

## Metadichol® and Red Cell Distribution Width (RDW) in CKD patients

Raghavan PR

Nanorx Inc., New York, USA

### Abstract

Red blood cells originate in the bone marrow. Red cell distribution width (RDW) show sizes of circulating erythrocytes (RBC) and has been explored in several large clinical databases to be a robust marker of adverse clinical outcomes in patients. The prognostic value of RDW is seen in other conditions with end-organ dysfunction such as renal failure or. Elevated RDW levels are of significance in diseases such as kidney diseases. The high RDW levels are an indication of increased oxidative stress and closely related to the presence and poor prognosis of the disease.

No known therapy exists that can normalize RDW levels. In this paper, we present here a case study using Metadichol® [1] that leads to normal RDW levels in patients with CKD and PKD.

**Keywords:** Red Cell Distribution Width; RDW; Metadichol; Bone marrow; Hematopoietic stem cells; Red blood cell; Erythropoietin; EPO; CKD; Peritoneal dialysis; Hemodialysis; EPO; TNF-alpha; Vitamin D; VDR; Inverse/protean agonist; Creatinine; eGFR; Iron and Iron saturation

### Introduction

In the 21st-century Chronic Kidney Disease (CKD) is becoming a worldwide health issue [2]. RDW elevation is seen in patients with CKD [3], Peritoneal Dialysis (PD) or Hemodialysis [4] which is a standard therapy for patients reaching End-Stage Renal Disease (ESRD). RDW has potential use as a biomarker in estimating the risk of mortality. A higher RDW is an independent risk factor for overall and CVD-related mortality in patients undergoing Continuous Ambulatory Peritoneal Dialysis (CAPD), and that its value was superior to others biomarkers of anaemia [5].

Although mechanisms are unknown, evidence suggests an independent relationship between RDW and clinical outcomes in many human diseases [6]. A high RDW Level indicates heterogeneity in RBC size (anisocytosis). Also, accelerating RBC destruction and ineffective erythropoiesis, are common in patients undergoing dialysis, and bone marrow dysfunction which leads to a high RDW level.

Bone marrow-derived mesenchymal stem cells have been reported to play a crucial role in the restoration of many injured vital organs [7]. Thus, hematopoiesis in dialysis patients leads to mortality associated with a high RDW.

Inflammation, which is prevalent in CKD patients, has been closely linked to RDW in many patient populations. Pro-inflammatory cytokines like TNF-alpha are well known to inhibit, induced RBC maturation and proliferation [8].

Malnutrition and protein-energy wasting, which is common in dialysis patients, increases RDW and is inversely related to nutritional index in a broad range of medical conditions [9].

The residual renal function was greater in the low RDW group than that in the high RDW group. The residual renal function has a beneficial effect on patient survival [10].

High RDW levels are associated with an increased risk of adverse outcomes in the general population and in patients with severe sepsis, heart failure, coronary artery disease, stroke, and acute kidney injury that required renal replacement therapy and kidney transplant [11].

High level of RDW impairs iron metabolism, and the resulting inflammation disrupts the process of erythropoiesis [12].

Cytokines are released when there is inflammatory stress and can inhibit erythrocyte maturation. These cytokines like TNF-alpha block the activity of erythropoietin inhibit erythrocyte maturation, and this results in the production of ineffective red blood cells and elevated RDW [13].

Given the importance of RDW in mitigating disease outcomes [14], there is only one reported study by Fici et al. [15] that evaluated the effects of nebivolol and metoprolol on RDW in hypertensive patients (Table1). Nebivolol decreased RDW marginally by about 4%. There are no known drugs available to treat this dysfunction today.

Metadichol®, as we have shown earlier, binds to VDR and is also a TNF-alpha [1] inhibitor and also demonstrated that it increased platelets in Dengue patients [16]. Since platelets result from hematopoietic stem cells which also is the pathway to normal erythropoiesis and normal RDW. We treated three patients with CKD and high RDW levels using Metadichol. In addition to improvement in RDW, other improvements in Creatinine, Iron, PTH is seen and a feeling of well-being [17].

