ASSOCIATION OF SERUM CORTISOL AND SERUM PROTEIN IN POSTMENOPAUSAL WOMEN WITH TYPE-2 DIABETES MELLITUS

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Abstract. The intricate interplay between hormonal and metabolic factors in post-maturity women with T2DM demands a comprehensive understanding of their interrelationships. This study delves into the connotation between serum cortisol and serum protein levels in postmenopausal women with T2DM, revealing significant insights. Elevated serum cortisol levels are linked to increased serum protein concentrations, indicating a connection to underlying inflammatory processes. This relationship highlights the multifaceted nature of diabetes in this demographic, where hormonal imbalances and chronic inflammation play pivotal roles in disease progression. In this study, hormonal and inflammatory factors need to be considered when assessing and managing T2DM in postmenopausal women. Elevated cortisol not only exacerbates metabolic dysfunction but also promotes a pro-inflammatory state, contributing to amplified levels of acute-phase proteins like C-reactive protein (CRP). These markers of inflammation are linked to cardiovascular diseases and microvascular complications, such as nephropathy, retinopathy, and neuropathy. By advancing our understanding of the association between serum cortisol, serum proteins, and T2DM, we can develop more targeted interventions. Addressing these factors through lifestyle modifications, pharmacological treatments, and stress management techniques can significantly mitigate the adverse effects, ultimately helping to prevent cardiovascular and microvascular complications. This holistic approach is crucial for improving the overall well-being and value of lifespan in postmenopausal females with T2DM.
Keywords: *diabetes mellitus, blood sugar, metabolic disorder, well-being, serum cortisol, postmenopausal women*

Introduction

A chronic metabolic condition named diabetes mellitus (DM) is characterized by persistently high levels of blood sugar (hyperglycemia) (Goyal et al., 2021). Two factors cause this metabolic disorder: inadequate insulin secretion by pancreatic cells and an inability of insulin-sensitive tissues to respond properly. This results in broken feedback loops between insulin action and secretion (Galicia-Garcia et al., 2020). In scientific discourse, the prevailing understanding posits that it is insulin resistance that contributes to the occurrence of hyperglycemia and compensatory initial hyperinsulinemia, which is a critical step in the progression to metabolic syndrome and ultimately to type 2 diabetes mellitus (Reaven, 1991). Nowadays, 90% of adults with diabetes mellitus have type 2 diabetes (T2DM), accounting for 1 in 11 cases of the disease worldwide, India bears a substantial portion of this encumbrance, with a distressing 77 million individuals affected, emerging as a major epicenter alongside China (Zheng et al., 2018; InformedHealth Web Portal, 2006). Type 2 diabetes mellitus, commonly referred to as adult-onset diabetes, typically manifests in individuals aged over 40, with a notable prevalence among those aged 60- 70, a trend influenced by both chronological and ovarian aging processes (Mayo Clinic Physicians, 2012; InformedHealth Web Portal, 2006). It is a chronic illness that requires long-term treatment to prevent the development of serious problems, both macrovascular (CAD)

and microvascular (cataract, glaucoma, diabetic retinopathy), and to successfully manage any that do occur (Poehlman, 2002). Moreover, diabetes increases one's vulnerability to cardiovascular disorders, especially in women (Zhang et al., 2020). The American Heart Association states that women who have diabetes have a three-to seven-fold increased risk of cardiovascular disease in comparison to those without the condition. Conversely, the risk for males with diabetes is twice that of those without the disease. In addition, women fare worse after a heart attack than do males. Therefore, diabetes does manifest in women in a distinct way. Furthermore, not all women with diabetes have the same symptoms (Laycock and Meeran, 2012). Particularly among postmenopausal women, who may face unique metabolic and hormonal changes such as low estrogen, which can cause unpredictable blood sugar fluctuations and complex challenges that demand deeper investigation into its underlying mechanisms (Poehlman, 2002). In recent years, researchers have turned their attention to the role of biomarkers such as serum cortisol and serum proteins in elucidating the pathophysiology of T2DM among postmenopausal women. Complications of diabetes such as infections, infarctions and inflammation can trigger a physiological stress response in the body. This stress response, called as metaflammation involves the release of cortisol and Acute Phase Proteins.

