The Nazareth Hospital - EMMS
Affiliated with Galilee Medical School – Bar-Ilan



# Impact of L-carnitine Pretreatment on Intravenous Iron Administration-induced Oxidative Stress and Inflammatory Response in Patients with CKD


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Healing in the name of Jesus of Nazareth for 150 years



# *CKD and Anemia*

- Chronic kidney disease (CKD) is a global public health problem, affecting tens of millions around the world (1, 2)

- Anemia is a common problem in CKD patients

- Anemia often occurs during moderate (stage 3)CKD, primarily from reduced erythropoietin production but also because of iron deficiency (3)

*1. Levey AS,et al. CJASN. 2007;2:401–5*
*2. Coresh J, et al. JAMA. 2007;298:2038–47*
*3. Fishbane S, et al. CJASN 2009; 4: 57–61*

# *Consequences of Anemia in CKD*

- Anemia increases incidence and severity of CVD, hospitalization and the risk of death
- Anemia contributes to a significant reduction in life expectancy and quality of life of HD patients
- Thus, correction of anemia is considered as a major component in the integral therapy of CKD adverse consequences (1,2)


*1. Fishbane S, et al. AJKD. 1997;29:319–33*
*2. Babitt JL, et al. JASN2012;23:1631–4*

# *Anemia in CKD*

- It is evident from clinical studies that a significant proportion of uremic patients still fail to reach target Hgb levels (1,2)

  - **Reasons for failure:**

    1- Decreased erythropoietin (EPO) production

    2- Low iron stores

    3- High PTH

    4- Chronic inflammatory milieu

*1. USRDS 2006; AJKD 2007;49:1–296*
*2. Kalantar-Zadeh K, et al. JASN 2009;20:479–87*

# *Reasons for ESA Therapy Failure*

- Although these agents are capable of increasing the number of circulating red cells and hence Hb levels, the quality of red cells reaching the blood stream may not be significantly affected by ESA treatment

- The quality of circulating red cells represented by their:

  - ability to ensure capillary perfusion
  - efficient oxygen uploading in the lungs
  - offloading in peripheral tissues

# *Reasons for ESA Therapy Failure*

- RBC disappearance from the blood stream is strongly dependent on their visco-elastic properties

- The disturbance of the visco-elastic properties of RBCs would affect:

  - their mechanical ability to pass through small capillaries
  - alter their ability to release ATP, hence, NO-dependent caliber vasodilation, in response to reduced $O_2$ tension

*Ellsworth ML, et al. Physiology (Bethesda) 2009;24:107–16*

# *Adverse Effects of Iron Replenishment*

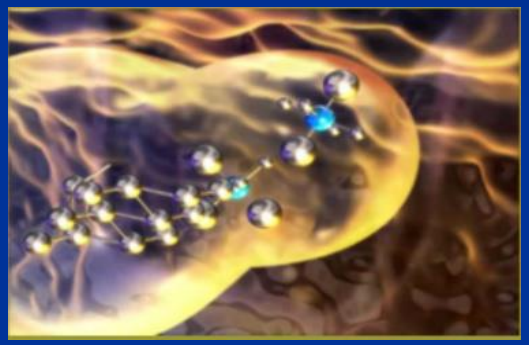
- The intravenous iron administration (IVIR) induces oxidative stress as well as inflammation (1, 2)

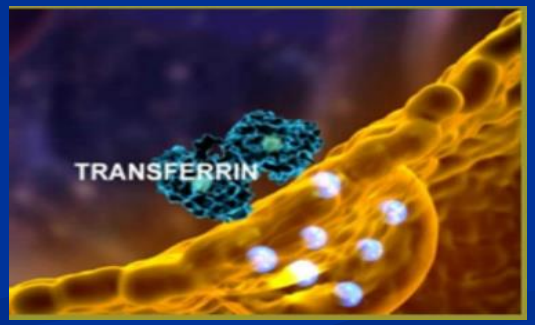
- Iron-induced injury may lead to an accelerated course of renal damage (3, 4), increased frequency of overall serious adverse events, C-V disease (5, 6) and infectious complications


*1. Agarwal R, et al. Kidney Int 2004; 65: 2279–2289*
*2. Agarwal R, et al. CJASN 2011; 6: 114–121*
*3. Haugen E, et al. Blood Purif 1999; 17: 58–65*
*4. Agarwal R, et al. REVOKE. Kidney Int 2015; 88: 905–914*
*5. Drueke T, et al. Circulation 2002; 106: 2212–2217*
*6. Becker BN, et al. JASN 1997; 8: 475–486*

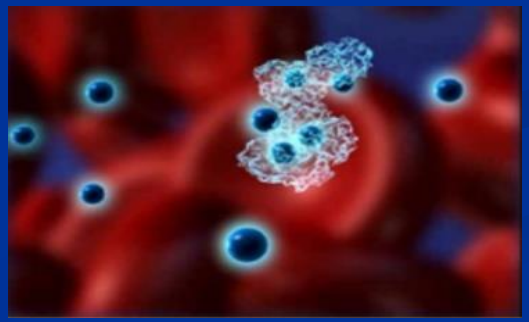
# *Intravenous Iron (IVIR)*

- Even though the IV iron preparation is absorbed by macrophages and most of it is released in a regulated manner to transferrin (Tf), 4-5% of the iron in the preparation is released as a free form to the plasma






- This iron may bind to Tf in a strong bind and be protected from reactions of Oxidation-Reduction and the creation of free oxide radicals (ROS-Reactive Oxygen Species)



# *Free Iron*

- Free iron may bind non-Transferrin ligands (Non-Transferrin Bound Iron – NTBI)

- These ligands include:

  - Albumin
  - Citrate
  - Bicarbonate
  - Sulfate
  - Phosphate
  - Oxalate

- NTBI is capable of penetrating into cells in transfer routes that are not under the control of iron cell state and the TfR and thus may cause an overload of iron in tissues

# *Free Iron*

- NTBI is more available for exploitation by bacteria as opposed to iron attached to Tf

- In addition to an overload of iron and worsening of sensitivity to infections, NTBI has the potential of Oxidation-Reduction reaction (1-5)


*1. Parkkinen J, et al. NDT 2000; 15:1827–1834*
*2. Zager et al.. Kidney Int 2004; 65: 2108–2112*
*3. Zager RA, et al. Am J Physiol Renal Physiol 2005; 288: F290–F297*
*4. Sengoelge G, et al. JASN 2003; 14: 2639–2644*
*5. Zheng H, et al. Kidney Int 2006; 69:679–684*

# *Oral Iron vs IV Iron Treatment*

- RCT-based evidence for optimal iron management in the treatment of anemia is still inadequate in CKD patients who do not yet need dialysis therapy


*1. Rozen-Zvi B, et al. AJKD 2008; 52: 897–906*
*2. Stoves J, et al. NDT 2001; 16: 967–974*
*3. Macdougall IC, et al. FIND-CKD. NDT 2014; 29: 2075–2084*
*4. Agarwal R, et al. REVOKE. Kidney Int 2015; 88: 905–914*

# *IV Iron Treatment*

- The general conclusion of these trials was that intravenous iron was more effective than oral iron for replenishing iron stores, improving anemia, and reducing ESA dosage requirements

# *Intravenous Iron*



## Benefits of IV Iron

1. Better bioavailability
2. Rapid efficacy
3. No compliance issue
4. Grater Hgb increase
5. Reduced ESA needs
6. Reduced transfusion needs

## Risk of IV Iron

1. Inflammation
2. Oxidative stress
3. Cytotoxicity
4. Endothelial dysfunction
5. Anaphylaxis
6. Hemosiderosis
7. Bacterial infections
8. Cardiovascular events
9. mortality

# *Our Dilemma!*

* Anemia is harmful and should be corrected!
* ESA can be harmful but we still need it!
* Iv iron can be harmful but we can't without it!
* PO iron is ineffective and can be  harmful!




