**Refractory Hyperkalemia with Hyporeninemic Hypoaldosteronism in Type 2 Diabetes Mellitus: A Case Study and Literature Review.**

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# **Abstract**

A 57-year-old male, known case of type II diabetes mellitus presented with 4 months history of recurrent hyperkalemia to emergency department for urgent management. However, recent hyperkalemia episode was not managed with medial management, consequently requiring emergency hemodialysis. Although, his renal function tests were within normal limits, his plasma aldosterone level and plasma renin activity were low in presence of hyperkalemia. After ruling out adrenal insufficiency, and diabetic nephropathy or renal impairment, diagnosis of hyporeninemic hypoaldosteronism was made. In most of the cases, hyporeninemic hypoaldosteronism is overlooked as cause of unexplained hyperkalemia in patient with type 2 diabetes mellitus. Therefore, this case reports highlights the fact that, hyporeninemic hypoaldosteronism should always be suspected and evaluated for cause of unexplained hyperkalemia in presence of type 2 diabetes mellitus.

Keywords: refractory hyperkalemia, dialysis, hyporeninemic hypoaldosteronism, type 2 diabetes mellitus

# **Introduction**

Hyporeninemic Hypoaldosteronism (HH), also known as type IV renal tubular acid, is the syndrome that occurs due to reduced production of renin from juxtaglomerular from kidney and aldosterone from adrenal gland.**[1]** It is more common among woman and occurs in patients of 50 to 70 years of age with diabetic nephropathy and tubulointerstitial disease having mild to moderate kidney failure.**[2]**

Most patients with HH are asymptomatic and on normal laboratory screening or during tests for an unrelated illness, hyperkalemia is found. The majority of individuals seek medical attention due to symptoms associated with hyperkalemia, including weakness in muscles or irregular heartbeats.**[3]** Despite this, most of cases of HH remain underdiagnosed. Thus, clinical evaluation for HH should be done if unexplained chronic hyperkalemia is presented in patients with normal kidney function.

In this case report, we present the case of a 57-year-old male with type 2 diabetes mellitus without micro vascular complications with hyperkalemia which is unresponsive to medical treatment. Consequently, emergency hemodialysis is done for refractory hyperkalemia. Which on further evaluation diagnosed to have hyporeninemic hypoaldosteronism.

# **Case discussion**

A 57-year-old male with 11 years long history of type 2 diabetes mellitus under insulin and metformin. He had 2 episodes of hyperkalemia in the last 4 months, for which he was managed with calcium gluconate and insulin glucose therapy and discharged. One month ago, he came to our center for a routine follow up with no new complaints. However, the laboratory parameters show a high serum potassium level of 6.5 mg/dl. Thus, he was admitted to the ward for further evaluation.

On general examination, vitals were within normal limits. The systemic examination was unremarkable. However, the ECG showed tall T-waves in most of the leads, as shown in Figure 1.