Cortisol is the single-most prevalent glucocorticoid hormone, which plays a crucial part in many metabolic processes; it serves as an insulin antagonist, boosting gluconeogenesis, lowering tissue sensitivity and glucose utilization by tissues, thereby worsening T2DM risk in this demographic (Zhang et al., 2020; Laycock and Meeran, 2012; Suzuki and Kondo, 2012). Acute Phase Proteins are a type of serum proteins which are used as biomarkers for elucidating the pathophysiology of T2DM. Other serum proteins which are also used as a biomarker are apolipoproteins such as ApoA1, ApoA2ApoH,ApoB,ApoC1,Apoc2, Cytokines and cytokine-related proteins (Leptin, IL-6), inflammatory proteins (CRP,aTNF), complement proteins(Adipsin, ASP) etc., (Marikanty et al., 2016; Riaz, 2015) Additionally, scientific evidence demonstrates that both Insulin and IL-6 adversely influence corticosteroid-binding globulin (CBG), which is the main plasma protein involved in the transport of cortisol, at least in vitro. This implies that both inflammation and insulin resistance might play a role in the drop of CBG levels which ultimately results in the increase of free cortisol, In postmenopausal women all these cascade of changes further trigger the rise in risk of the complications of type 2 DM. So, we hope to analyse more about these biomarkers and their possible links to elusive T2DM-related problems in this investigation. Our study intends to pave the path for improved therapeutic management and better health outcomes for this vulnerable population of postmenopausal women with type 2 diabetes by exploring the complex relationships between blood cortisol, serum protein, and T2DM.

Materials and Methods

This study explored the relationship between serum cortisol and serum protein levels in postmenopausal women diagnosed with Type 2 Diabetes Mellitus (T2DM). The inclusion criteria focused on postmenopausal women aged between 50 to 70 years who were diagnosed with T2DM according to the American Diabetes Association's 2015 criteria. Participants were evaluated based on their serum cortisol and serum protein levels. The exclusion criteria were designed to eliminate confounding factors, including

women with chronic kidney disease, liver disease, thyroid dysfunction, acute infections, and those on corticosteroid therapy. The total number of participants was 179, recruited from Saveetha Medical College, with 89 participants not suffering from hypertension, and 57 were hypertensive. Informed consent was obtained from all participants, and the study was approved by the institutional ethics committee. Participants' medical histories, including the duration of menopause, diabetes, and medication usage, were documented, while key health parameters such as BMI and blood pressure were also recorded.

Fasting blood samples were collected in the morning from all participants and analyzed using a Vitros5600 analyzer. Serum cortisol and protein levels were measured, with serum protein levels determined using the biuret method. Data analysis was conducted using the Statistical Package for Social Science (SPSS) version 25.0. Descriptive statistics such as mean, standard deviation, median, and range were calculated for quantitative variables. To examine differences between groups, the Student t-test was used to compare serum cortisol and protein levels, while Pearson's Correlation was employed to explore the association between these two parameters. Multiple regression analysis was applied to account for potential confounders, including age, BMI, duration of diabetes, and medication use. All blood samples were handled under aseptic conditions, with 5 milliliters of blood drawn from the antecubital vein, then centrifuged to separate the serum. The serum was stored in stoppered containers at temperatures of 2-8˚C for short-term storage and at -20˚C for long-term storage to prevent contamination and evaporation.