Give iron IV with some protection!

# Who Is The New Candidate?







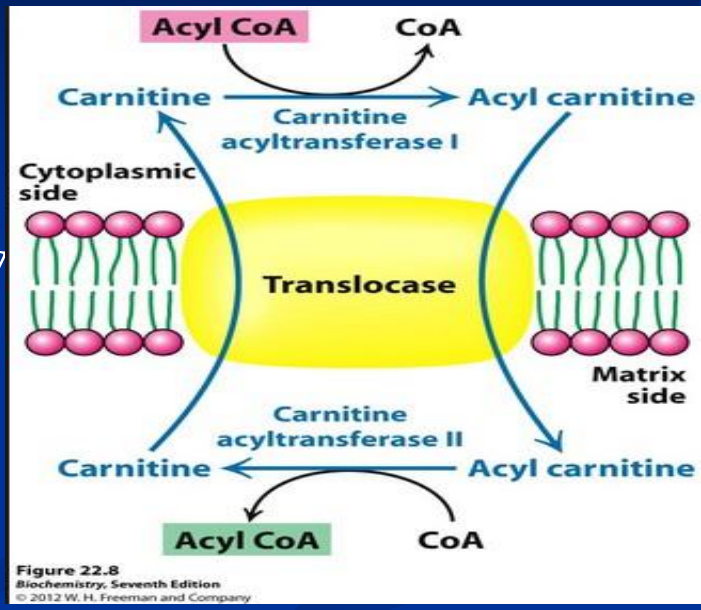

- *Thiols*
- *Vit.C, E, B complex*
- *Selenium*
- *NAC*

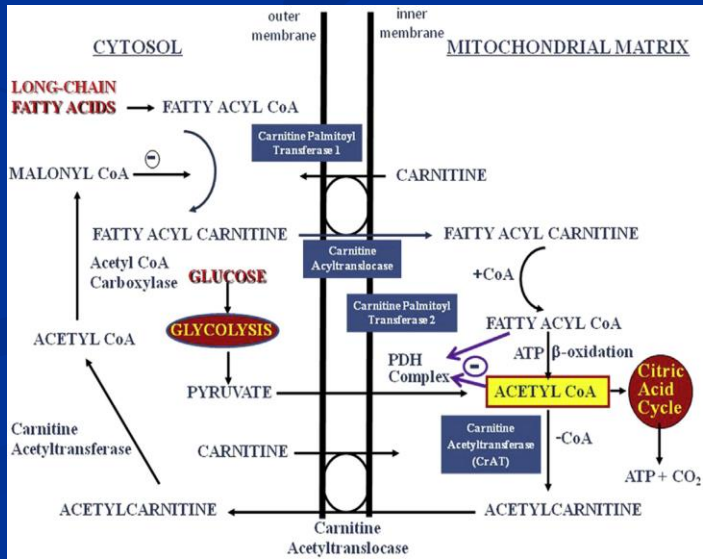


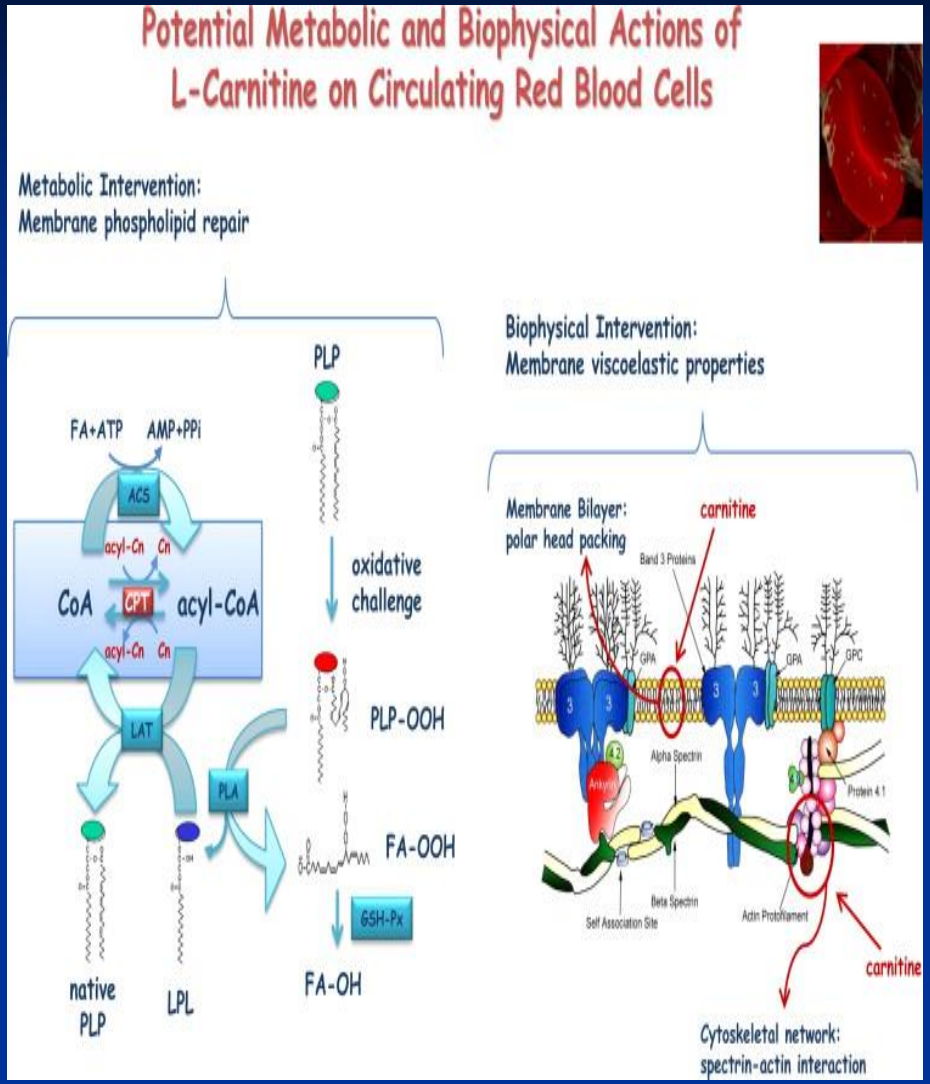
**Carnitine**

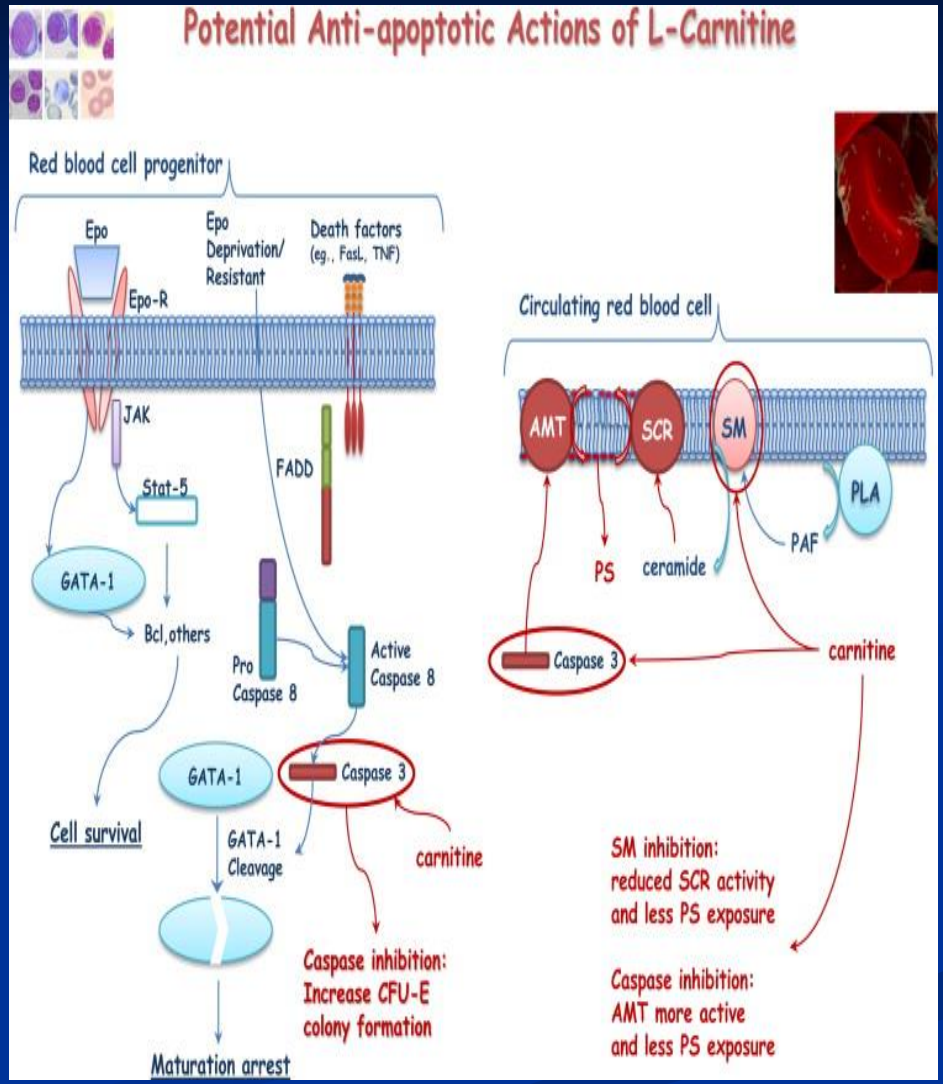
# What is Carnitine?

- Carnitine is a essential cofactor required for transport of long chain FA into the mitochondrial matrix for FAO and energy production
- Carnitine buffers potentially toxic acyl-CoA metabolites and modulate the ratio of acyl-CoA/CoA
- The latter regulates the activity of many mitochondrial enzymes involved in the citric acid cycle, gluconeogenesis, urea cycle and fatty oxidation





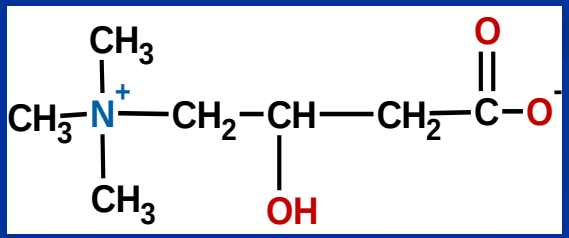

Pharmacological Research, Volume 63, Issue 3, 2011 157–164

# *Carnitine Sources*

- 75% provided in diet; 25% synthesized in kidney, liver and brain

  - meat, poultry, fish & dairy products
  - 70 – 80% of dietary intake is absorbed

- Although 99% of the carnitine amount is intracellular, the relationship between serum acylcarnitine (AC) and free carnitine (FC) is highly sensitive to intramitochondrial metabolic alterations



# *Carnitine Levels*

- Under normal circumstances, 80% of serum carnitine is free carnitine and normal AC/FC ratio is 0.25%

- AC/FC ratio > 0.4 are considered as abnormal (carnitine insufficiency)

# *Causes of Carnitine Deficiency*

- **Primary**: several inborn errors of metabolism mainly organic acidurias

- **Secondary**:

1. Fasting
2. Pregnancy
3. Neonates
4. Diabetes
4. aging
5. Heart failure
5. **CKD &Dialysis**
6. Alzheimer dis.
7. Cirrhosis
8. Acquired: valproate…

# *Causes of Carnitine Deficiency in CKD*

1. Impaired synthesis
2. Dietary deficit
3. Intestinal malabsorption
4. Lipid metabolism disorders
5. The loss of the physiological preference for renal excretion of AC with exaggerated FC losses
6. Reduced activities of carnitine system enzymes and increased requirement

# *Consequences of Carnitine Deficiency*

- Dysfunction of mitochondrial FA oxidation leading to:

1. abnormal energy production
2. toxic acyl moieties accumulation
3. oxidative stress
4. inhibition of key enzymes of the metabolism