Figure

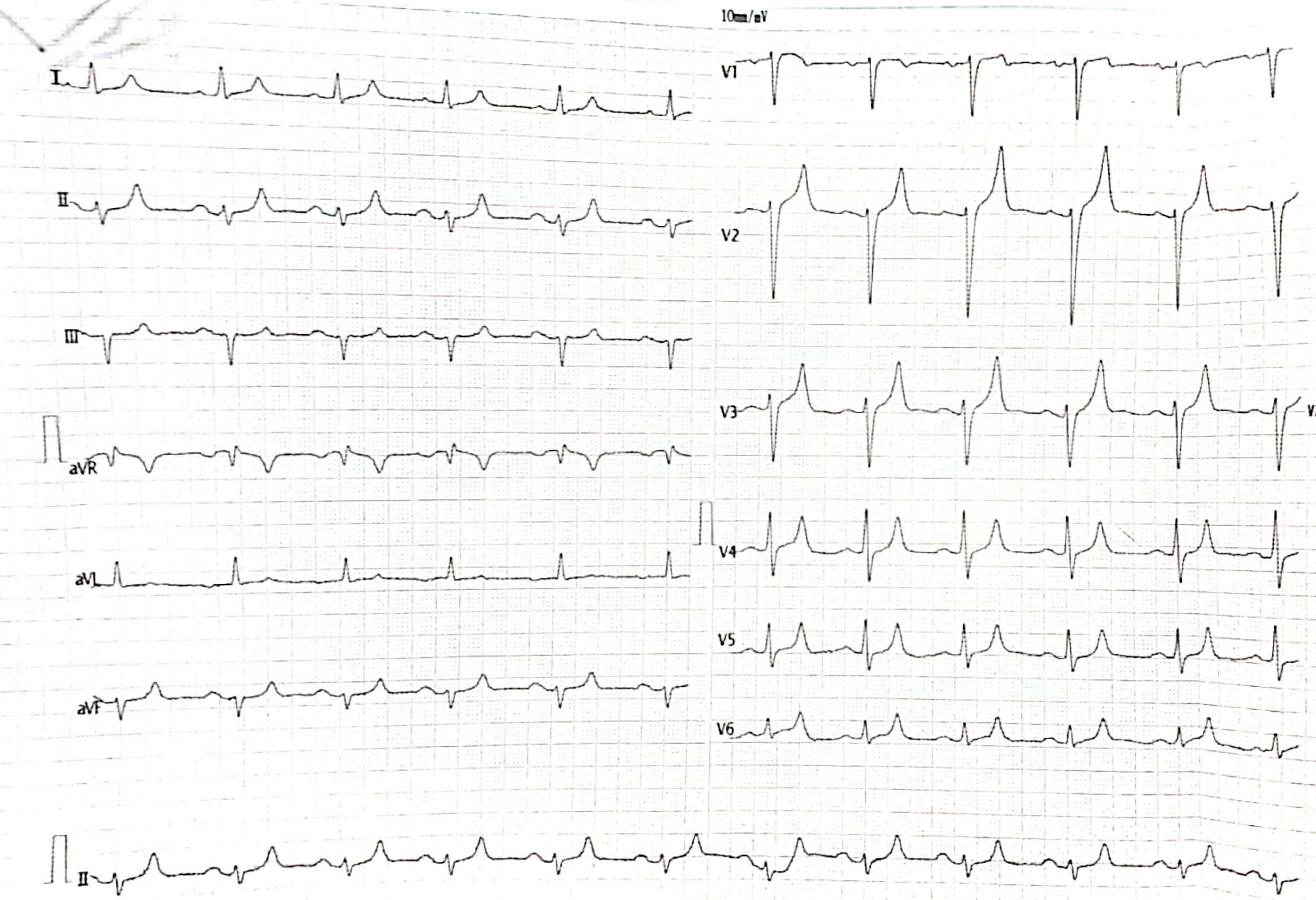


Figure 1: ECG showing tall T-waves.

His serum creatinine and urinary albumin-creatinine ratio were normal, and an ultrasound scan revealed normal kidneys. Therefore, renal impairment and diabetic nephropathy were ruled out as a cause for hyperkalemia.

His laboratory parameters given below in Table 1 confirmed hyporeninemic hypoaldosteronism and ruled out adrenal insufficiency.

Table

|  |  |  |
| --- | --- | --- |
| **Parameters** | **Results** | **Reference range** |
| Urea (mg/dl) | 20 | 6-24 |
| Creatinine (mg/dl) | 0.9 | 0.3-0.2 |
| Sodium (mmol/L) | 138 | 135-145 |
| Potassium (mmol/L) | 6 | 3.5-5 |
| Chloride (mmol/L) | 112 | 88-108 |
| ABG  pH  pCO2 (mmol/L)  pO2 (mmol/L)  Bicarbonate (mmol/L)  Anion Gap (mmol/L) | pH:7.35  pCO2: 24  pO2:93  Bicarbonate: 17  Anion Gap:16 | pH: 7.35-7.45  pCO2 :35-45  pO2: 83-106  Bicarbonate: 22-26  Anion Gap:8-16 |
| Morning 8 AM Plasma cortisol level (mcg/d) | 16 | 5-25 |
| Plasma renin activity (ng/ml/hr) | 0.5 | 0.7-3.3 |
| Plasma Aldosterone concentration (ng/dl) | 4 | 7-30 |
| Glycosylated hemoglobin (HbA1c) | 7.2% | <6.5% |

