# Reset Osmostat: Facts and Controversies

**Abstract**

Reset osmostat (RO) consists of a change in the normal plasma osmolality threshold (reduction or increase), which consequently induces chronic dysnatremia (hyponatremia or hypernatremia). Although the early papers on RO state that hyponatremic patients with this condition are usually not symptomatic, the current view is that most patients with hyponatremia are symptomatic and should be treated. RO has been associated with a myriad of clinical conditions and has clear diagnostic criteria which are crucial to arrive at the correct diagnosis and treatment.

**Keywords:** *Hypernatremia, hyponatremia, reset osmostat*

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## Introduction

In 1976, a sort of hypoosmolar hypotonic hyponatremia (serum sodium <135 mmol/L and measured serum osmolality <280 mOsm/kg) was described, which was characterized by having a normal renal function but was extremely difficult to correct by neither free water restriction nor salt supplementation. This condition was described as a subtype of the syndrome of inappropriate antidiuretic hormone (SIADH) secretion and was named "reset osmostat" (RO), and then classified as Type C SIADH.[1,2] RO hyponatremia is currently considered a condition which has a low normal plasma osmolality threshold (usually 280 mOsm/kg), that induces an elevation of ADH at a lower plasma osmolarity with normal water load excretion and intact urine diluting ability while maintaining normal sodium balance.[1-4]

## Pathophysiology and Causes

Hyponatremia occurs in up to a third of long-term care facility, and RO constitutes more than half of that number.[5] Several clinical situations can induce it, such as pregnancy, elderly, quadriplegia, psychosis, cerebral hemorrhage, encephalitis, dementia (Lewy bodies), alcoholism, malnutrition, malignancy (gastric, colonic, and oat cells carcinoma), and other debilitating diseases including infections such as tuberculosis and pneumocystis carinii pneumonia. It has been proposed that an alteration in the osmoreceptor cells metabolism could be responsible for the RO malfunction. Besides, the successful treatment of some of the above mentioned reversible conditions (e.g., pneumocystis pneumonia), usually corrects the RO hyponatremia.[1-9]

RO has been reported in pregnant women. In a regular pregnancy, the average plasma-osmolality is down by 5–10 mOsm/kg, and the serum sodium concentration is down by 4–5 mmol/L.[1-4] The exact mechanism of why this occurs is not known, but the fetal-placental unit appears to be an absolute requirement. However, in one paper, the human chorionic gonadotropin (that is secreted by the placenta) has been seen as one of the factors responsible for the readjustment of the osmoregulatory system, but that was evidenced in molar pregnancies.[1-4] Besides, hyponatremia has been documented in congenital RO associated with midline defects (cleft lip and palate), corpus callosum agenesis, and hypothalamic cyst.[3,6,10]

It is worth mentioning that RO has also been described in hypernatremic patients, a condition known as "essential hypernatremia" (EH). This entity should be suspected in those patients who present stable hypernatremia despite the variation in sodium and water intake, their kidneys conserve the ability to dilute and concentrate urine, but an increased fluid intake fails to normalize their plasma osmolality. EH is usually associated with

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**Table 1: Reset osmostat diagnostic criteria**

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|---|
| Normal serum volume with low serum sodium that maintain a sodium balance without a correction in hyponatremia when salt was provided |
| The urinary ability of dilute urine is normal, and urine osmolality is low, since a low urine osmolality indicates that kidneys retain their ability to excrete maximally dilute urines. They thus have normal water loading tests by excreting >80% of the water load |
| A normal FEUA is highly consistent with RO in the absence of psychogenic polydipsia |
| Normal glomerular filtration rate, reduced electrolyte free water clearance, increased sodium clearance and fractional excretion of sodium (depending on the patient's diet). Heart, liver, adrenal, and thyroid glands have normal function |