# *Consequences of Carnitine Deficiency in CKD &Dialysis*

## Carnitine deficiency in CKD patients contributes to:

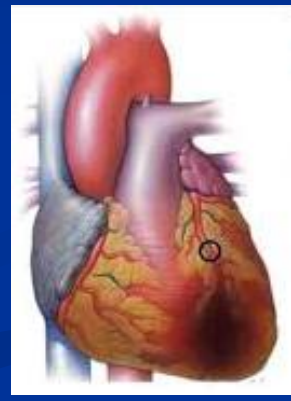
1. Muscle weakness and myopathy
2. Loss of body protein and cachexia
3. Insulin resistance and glucose intolerance
4. Plasma lipid abnormalities
5. Anemia refractory to ESA
6. Cardiomyopathy and cardiac arrhythmias
7. Intradialytic symptoms

## *Benefits of Carnitine Supplementation*

1. L-Carnitine and C-V events
2. L-Carnitine and AKI & CKD
3. L-Carnitine and Fatty Liver & Insulin Resistance
4. L-Carnitine and Cognitive Function
5. L-Carnitine and Proteinuria (N.S)

# *L-Carnitine and CV Outcome*

- It is known that during ischemic events L-Carnitine levels are depleted



- L-carnitine was associated with:

  - significant 27% reduction in all-cause mortality

  - highly significant 65% reduction in ventricular arrhythmias

  - significant 40% reduction in the development of angina

  - reduction in infarct size



*DiNicolantonio JJ, et al. Mayo Clin Proc. 2013 Jun;88(6):544-51*

# *L-Carnitine and CV Outcome*

- "The potential mechanisms responsible for the observed beneficial impact of L-carnitine in acute MI are likely multifactorial:
  - the ability of L-Carnitine to improve mitochondrial energy metabolism in the heart
  - removing toxic FA intermediates
  - reducing ischemia induced by long-chain FA concentrations
  - replenishing depleted carnitine concentrations seen in ischemic, infarcted and failing myocardium

*DiNicolantonio JJ, et al. Mayo Clin Proc. 2013 Jun;88(6):544-51*

# *Carnitine in CKD?*

- Previous studies suggested that L-carnitine supplementation might have positive effects on the response to ESA in long term hemodialysis patients

- **There is no evidence whether this approach is also beneficial in earlier-stage CKD patients**



## *Hypothesis*

- Carnitine may act as a protector against deterioration of oxidative stress and inflammation associated with IVIR administration in predialytic CKD patients with consequent more efficacious response to IVIR

## *Aim*

- The present study examined whether L-Carnitine prevents oxidative stress and inflammatory responses to intravenous iron administration (IVIR) in CKD patients

