
|                    | Prediabetes subject      | 5.95 ± 0.19        | S          |

Fig2: mean ± SD for serum glucose
Fig 3: mean ± SD for HBA1C

1-Serum cortisol under normal condition

Also showed significant ( p≤ 0.05) difference among and between group (table2) with mean ± SD Are shown in the table2 (fig4).

Table2: mean ± SD for serum cortisol

| Studied parameter | Studied groups            | mean ± SD      | F-Test sig |
|-------------------|---------------------------|----------------|-----------|
| s.cortisol µg/dl  | Healthy subject           | 9.27 ± 1.53    | p≤ 0.05   |
|                   | Prediabetes subject       | 10.71 ± 3.50   | S         |

2- serum cortisol under stress state

Show significant (p ≤ 0.05) difference in person’s (7 persons) under stress state with mean ± SD (11.68 ± 5.23 μg/dl) (fig5)

Fig5: mean ± SD for serum cortisol under stress state
Sensitivity, specificity, area under curve, and cut-off point for serum cortisol Finding Clearfield by (table3) (fig6)

Table3: ROC analysis for serum cortisol.

| Parameter | sensitivity | Specificity | AUC  | Cut off value |
|-----------|-------------|-------------|------|---------------|
| s.cortisol| 93%         | 62%         | 0.66 | 13.30         |

Fig6: ROC analysis for serum cortisol

s.Cortisol in prediabetes showed appositive significant correlation with each of s.Glucose and HBA1c with \( r = 0.43, p \leq 0.05 \) \( r = 0.50, p \leq 0.05 \) respectively as fig 7, fig 8.
Discussion

Prediabetes states are important because individuals with glucose concentrations in this range are at elevated risk of developing complications of T2D and diabetes[16][17]. High significant differences (p ≤ 0.05) among and between groups for serum cortisol in both conditions (normocaloric and stress) whereas Glucocorticoids stimulate gluconeogenesis by inducing gluconeogenic gene expression in the liver; and by suppressing glucose uptake in the skeletal muscle and
adipocytes (inhibiting the translocation of GLUT 4 to the cell surface) [18][19][20][21][22].

That contributes to insulin resistance Insulin resistance is therefore likely to be a significant mechanism by which an excess of Glucocorticoids cortisol causes diabetes. Insulin secretion generally increases compensatory along with decreases in insulin resistance in order to maintain as natural a plasma glucose levels as possible. Previous research investigated the longitudinal relationship between cortisol components and potential T2D, and a group of adults living in the community affected fasting glucose. Find that increased evening cortisol levels were predictive around 9 years later for new-onset T2D[23], Obesity is risk factor for T2D[24], and weight loss is the recommended prediabetes treatment[17]. The visceral adipose tissue exhibits elevated levels of glucocorticoid receptors[25], BMI was correlated with cortisol slope and evening cortisol and expected a new onset of T2D and a wider category of glucose imbalance[23]. Notwithstanding this, the relationship between potential glucose status and these tests for cortisol was robust to adjust for BMI[23], This indicates that obesity isn't the factor that raises the risk of T2D and IFG through diurnal cortisol secretions[23]. Abnormal regular rhythms of cortisol can interfere with both immune and inflammatory processes. Inflammatory cytokines play a role in T2D, and increased concentrations of cytokines are predictive of developing T2D[26], Besides changes in the immune and inflammatory processes, disruptions in circadian rhythms that act on IFG and T2D by altering the metabolism of glucose. Experimental research indicates that circadian disturbance by inadequate insulin secretion raises both the fasting and postprandial levels of plasma glucose[27]. Increasing body of literature indicates psychosocial stress factors increase T2D risk[8], and adipocytes are believed to be a source of cortisol. If that compensatory rise in the secretion of Insulin fails Rate increases in plasma glucose leading to diabetes, in addition most studies with Cushing syndrome or Glucocorticoid cortisol administration, increased serum insulin levels were observed[28][29][30][31][32][33][34], High cortisol levels in the body, reduces the glucose metabolism, and increases fat mobilization and breakdown. Diminished glucose metabolism leads to hyperglycaemia, and elevated levels of blood fat contributes to insulin resistance, blood fats and hyperglycemia are classic symptoms of diabetes An elevated cortisol level antagonizes insulin's effect on blood glucose[35].
Cortisol influences blood glucose levels in peripheral tissues such as skeletal muscle and fat\[36\]. Thus cortisol may contribute to elevated blood glucose levels by causing inefficient glucose uptake in the peripheral tissue in diabetics. Higher levels of cortisol in the body can increase the production of glucose in the liver, increase the accumulation of lipids, inhibit glycogen synthesis and reduce insulin secretion\[9]\[37\].