### Case Presentation 1

70 years old male has been on Hemodialysis 3 days a week for five years. Treated with Metadichol at 10 mg per day. The patient is also on statins, phosphate binders and Vitamin D. He reports improved energy and no sudden drops in pressure during dialysis (Figure 1).

RDW	Nebivolol (n=37)	Metoprolol (n=35)	P*
Before	15.75 ± 1.49	15.68 ± 1.60	0.85
After	15.07 ± 1.26	15.62 ± 1.59	0.11
P†	<0.001	0.35	

Table 1: Effects of nebivolol and metoprolol on RDW in hypertensive patients.

\*Corresponding author: Raghavan PR, Nanorx Inc., PO Box 131, Chappaqua, NY 10514, USA, Tel: +1-914-671-0224; E-mail: [raghavan@nanorxinc.com](mailto:raghavan@nanorxinc.com)

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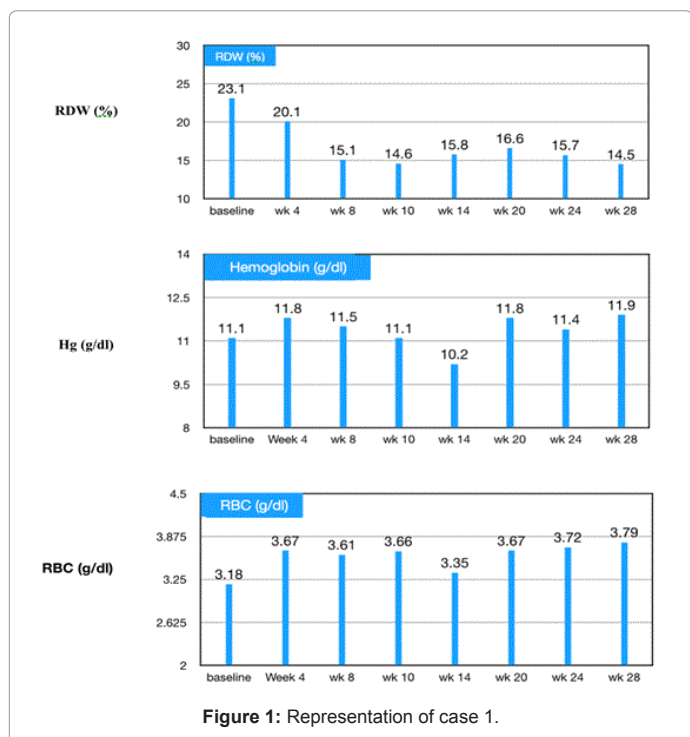


Figure 1: Representation of case 1.

### Case Presentation 2

62 years old male patient with CKD for four years. He is obese, diabetic and hypertensive and has been on hemodialysis three days a week. Treated with Metadichol® 10 mg per day. The patient was on hypertension drugs, and insulin and metformin. Also, he had an accumulation of water retention in legs and was on diuretics as well. The patient lost 22 lb after starting with Metadichol®, his swelling is gone, and blood sugar has normalized. He is off insulin and metformin but still on hypertensive drugs (Figure 2).

### Case Presentation 3

A 65 years old female patient diagnosed with Polycystic Kidney disease on dialysis for seven years before she had a kidney transplant. Undergoes infusion once a month for anti-rejection therapy but is not on dialysis. A year after the transplant she still did not feel completely normal. She had a lot of water retention and weight increase. After using Metadichol® at 5 mg per day, she feels much improved and energetic. She also lost 15 lb in weight, mostly water, and is feeling very energetic (Figure 3).

### Discussion

The results show that all three patients have experienced a decrease in their RDW. Also, all of them showed improvement in RBC and Hemoglobin levels. Statistical Analysis of Variance one way was carried out using JMP software from SAS showed that the following RBC were significant at 0.023, but Hemoglobin was not significant with a p-value of 0.23.