# *Methodology*

- CKD patients stage 3-5 not on dialysis
- T. sat. < 20% Ferritin < 100 after 3 months of orally iron treatment failure
- Normal levels of Vit.B12, Folic acid
- No ongoing ESA treatment

# Methodology

- This Study included 2 groups of CKD anemic patients consist of 32 subjects each receiving IVIR for 12 weeks

i. One group was treated with saline 30 min prior to IVIR (Sodium ferric gluconate, [125 mg/100 ml]) only

ii. The other group was treated with additional of Carnitine (20mg/kg, IV) 30 min prior to IVIR administration

iii. Blood samples were drawn weekly at baseline and 30 min after completing IVIR

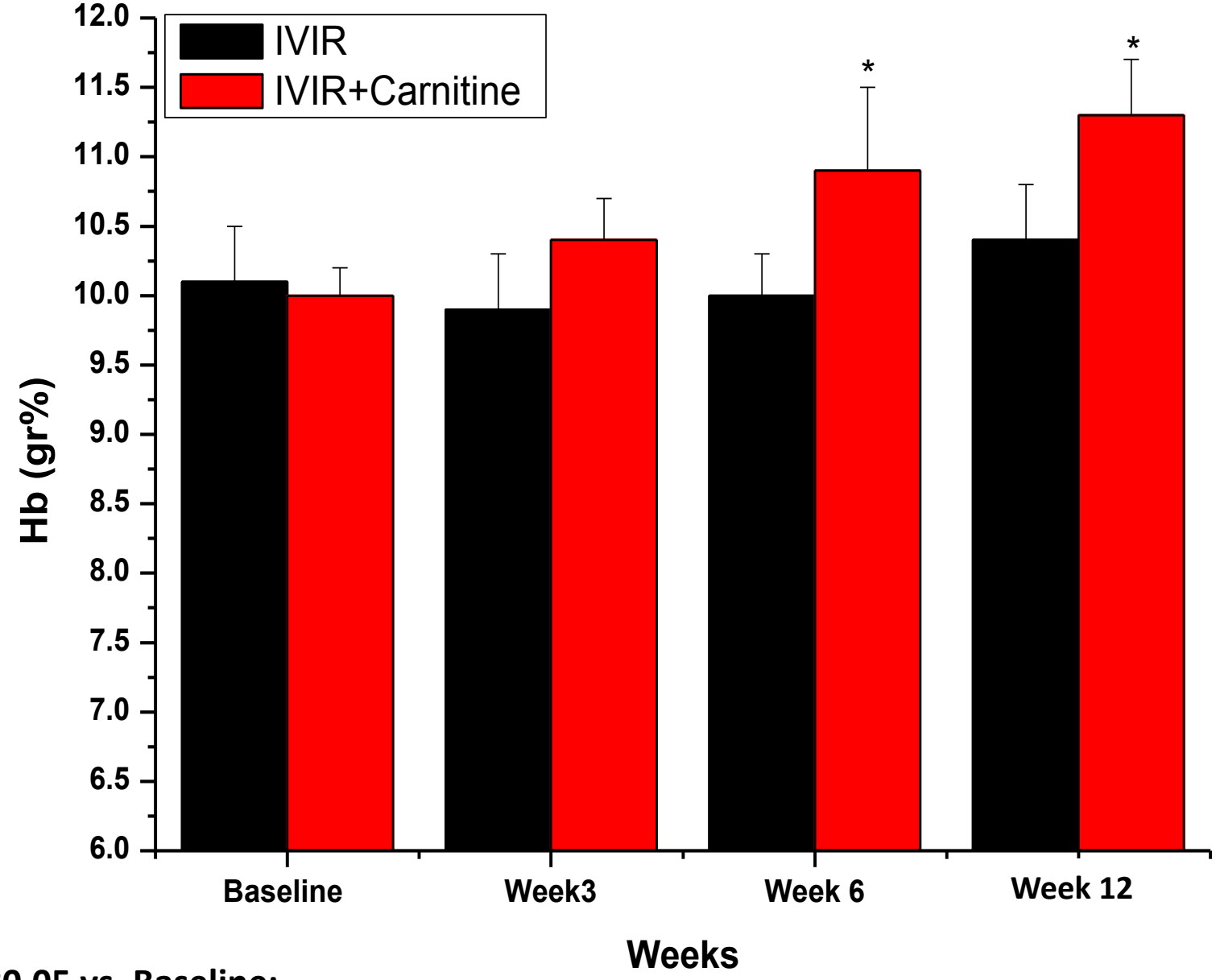


# *Patient's Characteristics*

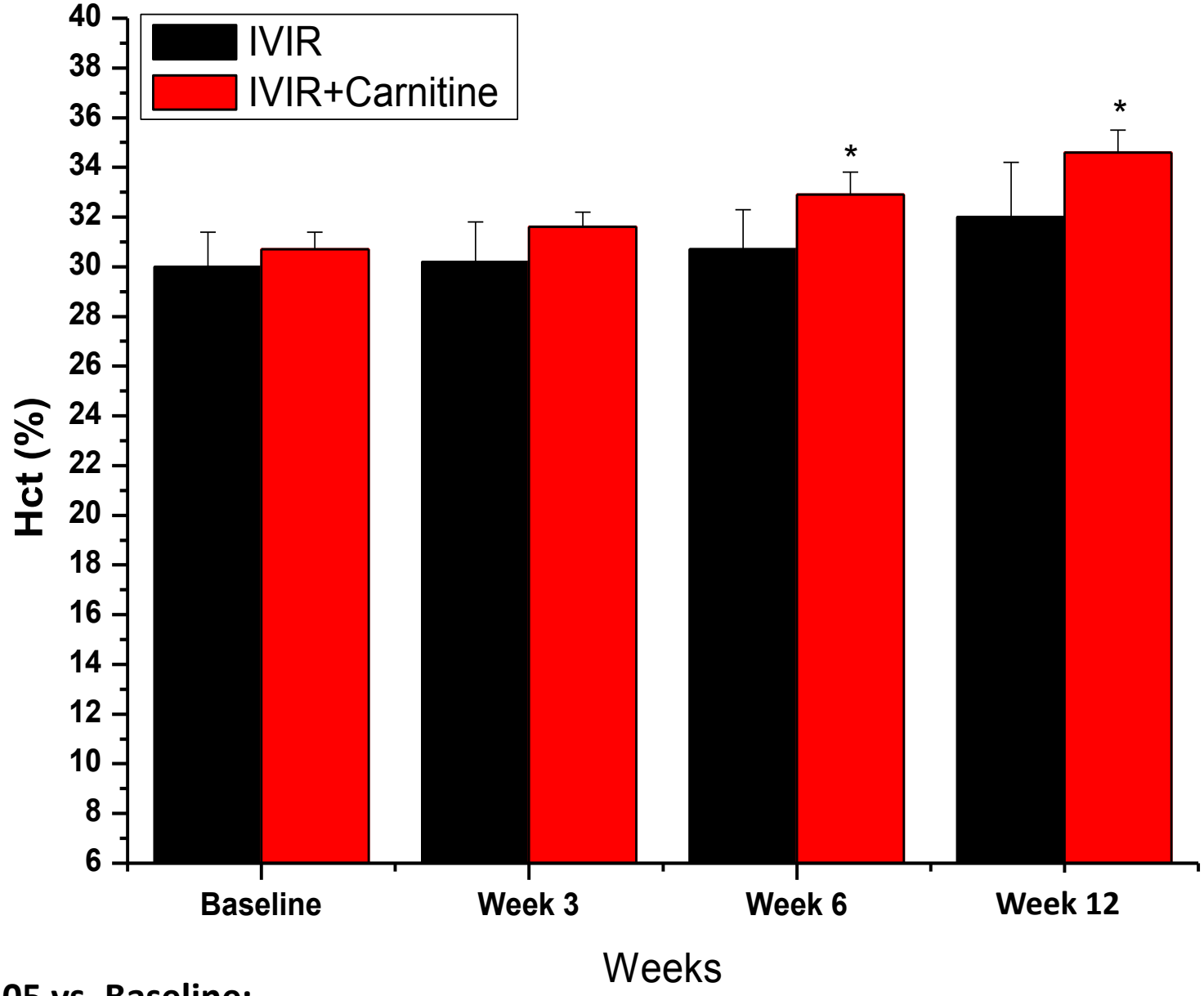
| | IVIR + Placebo | IVIR + Carnitine |
|---|---|---|
| | n=16 | n=16 |
| Age (year) | 72.7 ± 2.5 | 68.9 ± 2.8 |
| Gender (M/F) | 9/7 | 8/8 |
| GFR Baseline (ml/min) | 33.6 ± 2.3 | 31.2 ± 3.3 |
| Hb (gr%) | 10.2 ± 0.3 | 10.2 ± 0.2 |
| Ferritin (ng/dl) | 48.06 ± 5.2 | 50.87 ± 5.97 |
| Tran. Sat.% | 12.1 ± 2.2 | 11.9 ± 2.3 |