In addition to these standard measures, the methodology also took a comprehensive approach by ensuring that potential confounding factors, such as medication usage, were adequately controlled. Statistical tests such as Pearson's Correlation and multiple regression analysis helped to adjust for variables like age, BMI, and the duration of diabetes, which are known to influence serum cortisol and protein levels. These analytical methods provided a rigorous assessment of the relationships between the measured biomarkers, offering a robust investigation of the underlying mechanisms connecting serum cortisol, serum protein levels, and T2DM in postmenopausal women. This research thus sought to contribute to a better understanding of the complex metabolic and hormonal interplay in this vulnerable population.

Results and Discussion

The study revealed significant differences between the patient and control sets across various parameters (*Table 1* and *Figure 1*). The patient cohort had a greater BMI (26.93±5.7 kg/m²) compared to the control cohort (25.08±2.86 kg/m², p=0.04). Fasting plasma glucose levels were significantly elevated in the patient set (185.3±15.86 mg/dl) versus the control set (99±17.6 mg/dl, p=0.01). Hemoglobin A1c (HbA1c) levels were also more in the patient category (8.11±1.4%) compared to the control category (4.11±1.4%, p=0.01). Serum cortisol levels were markedly ranged high in the patient faction (700±65.86 nmol/L) versus the control faction (168.3±2.2 nmol/L, p=0.01). This rise in serum cortisol levels, associated with inflammation, correlated with higher serum protein levels in the patient division (9.2±0.60 gm/dl) compared to the control division (7.28±0.80 gm/dl, p=0.01).

Table 1. *Comparison of clinical parameters between postmenopausal women with type 2 diabetes mellitus (patient group) and healthy controls (control group).*

Parameter	Patient Group	Control Group	P Value
Age (years)	51.57 ± 8.08	51.76 ± 7.76	0.02
Body Mass Index (kg/m²)	50.93 ± 5.7	21.08 ± 2.86	0.04
Fasting Plasma Glucose (mg/dl)	185.3 ± 15.86	99 ± 17.6	< 0.01
Hgb A1c (%)	8.11 ± 1.4	4.11 ± 1.4	< 0.01
Serum Cortisol (nmol/L)	385.3 ± 65.86	9.38 ± 2.2	< 0.01
Serum Protein (gm/dl)	16.47 ± 8.11	4.28 ± 0.68	< 0.01

Note: p-value for serum cortisol and protein is less than 0.01; highly significant.

