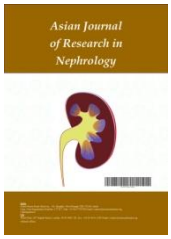

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An Investigation into the Molecular Mechanism of Inverse Relationship between S. Creatinine and HDL-C in CKD

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Author's contribution

The sole author designed, analyzed, interpreted and prepared the manuscript.

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Review Article

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ABSTRACT

An inverse relationship between the raised Serum creatinine (Crn) and High density lipoprotein cholesterol (HDL-C) is well known. A raised S. Creatinine / low estimated glomerular filtration rate (eGFR) is a marker of chronic kidney disease (CKD). Besides, the eGFR, indicates the rate of progression of CKD and helps in the staging of CKD. Any relationship involving the raised creatinine or reduced eGFR necessitates the presence of the CKD in the background. While the CKD itself can cause both high S .Creatinine and low HDL-C, the mechanism of the inverse relationship between the two is not clear. Each of the raised creatinine and low HDL-C, have independent risk factors, but the only common risk factor for both, is the sedentary life style. The role of the sedentary life style in the inverse relationship between the raised Cr and low HDL-C, is examined. A possible molecular mechanism is being suggested, connecting the four variables - the raised Crn , low HDL-C, the CKD and the sedentary life style. To this extent the relevant metabolism of both S creatine and HDL-C, are briefly reviewed, as knowledge of the same is intricate to the better understanding of the molecular mechanism proposed.

Keywords: Creatine phosphate; creatine kinase; ABC 1 transporter; Ubiquitous mitochondria; Sarcolemmal mitochondria; creatine shuttle; High density cholesterol, creatinine; Reverse cholesterol transport.

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1. INTRODUCTION

A perusal of the literature reveals that, the relationship between the low HDL-C and CKD has been studied from several angles, as seen below. The criteria for CKD, as used in the studies are , a raised creatinine or a decline in the eGFR or increased micro-albuminuria.

Low HDL-C is reported as an independent predictor of increased renal dysfunction as evidenced by the MDRD study [1]. and the Atherosclerosis Risk in Communities (ARIC) cohort study [2]. Bowe et al. in a retrospective cohort study using the U.S. Veterans Administration (VA) databases, found that low HDL-C was significantly associated with the risk of incident kidney disease [3]. Low HDL-C levels are associated with the risk of progression of CKD [4]. It is shown that the individuals with HDL-C concentrations <30 mg/dl had a 10%–20% higher risk for CKD and/or progression of CKD, compared with individuals with concentration of ≥40 mg/dl [5]. Association between low HDL-C or a high triglyceride to HDL-C ratio and poor kidney function or progression of CKD, Is noted [6-9]. studies showed that the level of oxidized low-density lipoprotein (LDL) cholesterol increases and high density lipoprotein (HDL) cholesterol d[dysfunction occurs as kidney function declines and inflammation becomes more pronounced [10]. Low HDl in particular were significantly associated with an increased risk of developing renal dysfunction in men with an initial creatinine level less than 1.5 mg/dl [11]. CKD is associated with increased plasma triglycerides and very low density lipoprotein (VLDL) cholesterol, as well as decreased HDL cholesterol [12,13].The proteome and lipidome of HDL particles is heavily disturbed not only in the uremic state, but also in very early stages of kidney impairmen [14].

1.1 Brief Review of Creatine Synthesis, Transport into the Cell, Resynthesis and Degradation to Creatinine

Some facts about creatine: Creatine (Cr) in the form of Creatine phosphate (CrP), is a quickly replenishable able source of energy (ATP), needed for muscle contraction. 95% of the total creatine and phosphocreatine stores are found in skeletal muscle, while the remaining is distributed in the blood, brain, testes, and other tissues [15-17] . The average amount of total creatine stored in the body is approximately 120 mmol/kg of dry muscle mass [18]. Average 70 kg young male has a creatine pool of around 120-140 g which varies between individuals [19,20].The creatine excreted /day is 1.7 mg [21].

1.1.1 Synthesis of creatine

Creatine is synthesized in two steps.