| Etiology of CKD | IVIR + Placebo | IVIR + Carnitine |
|---|---|---|
| D.N | 76.92 % | 73.33 % |
| HTN | 15.38 % | 20 % |
| S.C.A. | 7.7 % | 0 |
| PKD | 0 | 6.67 % |
| | | |

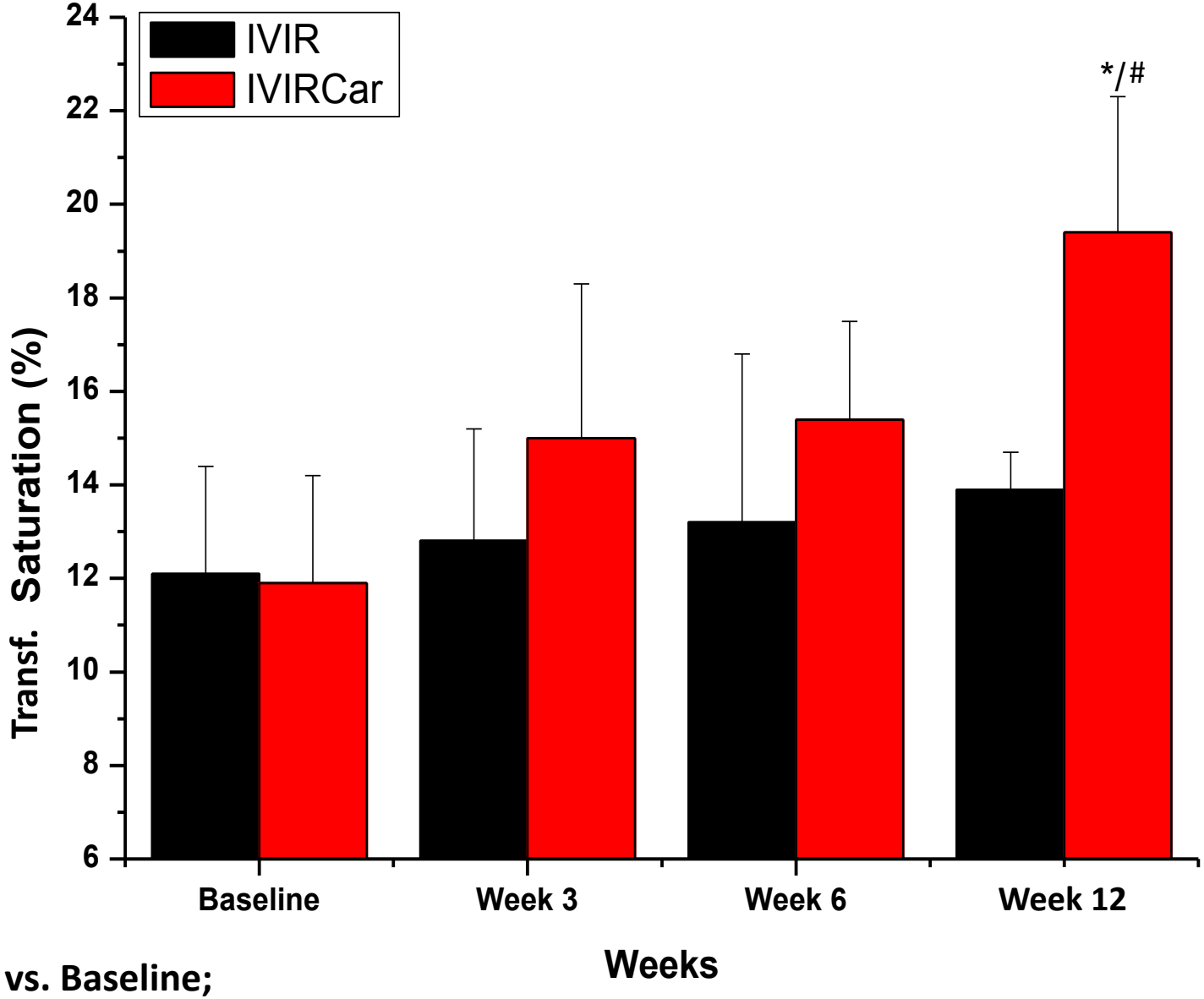
# *Results*




*, P<0.05 vs. Baseline;