For the increased serum potassium, immediate medical management with intravenous calcium gluconate, intravenous regular insulin with glucose, and salbutamol nebulization were given. A repeat laboratory evaluation after 6 hours revealed a further increase in serum potassium levels, from 6.5 mg/dl to 6.7 mg/dl. Again, even after repeated doses of intravenous calcium gluconate, insulin with glucose, and salbutamol, a further increase in serum potassium was noted from 6.7mg/dl to 6.9mg/dl after 6 hours. Thus, this condition was labeled as refractory hyperkalemia. As a result, continuous renal replacement therapy was advised for the patient. All the benefits and adverse effects of renal replacement therapy were explained to the patient. After patient consent, emergent hemodialysis was arranged and performed for 2 hours with zero ultrafiltrate in the intensive care unit uneventfully. After hemodialysis, his serum potassium level decreased to 4.9 mg/dl. The oral sodium-polystyrene sulfonate 30mg once daily and intravenous furosemide 20 mg twice daily was started. As a result, the subsequent potassium level was within normal limits. Thus, the patient was discharged with a oral sodium-polystyrene sulfonate 30mg and oral form of furosemide 20 mg twice daily. Also, he was advised to avoid potassium rich diets such as spinach, orange juice, honeydew melon, nuts, etc. On follow-up after 1 month, his serum potassium level was within normal limits.

# **Discussion**

A high blood potassium (K+) concentration of more than 5.0 or more than 5.5 mEq/L (mmol/L) is known as hyperkalemia. This electrolyte anomaly has potentially life-threatening consequences.**[4]** Potassium is the most abundant intracellular cation in our body. It plays a key role for nerve conduction and muscle contraction. Only 2% of potassium is present in extracellular fluid while nearly eight percent is found inside cells.[**5]** Potassium consumption, renal potassium excretion, mineralcorticosteroid function, and the control of intracellular potassium transport by insulin and glucose is crucial in maintaining normal levels of blood potassium.**[6]**

Hyporeninemic hypoaldosteronism is caused by reduced secretion of renin from the juxtaglomerular cells of the kidney. The adrenal glands secrete less aldosterone as a result of this decrease in renin production, which also causes a malfunction in the RAAS. Aldosterone plays a key role in controlling the amount of K+ in the body by facilitating the reabsorption of Na+ and the release of K+ into the cortical collecting duct lumen.**[1]** Diabetes is the common cause of hyporeninemic hypoaldosteronism , and various factors specific to the diabetic contribute to the system's decreased renin release.**[1]** Interstitial disease such as amyloid, monoclonal gammopathies and interstitial nephritis associated with NSAIDS are also cause hyporeninemic hypoaldosteronism.**[2]**

Impairment of renin secretion in diabetes is thought to result from: 1) direct damage to the JC cells; 2) problems with prorenin's conversion to active renin; 3) autonomic dysfunction with decreased beta-adrenergic stimulation; or 4) a primary increase in renal salt retention with volume expansion, which inhibits the production of renin because of atrial natriuretic peptide release. This above result in hyporeninemic hypoaldosteronism in diabetics patient. Impairment in RAAS in diabetic also causes type IV renal tubular acidosis. Thus, they are often considered similar.**[2]** The non-ionic gap metabolic acidosis occurs in this condition because hyperkalemia causes impairment of amino-genesis as it reduces ammonia production as well alters medullary osmotic gradient.**[2]** Furthermore, it is important to remember that hyperkalemia occurs in diabetes due to insulin deficiency, kidney disease, ACE inhibitors use as well as concurrent adrenal insufficiency in case of autoimmune polyendocrine syndrome**.[7]**