The first step is the reaction catalysed by adenine guainine amido transferase (AGAT) is the synthesizes guanidinoacetate from arginine and glycine, This is the rate limiting step. . AGAT activity in tissues is regulated by

1. Induction by growth hormone [22]. and thyroxine [23].
2. Inhibition of the enzyme by ornithine.
3. Repression of synthesis of the enzyme by creatine, present in the cell, both, intra and extracellularly. [24,25].

The guanidinoacetate produced is then combined with *S*-Adenosyl-L-methionine, a reaction catalyzed by (Guanine alanine methyl transferase (GAMT,) to produce creatine and *S*-Adenosyl-L-homocysteine. in exchange for a proton to become guanidinoacetate and renew the catalyst, as shown by reaction 1 , below.

S-adenosyl-L-methionine + guanidinoacetate→S-adenosyl-L-homocysteine + creatine. ---- (1)

1.2 The intracellular Transport of Creatine

The creatine, thus synthesized, is transported to the cell through blood. In the cell, the creatine is compartmentalized into 3 compartments, - the mitochondria, the cytosol and blood. There are two types of mitochondria, the ubiquitous (uMtCK) and the M line of the sarcomere.(sm Mtck) Creatine Kinase (CK), the enzyme that catalyzes the reverse reaction of creatine to creatine phosphate, is present in both the types of mitochondria, but plays different roles. In the ubiquitous mitochondria, it phosphorylates to form creatine phosphate, which is an endergonic reaction and hence depends on the supply of ATP energy. It is transported through cytosol, into Sarcolemmal M line mitochondria, where the reverse reaction occurs ie dephosphorylation, leading to breakdown of CrP into creatine and Pi. The high energy pi bond is added to ADP, resulting in ATP formation. The ATP, thus formed, is used by the myosin and contractile

actin resulting in muscle contraction. The reversible conversion between creatine and phosphocreatine, which is coupled to the equilibrium between ATP and ADP, CK helps maintain energy homeostasis in tissues. The ATP from the CrP is the immediate source of energy for sustaining the Intermittent excercise like walking, etc.

The ATP is replenished by resynthesis during the resting phase of the exercise, by a resynthesis mechanism of CrP described below.

1.3 The Creatine Shuttle Mechanism of Resynthesis of Creatine

While the ATP is used up by the contracting muscle, the creatine released into the M line mitochondria of the Sarcolemma, is recycled to creatine phosphate, in the uMtc. This CrP, so formed , is readily transported into the M line Sarcolemmal Mtck for furnishing ATP, for the next contraction. This resynthesis mechanism of CrP is known as " "Creatine shuttle". Thus, a continuous and uninterrupted supply of energy for carrying out light, and Intermittent type of muscular exercise, is ensued. During moderately severe and sustained excercise, the energy supplied by the hydrolysis of CrP is not sufficient and hence, the energy dependence is on substrate and oxidative phosphorylation(OX Phos), generating the ATP.

The intracellular creatine transporters: The creatine that is synthesized, is transported through the blood stream and taken up through sodium-dependent creatine transporters by cells that require creatine [26].

Two types of creatine transporters (CrT) are known.

1. Mitochondrial CrT (Mtc CrT)
2. Plasma membrane CrT. (Pm CrT)

Intracellular compartmentalization of creatine: This is a crucial factor in the formulation of the proposed mechanism, as could be seen in the discussion part. The three compartments in which the creatine is sequestered are – the blood, the cytosol and mitochondria.

A huge gradient of Cr, between the blood and cytosol exists. Against this gradient and with the help of Na cl transporter, cr enters the cytosol. About 2/3 of Cr thus entered is converted into phosphocreatine. Pm CrT allows Cr but not Cr P and hence Cr is trapped inside the cell. Since it is not in equilibrium with creatine in the blood, the quantities of creatine and CrP/Cr ratios differ. The mitochondrial CrT allows creatine to be transported into the mitochondria. Since the biological membranes of cell and its organelles are impervious to both Cr and CrP, Compartmentation of the 3 pools is complete.