A combination of events is likely to contribute to type 2 diabetes development.

**Conclusion**

The level of serum cortisol was higher in prediabetes subject than in normal healthy group under normal condition while the concentration greater under stress state this supports the hypothesis that cortisol will effect to prediabetes but this is too early to consider serum cortisol as an influential and major cause of prediabetes before taking a large sample under stress state taking into account all the causes of high level of serum cortisol in the blood.

**References**

[1] N. Bansal, “Prediabetes diagnosis and treatment: A review,” *World J. Diabetes*, vol. 6, no. 2, p. 296, 2015.

[2] M. L. Olson *et al.*, “Decreased GlycA after lifestyle intervention among obese, prediabetic adolescent Latinos,” *J. Clin. Lipidol.*, vol. 13, no. 1, pp. 186–193, 2019.

[3] X. Wang *et al.*, “People-centred integrated care in urban China,” *Bull. World Health Organ.*, vol. 96, no. 12, p. 843, 2018.

[4] M. J. Davies *et al.*, “Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD),” *Diabetologia*, vol. 61, no. 12, pp. 2461–2498, 2018.

[5] W. F. Ganong, “Review of medical physiology 23rd ed,” *Lange med. Public*, vol. 19, pp. 306–326, 2003.

[6] A. C. Guyton and J. E. Hall, “Textbook of medical physiology 11th ed,” *Philadelphia, Perm Elsevier Saunders*, 2006.

[7] M. Novak, L. Björck, K. W. Giang, C. Heden-Ståhl, L. Wilhelmsen, and A. Rosengren, “Perceived stress and incidence of Type 2 diabetes: a 35-year
follow-up study of middle-aged Swedish men,” *Diabet. Med.*, vol. 30, no. 1, pp. e8–e16, 2013.

[8] F. Pouwer, N. Kupper, and M. C. Adriaanse, “Does emotional stress cause type 2 diabetes mellitus? A review from the European Depression in Diabetes (EDID) Research Consortium,” *Discov. Med.*, vol. 9, no. 45, pp. 112–118, 2010.

[9] R. Rosmond, “Stress induced disturbances of the HPA axis: a pathway to type 2 diabetes?,” *Med. Sci. Monit.*, vol. 9, no. 2, pp. RA35–RA39, 2003.

[10] T. M. Matos and J. N. De Souza-Talarico, “How stress mediators can cumulatively contribute to Alzheimer’s disease An allostatic load approach,” *Dement. Neuropsychol.*, vol. 13, no. 1, pp. 11–21, 2019.

[11] C. M. Friedenreich *et al.*, “The effect of prescribed exercise volume on biomarkers of chronic stress in postmenopausal women: Results from the Breast Cancer and Exercise Trial in Alberta (BETA),” *Prev. Med. reports*, vol. 15, p. 100960, 2019.

[12] E. Scott, “Cortisol and stress: How to stay healthy,” *About. com. Retrieved*, vol. 29, 2011.

[13] M. D. Taves, C. E. Gomez-Sanchez, and K. K. Soma, “Extra-adrenal glucocorticoids and mineralocorticoids: evidence for local synthesis, regulation, and function,” *Am. J. Physiol. Metab.*, vol. 301, no. 1, pp. E11–E24, 2011.

[14] E. N. Marieb, *Human Anatomy & Physiology Passcode*. Benjamin-Cummings, 2010.

[15] P.-M. Wippert, M. Rector, G. Kuhn, and K. Wuertz-Kozak, “Stress and alterations in bones: an interdiscipliary perspective,” *Front. Endocrinol. (Lausanne)*, vol. 8, p. 96, 2017.

[16] D. H. Morris *et al.*, “Progression rates from HbA 1c 6.0–6.4% and other prediabetes definitions to type 2 diabetes: a meta-analysis.” Springer, 2013.

[17] A. G. Tabák, C. Herder, W. Rathmann, E. J. Brunner, and M. Kivimäki, “Prediabetes: a high-risk state for diabetes development,” *Lancet*, vol. 379, no. 9833, pp. 2279–2290, 2012.

[18] M. Roldan, A. J. Rose, and S. Herzig, “Glucocorticoid hormones and energy homeostasis,” *Horm. Mol. Biol. Clin. Investig.*, vol. 19, no. 2, pp. 117–128, 2014.
[19] A. Rafacho, H. Ortsäter, A. Nadal, and I. Quesada, “Glucocorticoid treatment and endocrine pancreas function: implications for glucose homeostasis, insulin resistance and diabetes,” *J Endocrinol*, vol. 223, no. 3, pp. R49–R62, 2014.