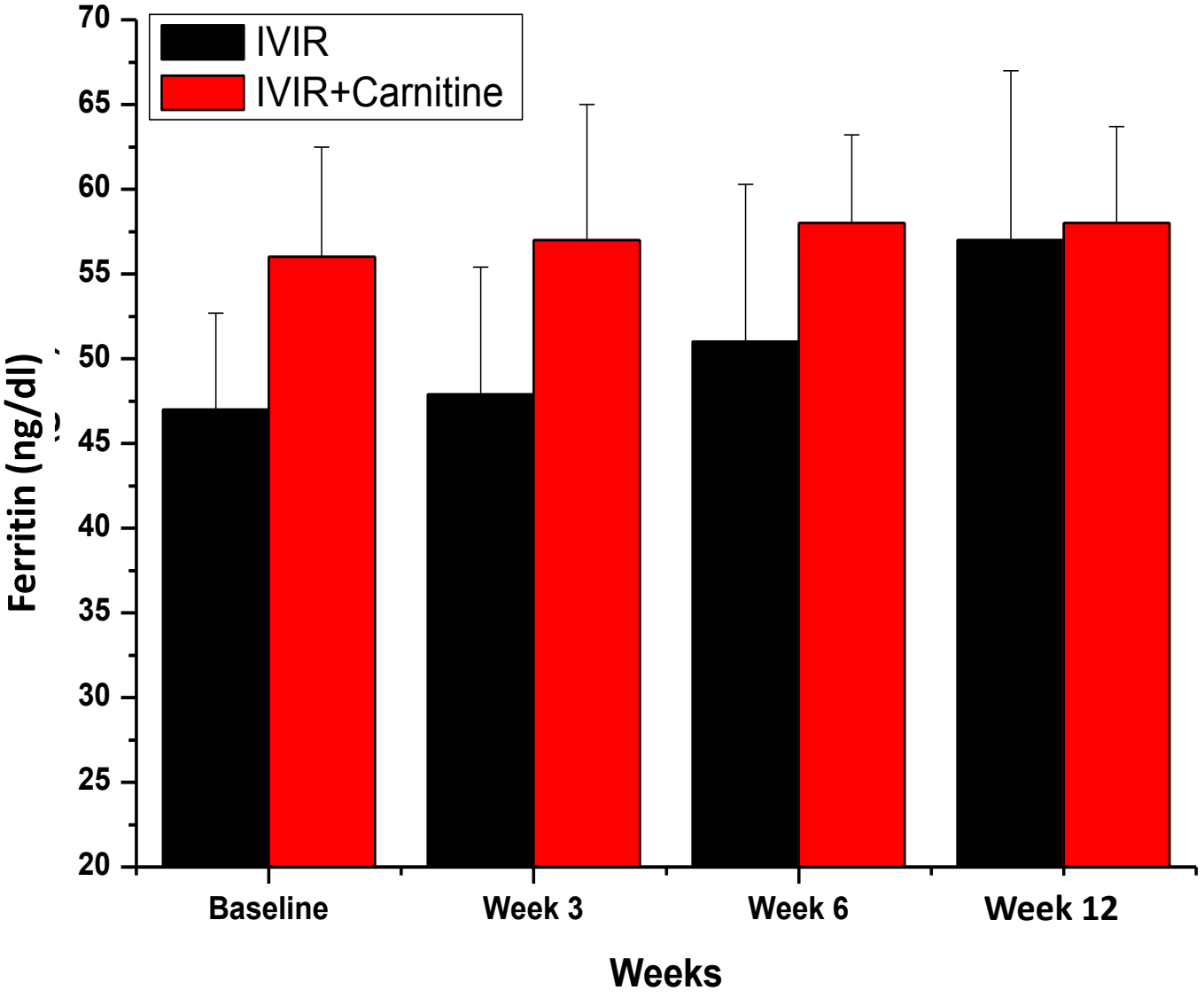



*, P<0.05 vs. Baseline;

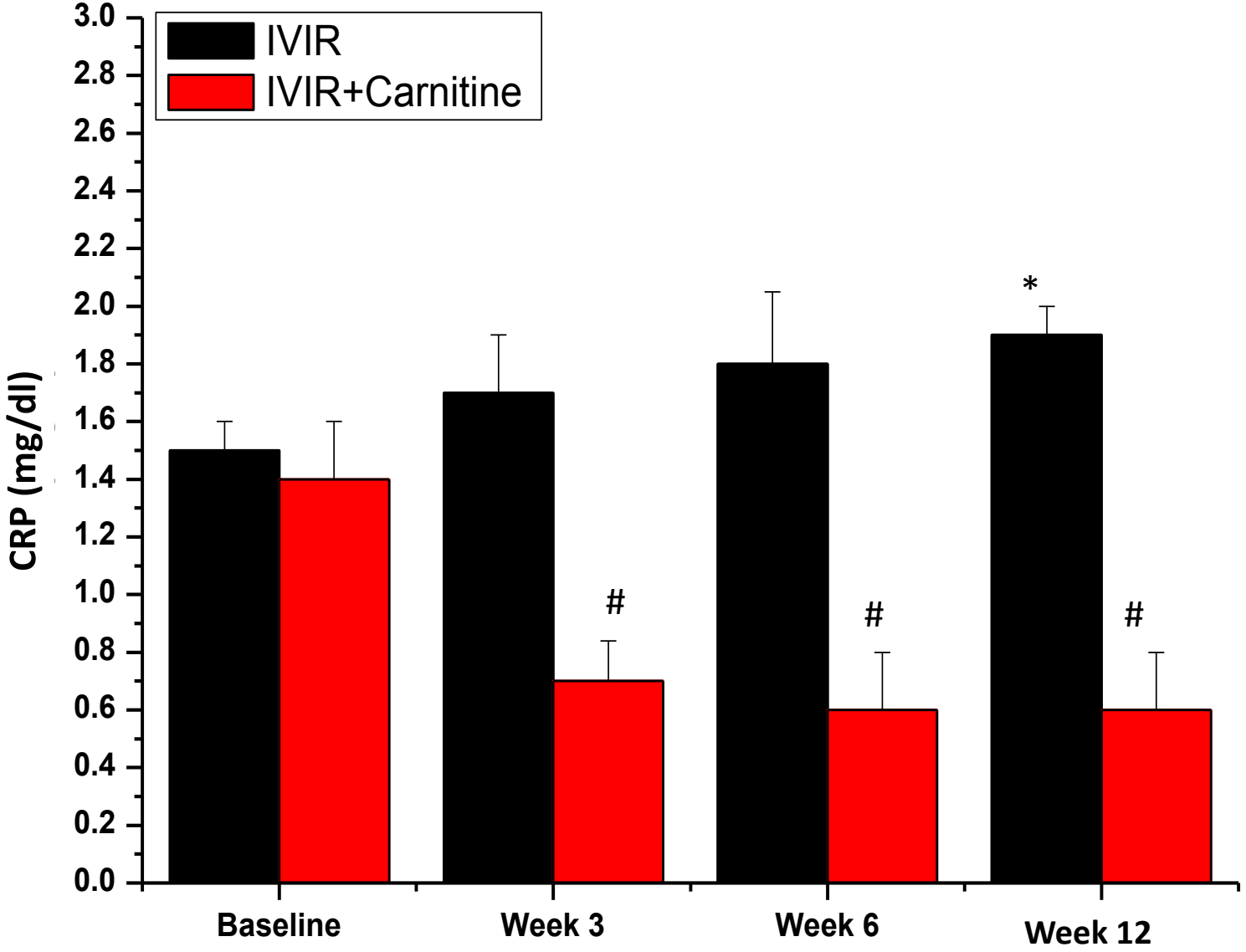



*, P<0.05 vs. Baseline;

#, P<0.05 vs. IVIR


IVIR
IVIR+Carnitine
70
65
60
55
50
45
40
35
30
25
20
Ferritin (ng/dl)
Baseline
Week 3
Week 6
Week 12
Weeks