Regulation of the CrT: Intracellular Cr regulates either the number or intrinsic activity of the CrT (Loike et a. [27], the data from both the cell-culture studies [28] and in vivo human experiments [29]. Support the regulation of CRT by the intracellular creatine. Basing on urinary Cr excretion, it was shown, that the short-term exposure to high extracellular Cr levels, inhibited cellular Cr uptake. High extracellular Cr causes an initial increase in Cr uptake as well as an elevation in intracellular Cr concentration, which inturn, subsequently inhibits Cr uptake by the feeds back inhibition of CrT. Wang et al. [30]. showed that this feedback inhibition occurs by reducing the activity of a non receptor protein tyrosine kinase, known as c-Src kinase.

Degradation of creatine into creatinine: While creatine is a source of energy, creatinine, it's metabolite, is, a waste product, which is completely eliminated, by the healthy kidneys. The degree of the creatinine clearance from the blood is dependent on the degree of the kidney damage. As soon as creatine enters the blood, it is non-enzymatically degraded into creatinine, which is flushed out of the body by the kidneys.

A brief review of HDL-C metabolism: The HDL is synthesized in the liver as a lipoprotein and phospholipid complex. The cholesterol in excess of the need of the cells, and the macrophages limning the blood vessels, is collected and returned to the liver by HDL, to be degraded and excreted in the bile. The efflux of the cholesterol from the cells is assisted by two transporter proteins, ABC 1 and ABG 1, the former transporting, the cholesterol, to Apo lipoprotein A1) (apo A1) [31,32] and the later to HDL [33,34]., respectively. ABC A1 and ABG1 both, thus have anti-atherogenic activity. [35,36] The free cholesterol in HDL is esterified by an enzyme, lecithin acetyl transferase (LACT) to cholesteryl ester and is sequestered into the hydrophobic core of the HDL particles. The enzyme cholesterol esters transferase enzyme exchanges, the cholesteryl ester of HDL, with the triglycerides of the Apo B containing lipoproteins (VLDL, iDL and LDL).The HDL

particles is either transported by a direct pathway to steroidogenic tissues like Testis, ovary, and adrenals etc., and is removed by the Scavenger cell receptors of HDL (SR-B1), which mediates the selective uptake of cholesterol from HDL or by indirect pathway to liver, where it is degraded by the hepatic lipase enzyme and excreted into the bile.

2. DISCUSSION

Some of the mechanisms suggested in the literature causing low levels of HDL-C are summed up below.

- Gene deletion of Apo a1/APOA 1 results in extremely low levels of HDL-C in mice [37] and in humans [38].
- Gene deletion of apo A-II in the mice markedly reduces HDL-C levels [39] suggesting that apo A-II is also required for normal HDL.
- LCAT deficiency in humans [40]. and in mice [41] causes markedly reduced levels of HDL-C and rapid catabolism of apoA-I and apo A-II [42].
- Endothelial lipase (EL) in mice causes a reduction in HDL-C levels [43]. and also reduces apoA-I levels because of increased catabolism primarily by the kidneys [44].
- The activity of lipoprotein lipase is inversely associated with HDL-C levels [45].
- Mice lacking PLTP have a significant reduction in HDL-C levels [46].
- Hepatic over expression of SR-BI in mice markedly increases hepatic HDL cholesterol uptake and reduces plasma HDL-C levels [47].
- Rodents naturally lack CETP, and when engineered to express it, they experience substantial reduction in HDL-C levels [48].
- The proof that CETP is important for human HDL metabolism came from the discovery of humans genetically deficient in CETP [49-51].
- Enhanced activity of cholesteryl ester transfer protein (CETP) Reduced the HDL-C levels [52].
- LCAT deficiency Causes the reduction of LCAT-mediated cholesterolesterification results in accelerated Apo A-I catabolism [53].
- Mice that lack ABC A1, specifically in the liver have HDL-C levels that are reduced by 80% [54]. and mice that lack ABCA1 in the intestine have a 30% reduction in HDL-C [55].
- The level of oxidized low-density lipoprotein (LDL) cholesterol increases and high density lipoprotein (HDL) cholesterol dysfunction occurs as kidney function declines and inflammation becomes more pronounced [56 ,57].