[20] R. Pivonello, A. M. Isidori, M. C. De Martino, J. Newell-Price, B. M. K. Biller, and A. Colao, “Complications of Cushing’s syndrome: state of the art,” *Lancet Diabetes Endocrinol.*, vol. 4, no. 7, pp. 611–629, 2016.

[21] S. P. Weinstein, C. M. Wilson, A. Pritsker, and S. W. Cushman, “Dexamethasone inhibits insulin-stimulated recruitment of GLUT4 to the cell surface in rat skeletal muscle,” *Metabolism*, vol. 47, no. 1, pp. 3–6, 1998.

[22] S. P. Weinstein, T. Paquin, A. Pritsker, and R. S. Haber, “Glucocorticoid-induced insulin resistance: dexamethasone inhibits the activation of glucose transport in rat skeletal muscle by both insulin-and non-insulin-related stimuli,” *Diabetes*, vol. 44, no. 4, pp. 441–445, 1995.

[23] R. A. Hackett, M. Kivimäki, M. Kumari, and A. Steptoe, “Diurnal cortisol patterns, future diabetes, and impaired glucose metabolism in the Whitehall II cohort study,” *J. Clin. Endocrinol. Metab.*, vol. 101, no. 2, pp. 619–625, 2016.

[24] D. P. Guh, W. Zhang, N. Bansback, Z. Amarsi, C. L. Birmingham, and A. H. Anis, “The incidence of co-morbidities related to obesity and overweight: a systematic review and meta-analysis,” *BMC Public Health*, vol. 9, no. 1, p. 88, 2009.

[25] M. Pou Karla *et al.*, “Visceral and Subcutaneous Adipose Tissue Volumes Are Cross-Sectionally Related to Markers of Inflammation and Oxidative Stress,” *Circulation*, vol. 116, no. 11, pp. 1234–1241, 2007.

[26] X. Wang *et al.*, “Inflammatory markers and risk of type 2 diabetes: a systematic review and meta-analysis,” *Diabetes Care*, vol. 36, no. 1, pp. 166–175, 2013.

[27] O. M. Buxton *et al.*, “Adverse metabolic consequences in humans of prolonged sleep restriction combined with circadian disruption,” *Sci. Transl. Med.*, vol. 4, no. 129, pp. 129ra43-129ra43, 2012.

[28] A. M. Isidori *et al.*, “The hypertension of Cushing’s syndrome: controversies in the pathophysiology and focus on cardiovascular complications,” *J. Hypertens.*, vol. 33, no. 1, p. 44, 2015.

[29] G. Mazziotti, C. Gazzaruso, and A. Giustina, “Diabetes in Cushing syndrome: basic and clinical aspects,” *Trends Endocrinol. Metab.*, vol. 22, no. 12, pp.
499–506, 2011.

[30] T. Mancini, B. Kola, F. Mantero, M. Boscaro, and G. Arnaldi, “High cardiovascular risk in patients with Cushing’s syndrome according to 1999 WHO/ISH guidelines,” Clin. Endocrinol. (Oxf.), vol. 61, no. 6, pp. 768–777, 2004.

[31] J. C. Beard, J. B. Halter, J. D. Best, M. A. Pfeifer, and D. Porte Jr, “Dexamethasone-induced insulin resistance enhances B cell responsiveness to glucose level in normal men,” Am. J. Physiol. Metab., vol. 247, no. 5, pp. E592–E596, 1984.

[32] P. Schneiter and L. Tappy, “Kinetics of dexamethasone-induced alterations of glucose metabolism in healthy humans,” Am. J. Physiol. Metab., vol. 275, no. 5, pp. E806–E813, 1998.

[33] B. Ahrén, “Evidence that autonomic mechanisms contribute to the adaptive increase in insulin secretion during dexamethasone-induced insulin resistance in humans,” Diabetologia, vol. 51, no. 6, p. 1018, 2008.

[34] D. H. van Raalte et al., “Islet-cell dysfunction induced by glucocorticoid treatment: potential role for altered sympathovagal balance?,” Metabolism, vol. 62, no. 4, pp. 568–577, 2013.

[35] N. Ganesan, J. Priya, and G. Devi, “Estimation of cortisol in Type II diabetes mellitus among South Indian population,” Drug Invent. Today, vol. 12, no. 9, 2019.

[36] L. Ørskov et al., “Skeletal muscle glucose uptake, glycogen synthase activity and GLUT 4 content during hypoglycaemia in type 1 diabetic subjects,” Scand. J. Clin. Lab. Invest., vol. 61, no. 5, pp. 371–381, 2001.

[37] M. F. Nielsen et al., “Impaired basal glucose effectiveness but unaltered fasting glucose release and gluconeogenesis during short-term hypercortisolemia in healthy subjects,” Am. J. Physiol. Metab., vol. 286, no. 1, pp. E102–E110, 2004.