In terms of clinical presentation, HH is often asymptomatic, and the majority of patients have mild to moderate hyperkalemia. On the other hand, people with HH may have severe hyperkalemia for longer periods of time without showing any symptoms, and they may occasionally be found by routine laboratory testing or during studies for unassociated illness. The diagnosis of HH due to diabetes is only established after excluding other causes of hyperkalemia, such as iatrogenic potassium intake, use of ARBs, potassium sparing diuretics, and heparin use.**[8]**

Thus, when unexplained hyperkalemia is present in patients with mild to moderate impairment in renal function, HH should always be considered.**[7]** Likewise, high clinical suspicion for hyporeninemic hypoaldosteronism is raised if hyperkalemia and mild non-anion gap metabolic acidosis are present with low PRA, low aldosterone, and a normal cortisol level.**[9]**

Management of acute hyperkalemia depends on potassium level as well ECG changes, regardless of its causes. If there are EKG abnormalities or when the plasma potassium level is higher than 6.5 mEq/L without EKG changes, immediate medical attention should be given.**[10]** Serum potassium level >6.5 mEq/L regardless whether ECG changes are present, calcium is indicated. It causes stabilization of myocardium membrane .10 ml of a 10% calcium gluconate or chloride solution is given intravenously over 2-3 minutes.**[10]** In Order for intracellular shifting of potassium from extracellular space, 10 units of regular insulin with 50 ml of 50% glucose is used. The glucose is used along with insulin to prevent hypoglycemia. Similarly, Beta agonist such as nebulized salbutamol 10-20 mcg is administered for redistribution of potassium inside cells. other medication , diuretics potassium binding resin are used for removal of potassium from the body. Sodium bicarbonate is used only when non-ionic metabolic acidosis is present.**[2]**

Hemodialysis is recommended when pharmacological therapy fails to adequately lowers and eliminate potassium from the body. Newer drug such as patiromer approved by FDA on 2015 October 21, is used for management of chronic hyperkalemia in those patients having chronic kidney disease and on RAAS inhibitors. Thus, it provides benefits for diabetics and heart failure patient with chronic hyperkalemia. It works by binding potassium in lumen of gastrointestinal tract and increase its fecal excretion.**[11]**

Fludrocortisone which is a mineralocorticoid is used for treatment of HH. It promotes reabsorption of sodium and secretion of potassium from kidney. As this medication can causes hypokalemic alkalosis, regular electrolytes monitoring is necessary.**[7]** But, when excessive sodium retention is present or hyperkalemia fails to response to fludrocortisone, potassium wasting diuretics can be used. In some patients, use of sodium bicarbonate also improves hyperkalemia. If the above measures fail, sodium potassium resin exchanger such as sodium polystyrene sulfonate is used.**[3]**

A similar case report with hyperkalemia with hyporeninemic hypoaldosteronism in diabetic patients was published in 2018 in the International Medical Case Report Journal by Chelaghma, N et. al. We hereby present the case of type 2 diabetes mellitus with hyporeninemic hypoaldosteronism, and hyperkalemia, which is unresponsive to medical treatment. The patient had undergone emergent hemodialysis for this condition and was well managed with potassium binder and furosemide. No any case of refractory hyperkalemia with hyporeninemic hypoaldosteronism in diabetes mellitus have been reported till date.

# **Conclusion.**

Hyperkalemia in diabetics who do not have ketosis or severe renal failure should raise the suspicion of hyporeninemic hypoaldosteronism. Rarely, hyperkalemia can be refractory in hyporeninemic hypoaldosteronism, which is a potential life-threatening condition. Therefore, optimization of blood sugar levels should be done to prevent potential life-threatening complications of type 2 diabetes mellitus, like refractory hyperkalemia.

**Acknowledgements**

None.

**Funding Information**

None.

**Conflict of Interest statement**

None declared.

**Ethics Statement**

Ethical approval was not required for the case report as per the country’s guideline.

**Informed Consent**

Written informed consent was obtained from the patient to publish the report.

**Data Availability Statement**

Data openly available in a public repository that issues datasets with DOIs.

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