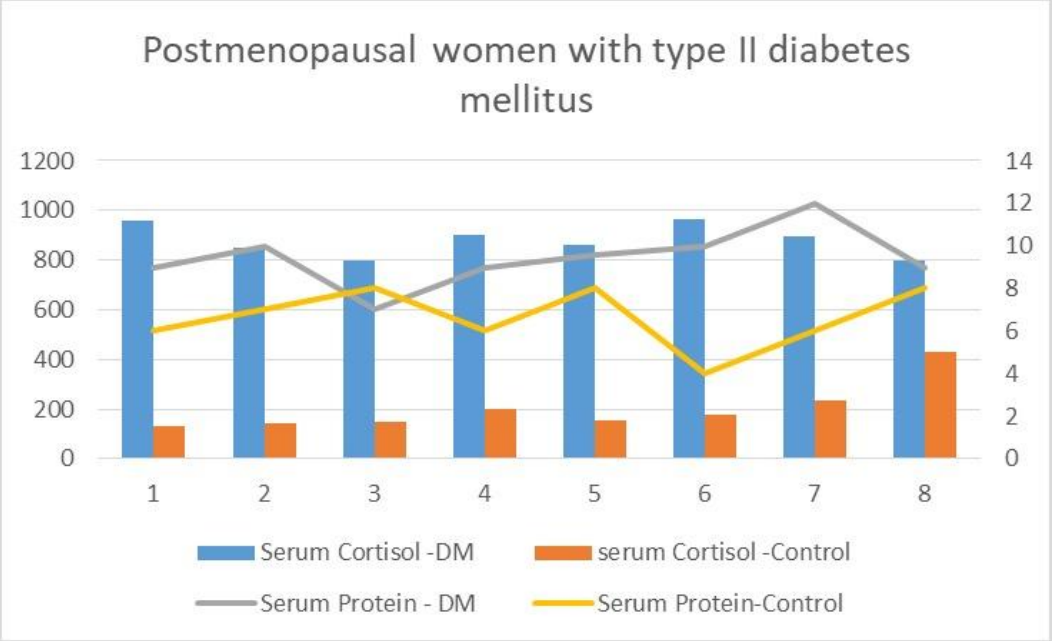

Figure 1. *Comparison of clinical parameters between postmenopausal women with type 2 diabetes mellitus and control group.*

In postmenopausal women, the intricate relationship between hormonal changes and metabolic dysfunctions is a significant area of concern, especially for those with type 2 diabetes mellitus (T2DM). Cessation of ovarian function causes a significant reduction in estrogen and progesterone levels, which affects a variety of physiological systems, including the hypothalamic-pituitary-adrenal (HPA) axis. This hormonal interplay contributes to increased serum cortisol levels, implicating stress-related mechanisms that exacerbate metabolic dysfunctions and complications, including inflammation. Inflammation further influences serum protein levels, typically causing an increase in acute-phase proteins, which are crucial markers of the body's response to hurt, infection, or other inflammatory stimuli. In addition to being a major part of the neuroendocrine system, the HPA axis also regulates a variety of various body processes including the immune system, digestion, emotions, and energy storage and expenditure. It is thought that the HPA axis controls reactions to stress and regulates a variety of body processes. In postmenopausal women, the decline in estrogen and progesterone levels disrupts this axis, leading to dysregulation of cortisol production. Estrogen typically exerts a modulatory effect on the HPA axis, and its deficiency results in an overactive response, thereby increasing cortisol levels. Elevated cortisol, a glucocorticoid hormone, is known to have several deleterious effects on metabolic processes. It promotes gluconeogenesis

and lipolysis, leading to hyperglycemia and increased free fatty acids in the bloodstream, respectively. These metabolic changes are particularly detrimental for women with T2DM, as they exacerbate the underlying insulin resistance and hyperglycemia characteristic of this condition.

Chronic elevation of cortisol due to persistent activation of the HPA axis in postmenopausal women with T2DM can lead to several adverse consequences. High cortisol levels contribute to central obesity, a common feature in metabolic disorder, which is itself a risk factor for cardiovascular diseases. Furthermore, cortisol influences the metabolism of carbohydrates, proteins, and fats, exacerbating insulin resistance and dyslipidemia. Increased cortisol also impacts the inflammatory response. It typically has an anti-inflammatory effect under acute conditions, but chronic exposure can lead to a paradoxical pro-inflammatory state. This occurs because prolonged high cortisol levels can desensitize tissues to its anti-inflammatory effects, promoting a state of chronic low-grade inflammation. Inflammation is particularly relevant in Type 2 diabetes, where insulin resistance and beta-cell dysfunction are pathognomonic of the condition. Serum protein levels are greatly impacted by inflammation, especially those of the acute-phase proteins (APPs). APPs are a type of protein whose plasma levels rise (positive APPs) or fall (negative APPs) in response to inflammation. These proteins are largely synthesised in the liver in response to intestinal inflammation caused by cytokines such as interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-A), and interleukin-1 beta. Positive acute-phase proteins include C-reactive protein (CRP), serum amyloid A, fibrinogen, and haptoglobin. These proteins play various roles in modulating the inflammatory response, clearing pathogens, and restoring homeostasis. For instance, CRP is a sensitive marker of inflammation and can bind to dead or dying cells and some types of bacteria to activate the complement system. Elevated levels of CRP are commonly observed in individuals with T2DM and are associated with increased cardiovascular risk.