Case 1 patient's Hemoglobin and RBC are heading in the direction of normality though at a slower pace compared to the other two cases presented. Also improvements in other parameters such as Creatinine, Iron, and Iron saturation, and loss of weight and increased energy as well as a general feeling of wellness. All the three patients have shown improvements in various biomarkers like Creatinine, PTH, and ferritin

and will be reported in due course. No adverse side effects have since Metadichol® is a natural food-based product that is completely safe [18-19].

Inflammation induced by cytokines like TNF-alpha, IL-1B, IL-6, etc. can have a suppressing effect on Erythropoietin (EPO) thus erythrocyte

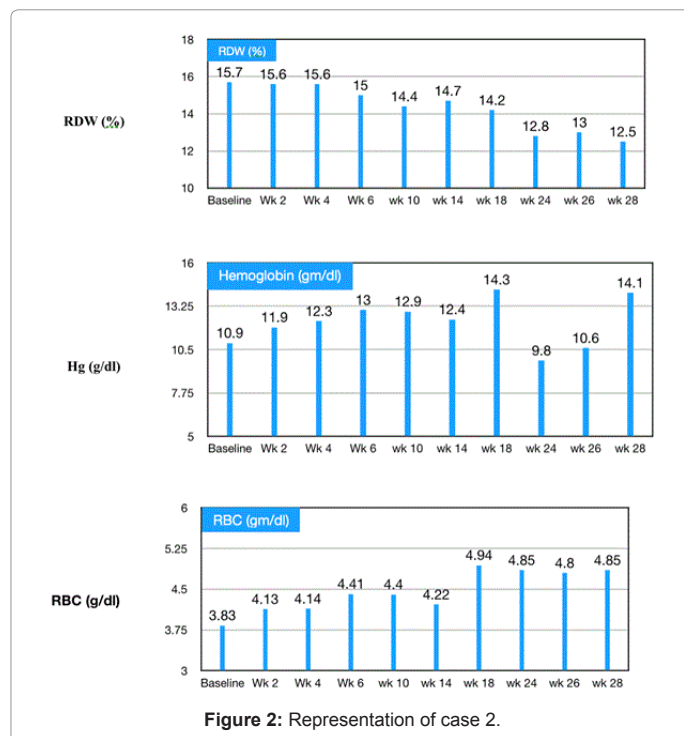


Figure 2: Representation of case 2.

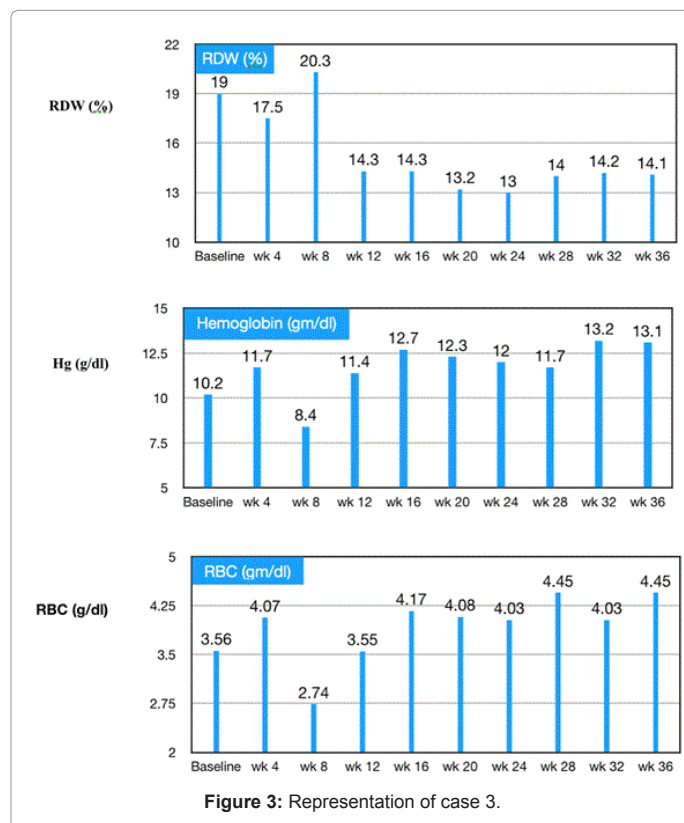


Figure 3: Representation of case 3.