# *Inflammation and Oxidative Stress Biomarkers!*

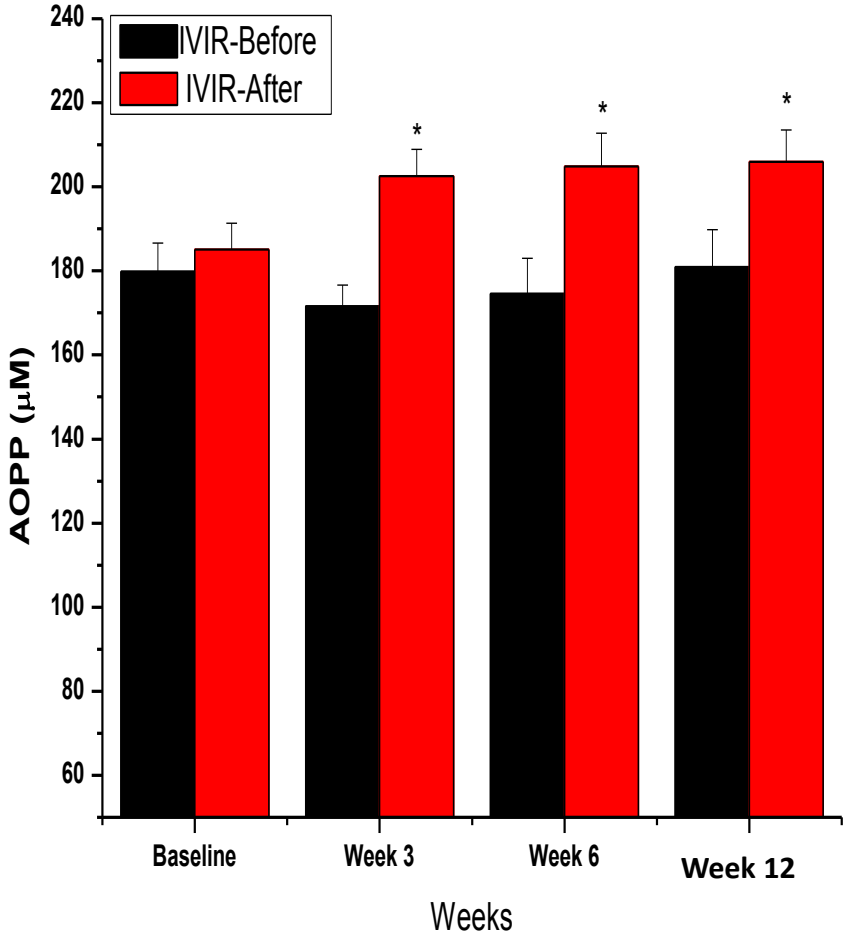



*, P<0.05 vs. Baseline;