Negative acute-phase proteins, such as albumin and transferrin, decrease during inflammation. The reduction in these proteins can be attributed to a reprioritization of protein synthesis by the liver, favoring the production of positive APPs. Additionally, inflammation can lead to increased capillary permeability and loss of albumin into the interstitial space, further decreasing serum levels. The increase in acute-phase proteins in response to inflammation has several implications for metabolic health in postmenopausal women with T2DM. Elevated levels of APPs like CRP and fibrinogen contribute to a pro-thrombotic state, increasing the risk of cardiovascular events. This is particularly concerning in individuals with T2DM, who already have an elevated risk of cardiovascular diseases. Furthermore, persistent inflammation and the resulting changes in blood protein levels can impede glucose metabolism. Inflammatory cytokines can cause insulin resistance by disrupting insulin signalling pathways. For example, TNF-α can inhibit insulin receptor substrate-1 (IRS-1) function, a critical component of the insulin signaling cascade, leading to reduced glucose uptake by cells. The interplay between increased cortisol levels and inflammation creates a vicious cycle that exacerbates metabolic dysfunction. Elevated cortisol promotes inflammatory cytokine production, which in turn can increase cortisol production through stimulation of the HPA axis. This cyclical relationship can lead to sustained hyperglycemia, insulin resistance, and further complications associated with T2DM.Given the significant impact of inflammation and hormonal imbalances on metabolic health, it is crucial to develop strategies to manage these factors in postmenopausal women with T2DM.

Lifestyle interventions, such as regular physical activity and dietary modifications, can help reduce inflammation and improve insulin sensitivity. Exercise has been shown to lower levels of inflammatory markers and improve metabolic profiles, while diets rich in anti-inflammatory foods, such as omega-3 fatty acids, can also mitigate inflammation.

Additionally, pharmacological therapies can be required. Anti-inflammatory medications such as aspirin or certain cytokine inhibitors may be used to lessen inflammation. Hormone replacement treatment (HRT) has been used to reduce menopausal symptoms and may be involved in cortisol and HPA axis modulation; however, because of the hazards involved, its usage needs to be carefully considered. Additionally, lowering cortisol levels and enhancing general metabolic health can be achieved by managing stress with psychological interventions like mindfulness, cognitive-behavioral therapy (CBT), and relaxation techniques. Since persistent stress can exacerbate inflammatory processes and disruption of the HPA axis, stress management is very crucial. For women with diabetes mellitus type 2 having postmenopausal, there is a decrease in estrogen and progesterone levels significantly impacts the HPA axis, leading to increased serum cortisol levels and contributing to metabolic dysfunction. The resulting chronic inflammation influences serum protein levels, particularly acute-phase proteins, further exacerbating metabolic complications. Grasping this complex interaction is vital for creating comprehensive management strategies that target hormonal imbalances, inflammation, and metabolic dysfunction in this population. By thoroughly understanding these underlying mechanisms, healthcare professionals can develop more effective treatments and interventions tailored to the specific needs of individuals. Effective interventions, both lifestyle and pharmacological, are essential to mitigate these effects and improve the health outcomes of postmenopausal women with T2DM.

Conclusion

Our study reveals significant disparities across all measured parameters between the patient and control groups, highlighting the multifaceted nature of type 2 diabetes mellitus (T2DM) in the women who had attained postmenopausal. These outcomes emphasize the critical importance of considering hormonal and inflammatory factors in the assessment and management of the disease. The intricate interplay between hormonal changes, particularly the decrease in estrogen and progesterone, and the dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, resulting in elevated serum cortisol levels, is a key factor in the exacerbation of metabolic dysfunction in this demographic. Elevated cortisol levels contribute to the chronic inflammation observed in postmenopausal women with T2DM, which in turn affects serum protein levels, particularly acute-phase proteins (APPs). The increase in APPs such as C-reactive protein (CRP) underscores the physique's inflammatory response, which is a significant contributor to the pathogenesis of insulin confrontation and beta-cell dysfunction. This chronic inflammatory condition worsens metabolic imbalances and increases the risk of cardiovascular illnesses like hypertension and atherosclerosis. Furthermore, it raises the risk of microvascular problems such as retinopathy, which can cause vision loss, nephropathy, which can lead to kidney failure, and neuropathy, which can cause substantial nerve damage and worse quality of life. The combined impact of these

disorders emphasises the significance of effective risk mitigation and intervention techniques to enhance overall health outcomes in afflicted persons.