maturation, leading to the production of ineffective red blood cells and elevated RDW hemoglobin synthesis and cause chronic inflammatory anemia [20]. Thus a simple explanation of the mechanism of action of Metadichol® that as a TNF-alpha inhibitor [1] it could reduce inflammatory cytokines and bring about the normalization of RDW, RBC, and HGB levels.

Previous studies have shown that Tumor Necrosis Factor alpha (TNF-alpha) as a therapeutic target in many human immune disorders, including inflammatory diseases, ischemia-reperfusion injury as well as trauma [21]. Also, it might also play an essential role in rapid necrotic regression of certain forms of tumors [22]. Therefore, it is crucial to understand the potential mechanisms that involved in the regulation of TNF-alpha in normal and disease-related cells. Recent observation indicated that histone methyltransferase G9a and heterochromatin-associated protein HP1 is essential for the silencing of TNF-alpha [23]. Epigenetically, G9a functions as the H3K9me1/2 writer whereas HP1 binds and maintains H3K9me3 at heterochromatin loci [24] suggesting that methylation of histone H3 lysine nine residues is critical for the regulation of TNF-alpha. Additionally, as G9a also interacts with DNA methyltransferase (DNMTs) and maintains DNA methylation at particular loci [25] the presence of DNA methylation might also affect the expression of TNF-alpha. Taken together, investigation of the H3K9me, as well as the DNA methylation patterns, might create a new direction for revealing the mechanisms that involved in the regulation of TNF-alpha.

Another explanation is the role of Vitamin D in the hematopoietic process. Suppression of erythropoiesis occurs in bone marrow by inflammatory cytokine due to blockage of erythroid progenitor cell proliferation and pro-erythroblast maturation. The inflammatory cytokine modulation on bone marrow erythroid progenitors desensitizes the cells to EPO, which blocks its anti-apoptotic and pro-maturation effects [26-28].

Vitamin D range of biological effects involve not just calcium and Phosphorus homeostasis, but it is also an immune modulator. This property allows it to modulate dysfunctional hematopoietic and this can affect in hematologic disorders. [29]. Immune cells express Vitamin D receptor (VDR) which are well known to modulate innate and adaptive immunity. VDR activation can inhibit production of inflammatory cytokines up-regulates interleukin-10 (IL-10) exerting both anti-inflammatory activity and proliferative effects on erythroid progenitors. In CKD patients, vitamin D deficiency stimulates immune cells within the bone marrow to produce cytokines, leading to dysfunctional erythropoiesis. Kiss et.al. have shown that there is an inverse association between vitamin D levels and EPO CKD patients [25]. Vitamin D supplementation and Paricalcitol therapy have been shown to lead to improvement in biomarkers of inflammation [30-42].

Metadichol is a TNF-alpha inhibitor and also it binds to VDR, and hence it could be working through more than one pathway in modulating RDW and normalizing RBC and Hemoglobin levels. We have previously shown how Metadichol works on other diseases through the Vitamin D receptor as an inverse/protean agonist and other nuclear receptors (32 a-i). The results of this study demonstrate that Metadichol is safe and effective as evidenced by the improvement of various biomarkers such as RDW that lead to improved RBC and Hemoglobin levels in CKD patients. Metadichol has the potential to be an anti-inflammatory molecule with a broad spectrum of activity. Its constituents (long-chain lipid alcohols) are present in foods commonly consumed on a daily basis and with no toxicity seen even with doses of up to 5000 mg/kg [18-19]. Metadichol could be used as a nutritional

supplement in renal and hematological diseases as a cheaper alternative. It can prevent complications from existing therapies that add to health care costs.

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