FEUA: Fractional excretion of uric acid, RO: Reset osmostat

**Table 2: Reset osmostat hyponatremia response to different syndrome of inappropriate antidiuretic hormone secretion treatments**

| Positive response | Negative response |
|---|---|
| Vaptan | Water restriction |
| | Sodium supplementation |
| | Fludrocortisone |

hypothalamic-pituitary structural lesions or the absence of "posterior pituitary bright spot (PPBS)" on T1 imaging on magnetic resonance imaging. The PPBS is defined as a neurohypophyseal T1 hyperintense signal in the sella behind the adenohypophysis, which has been interpreted as proteins, phospholipid vesicles, or vasopressin hormone accumulation. The absence of PPBS has been associated with some diseases, such as craniopharyngioma, diabetes insipidus, and Langerhans cell histiocytosis.[5,11,12] The relation between the loss of the PPBS and EH leads to the hypothesis that this sort of hypernatremia could be secondary to ischemic (small vessels disease or stroke) or autoimmune damage in the thirst and osmoregulation centers.[11,12]

## Clinical Presentation and Diagnosis

Early papers reported that this condition causes no symptoms, and it is usually an accidental discovery while studying other pathology, although one paper showed a psychomotor delay induced by hyponatremia considered to be caused by RO but this diagnosis was unclear.[5,10] However, the current view is that most patients with hyponatremia are symptomatic and should be treated.[13-17]

RO can also be associated with other subtypes of SIADH (36%), and this situation can be suspected when despite treating SIADH adequately, serum sodium remains still low.[3,5,12] Besides, since RO hyponatremia is apparently asymptomatic, it should be distinguished from pseudohyponatremia, and hypertonic hyponatremia (hyperglycemia): RO runs with low, pseudohyponatremia with normal, and hypertonic hyponatremia with high plasma osmolality.[4] RO is classically suspected in patients who usually have asymptomatic and moderate-to-mild hyponatremia (125–134 mmol/L), which is stable over many days despite the variation in sodium and water intake, and serum sodium levels usually do not seem to respond to treatment.[1,5,10] A spontaneously excreted dilute urine, defined as a urine osmolality less than plasma osmolality, and normal (4%–11%) fractional excretion of uric acid (FEUA) are diagnostic of an RO.[7] Moreover, a normal FEUA value is an important indicator of RO regardless of urine osmolality or serum uric acid levels. Even though FEUA is also normal in psychogenic polydipsia, it can be differentiated from RO by the large intake of water that these patients have.[7] In addition, FEUA is usually high (>12%) in patients suffering from hyponatremia secondary to SIADH secretion and cerebral or preferably named "renal" salt wasting; while it is usually low (<4%) FEUA in hypervolemic hyponatremia: cardiac failure, cirrhosis, and nephrotic syndrome.[10-12]

However, the diagnosis of RO can only be definitively made by performing a water loading test. It consists of oral water load (10–15 ml/kg) to suppress vasopressin secretion, and if RO is present patients will excrete more than 80% of the water load within 4 h [Table 1].[4,6,7,10]

## Treatment

The treatment of RO and the other subtypes of SIADH is quite different,[5] since non-RO SIADH hyponatremia quickly responds to fluid restriction while the hyponatremia of RO do not.[9] In addition, RO does not respond to oral sodium supplementation nor fludrocortisone treatment.[3,7,9]

When RO occurs as a consequence of a reversible illness, the osmostat often resets to normal after recovering from it, but when RO etiology is irreversible or unknown (permanent hyponatremia), since RO hyponatremia is mild, does not progress under the osmolality at which the osmostat has been reset, and does not respond to different therapeutic options, RO hyponatremia is commonly not treated.[7,9] However, the current tendency to treat even mild hyponatremia creates a therapeutic query that needs to be resolved. The utilization of the vaptan class of drugs has pathophysiologic advantages in RO but may also induce potential harm (overcorrection, liver toxicity), thus it needs further confirmation by prospective studies.[3,16] Futures studies will hopefully solve this dilemma [Table 2].

## Conclusion

RO can be observed in a myriad of clinical conditions that can induce hyponatremia or hypernatremia. It is important

to become proficient at understanding the diagnostic criteria and characteristics of this common clinical entity to improve clinical outcomes.

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### Conflicts of interest

There are no conflicts of interest.

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