Understanding the association between elevated serum cortisol, serum proteins, and T2DM provides valuable insights into the underlying mechanisms contributing to these complications. This knowledge can inform the development of targeted interventions aimed at reducing inflammation and managing hormonal imbalances. For instance, lifestyle modifications like regular physical activity and anti-inflammatory diets, along with pharmacological approaches such as hormone replacement therapy (HRT) and anti-inflammatory medications, can be effective in mitigating these adverse effects. By advancing our understanding of these associations, we can better prevent and manage cardiovascular diseases and microvascular complications in postmenopausal women with T2DM. This holistic approach to managing T2DM, which includes addressing hormonal and inflammatory factors, is crucial for improving health consequences and enhancing the value of lifespan in this vulnerable population.

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Conflict of interest

The authors confirm that there is no conflict of interest involve with any parties in this research study.

REFERENCES

[1] Galicia-Garcia, U., Benito-Vicente, A., Jebari, S., Larrea-Sebal, A., Siddiqi, H., Uribe, K.B., Ostolaza, H., Martín, C. (2020): Pathophysiology of type 2 diabetes mellitus. – International Journal of Molecular Sciences 21(17): 34p.

[2] Goyal, R., Singhal, M., Jialal, I., Castano, M. (2021): Type 2 diabetes (nursing). – In: StatPearls [Internet], Treasure Island (FL): StatPearls Publishing 7p.

[3] InformedHealth Web Portal (2006): Depression: What Is Burnout? – Cologne, Germany: Institute for Quality and Efficiency in Health Care (IQWiG) 3p.

[4] Laycock, J., Meeran, K. (2012): Integrated endocrinology. – John Wiley & Sons 30p.

[5] Marikanty, R.K., Gupta, M.K., Cherukuvada, S.V.B., Kompella, S.S., Prayaga, A.K., Konda, S., Polisetty, R.V., Idris, M.M., Rao, P.V., Chandak, G.R., Dakshinamurty, K.V. (2016): Identification of urinary proteins potentially associated with diabetic kidney disease. – Indian Journal of Nephrology 26(6): 434-445.

[6] Mayo Clinic Physicians (2012): Mayo Clinic The Essential Diabetes Book. – Oxmoor House 320p.

[7] Poehlman, E. (2002): Menopause, energy expenditure, and body composition. – Acta Obstetricia Et Gynecologica Scandinavica 81(7): 603-611.

[8] Reaven, G.M. (1991): Insulin resistance and compensatory hyperinsulinemia: role in hypertension, dyslipidemia, and coronary heart disease. – American Heart Journal 121(4): 1283-1288.

[9] Riaz, S. (2015): Study of protein biomarkers of diabetes mellitus type 2 and therapy with vitamin B1. – Journal of Diabetes Research 10p.

[10] Suzuki, H., Kondo, K. (2012): Chronic kidney disease in postmenopausal women. – Hypertension Research 35(2): 142-147.

[11] Zhang, X., Deng, X., Zhou, J., Qiu, K., Deng, M., Lin, Z., Mosha, S.S., Li, W. (2020): The association of serum cortisol level with microalbuminuria in patients with type 2 diabetes and prediabetes. – International Journal of Medical Sciences 17(18): 2998-3004.
[12] Zheng, Y., Ley, S.H., Hu, F.B. (2018): Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. – Nature Reviews Endocrinology 14(2): 88-98.