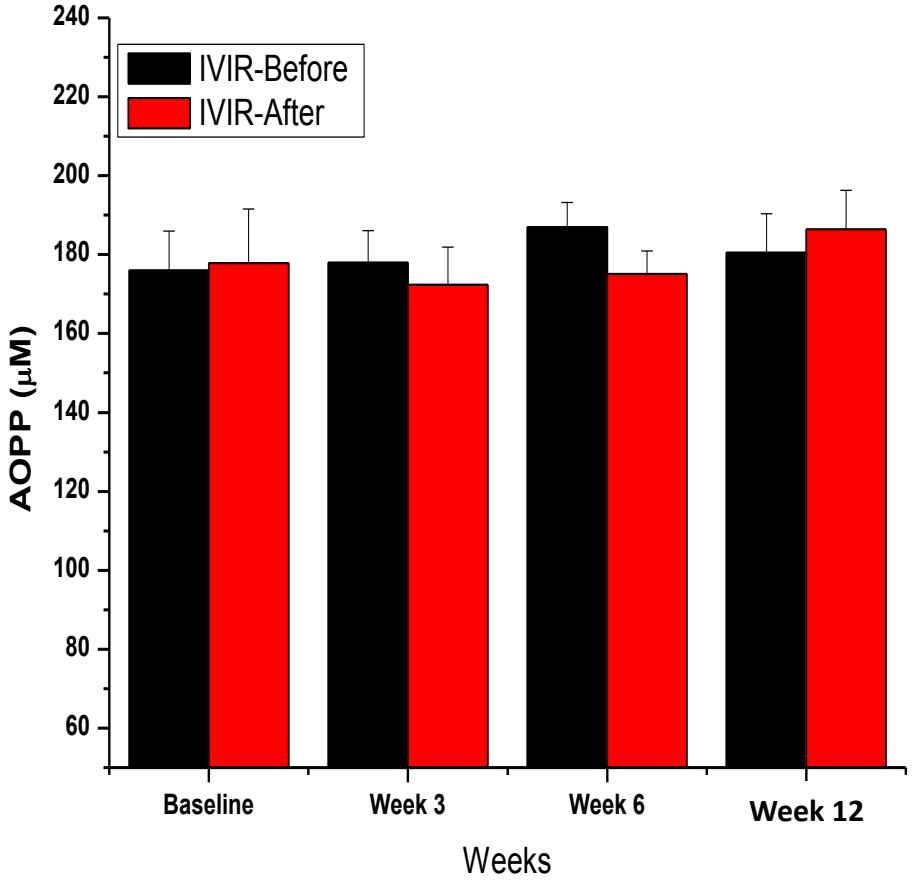
#, P<0.05 vs. IVIR

# AOPP

## Placebo



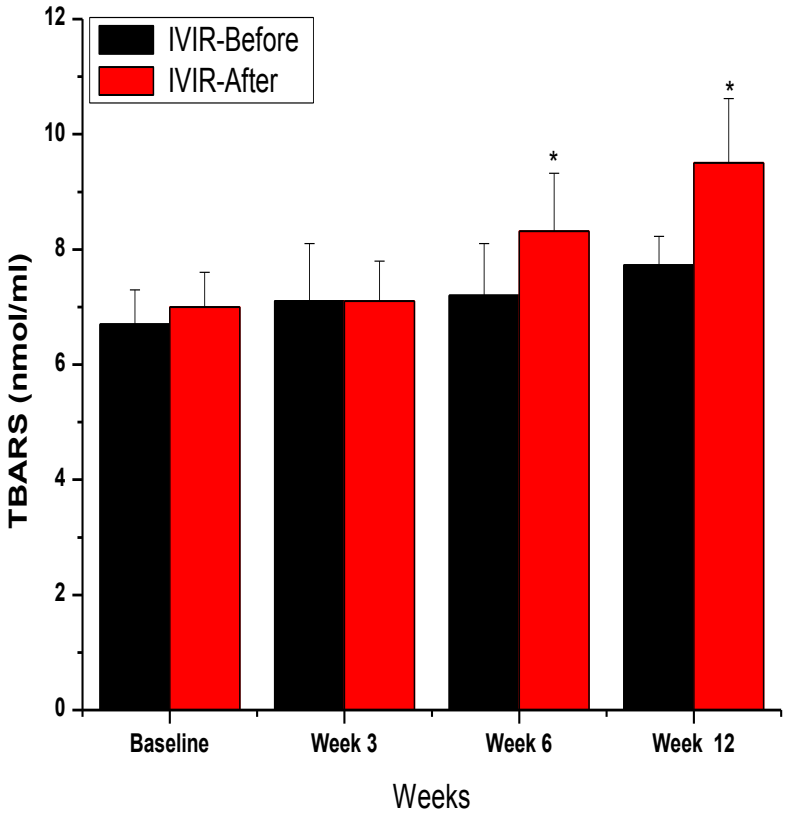

## Carnitine



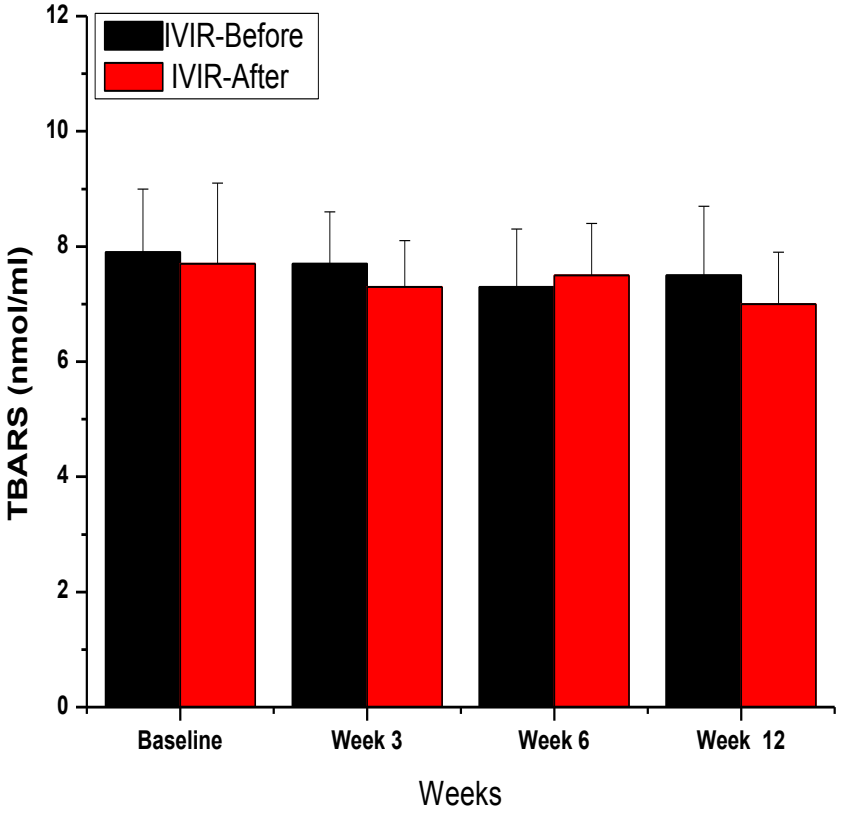

***, P<0.05 vs. Baseline;** **AOPP**: Advanced oxidation protein products

# TBARS

## IVIR+Placebo

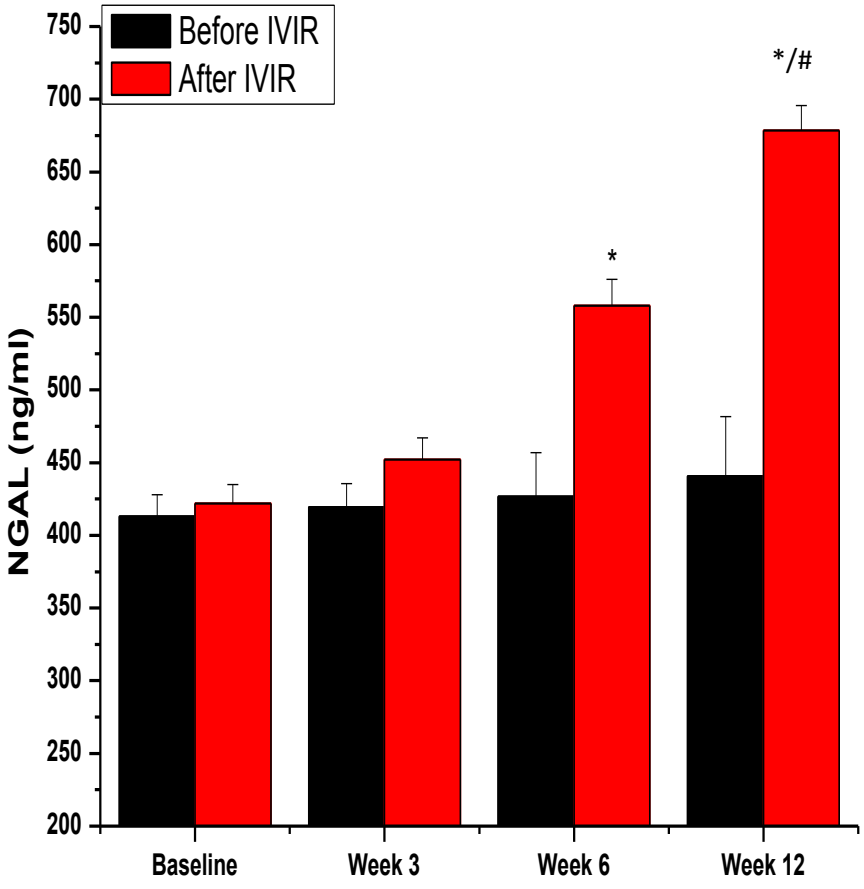



## IVIR+Carnitine

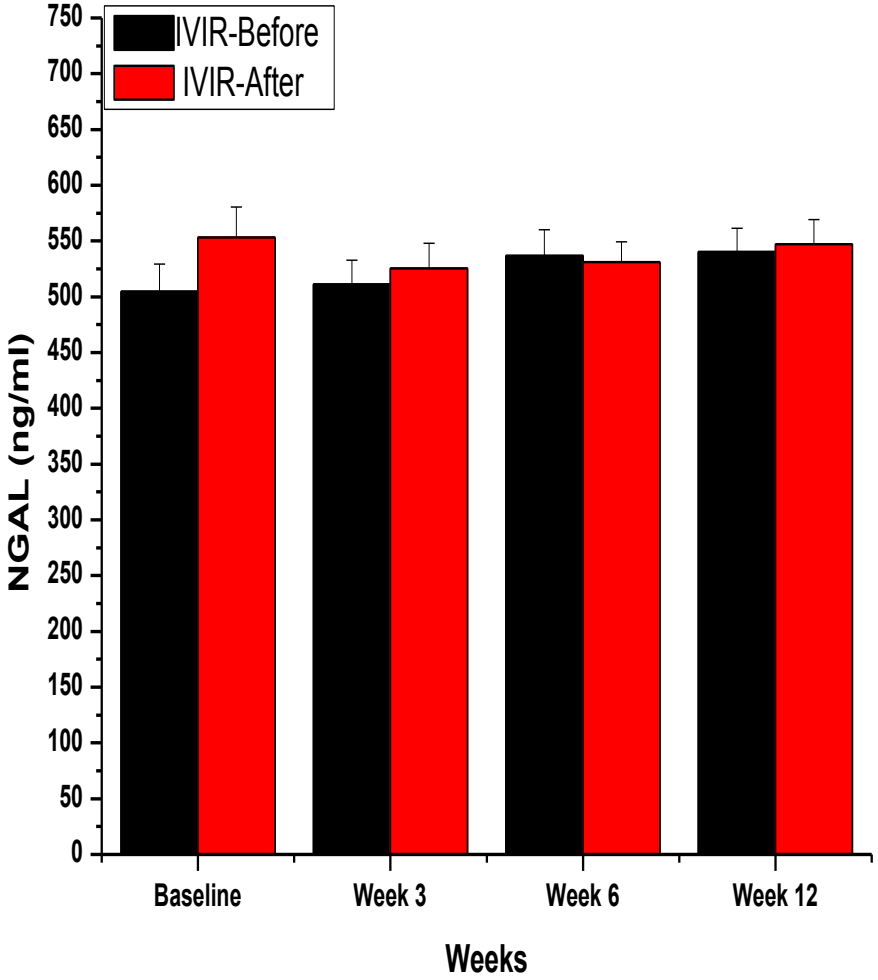


# Plasma NGAL

## IVIR+Placebo




## IVIR+Carnitine




***, P<0.05 vs. Baseline;**

**#, P<0.05 vs. Before IVIR**

**NGAL**: Neutrophil gelatinase associated lipocalin

# *Summary & Conclusions*

- Our finding, that co-administration of Carnitine with IVIR preferentially increased Hgb levels more efficiently and attenuates the adverse consequences of IVIR

- Administration of Carnitine may attenuate the uremic milieu and by this the progression of the renal failure

- Cost saving

# *Summary & Conclusions (Cont.)*

- These findings suggest a therapeutic role for co-administration of Carnitine in CKD patients treated with IVIR

# *Thank You*





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# *Welcome to Nazareth*

# *2018*







*Healing in the name of Jesus of Nazareth for 150 years*