2.1 Role of Sedentary Life Style

- Several previous studies have reported the associations of sedentary behaviour and physical activity with renal function [58-61]. Insufficient moderate- to vigorous-intensity physical activity (MVPA) are known to be associated with the onset of renal dysfunction [62].
- Evidence suggests that sedentary behaviour, defined as any waking behaviour characterised by an energy expenditure ≤1.5 metabolic equivalents, such as television viewing time [63]. may be another risk factor for renal dysfunction [64,65].
- Patients with CKD should undertake moderate physical activity for at least 30 min five times per week, in line with recommendations for the general population [66].
- Sedentary behaviour (detrimentally) and physical activity (beneficially) may affect renal function and that replacing sedentary behaviour with MVPA may benefit renal health in older adults [67].

2.2 The proposed Mechanism

- The proposed mechanism of inverse relationship between raised Crn and low HDL-C envisages, a competition for ATP, between the ABC 1/ABG 1 transporters involved in the efflux of cholesterol into the HDL, and synthesis of CrP by Creatine kinase enzyme, both of which are ATP dependent and ATP driven.
- There is no competition for ATP, when CrP in the Sarcolemmal mitochondria is hydrolysed, as the reaction does not need ATP, and the reaction itself is exergonic.
- In the resting physiological state of the skeletal muscles, the source of energy is the stored ATP in the cells of myofibrils. When Intermittent light exercises like walking and sprinting etc are indulged in, the stored energy (ATP), is supplemented by the ATP produced by the hydrolysis of

CrP, (which is the immediate source of energy for the muscles to work). The combined sources of energy, from the stored and that from CrP, together is called " phosphagen system". which lasts for less than ten seconds, but it is quickly replenished by means of the "creatine shuttle", (described above) which creates a buffer stock of CrP/ATP.

- The hydrolysis of CrP occurs, when muscles are under exercise, and need extra energy, as in the case of Intermittent exercise with periods of rest. But during moderate to severe sustained exercise, the supplementation of ATP from glycolysis along with the energy released by OX Phos, is utilised.
- Accordingly, the stored ATP is freely available for the ABC transporter's use, when CrP is not synthesized,(ie. During the rest period of the Intermittent exercise), which helps maintain normal blood level of HDL-C.
- This is expected when Cr metabolism is occurring under physiological conditions. But suppose, the mechanism of the CrP synthesis from Cr, in the mitochondria, is deranged pathologically, the continuous synthesis of CrP would curtail the availability and supply of ATP for the ABC 1/ ABG 1 transporters, necessary to perform their function. Obviously the HDL-C level, then, is bound to fall, as the efficiency of the enzymes concerned, which in turn depends on the supply of ATP, diminishes.
- This situation is possible when the sedentary lifestyle, with little excercise carried out, co – exists. (as explained here under).
- The rate limiting step catalysing the first step in the creatine synthesis, involving the AGAT enzyme, controls the amount of creatine present in the cell (uMtck) (see above) Conversely, absence of creatine in uMtc (due to disturbed resynthesis of creatine by the creatine shuttle, stimulates the synthesis of creatine by AGAT, again.
- There is evidence indicating that the Cr in the mitochondria exerts a repressive effect on the step catalyzed by AGAT. (see ref.24 & 25 above).
- Likewise the CrTs are also under feedback inhibition from the concentration level of the Cr in the cll (both intracellular and extra cellular) (see ref 27 to 30 above). This reciprocal arrangement between the intracellular creatineconcentration and its synthesis as well as its transporters, help to regulate the creatine concentration commensurate with the capacity of the enzyme, CK in the uMtck which phosphorylate Cr to CrP. Subsequent renuel of creatin for resynthesis of CrP is supplied through the "creative shuttle".
- It follows that the creatine from the resynthesis by creatine shuttle, in the uMtck inhibits the AGAT, as long as the creatine shuttle is operating. In other words, if the creatine from the creatine shuttle is not available, the absence of creatine, repressive effect in the uMtck is no longer operating, and accordingly the AGAT starts synthesizing creatine, which is transported into the uMtck, by the CrT.
- How the disturbed creatine shuttle, as envisaged above, occurs needs to be explained. Here comes the role played by the lack of exercise due to the sedentary life style, with little physical exercise, precludes the hydrolysis of the CrP, as the same is coupled to .the muscle contraction process.
- This has two effects. Firstly the creatine is not available to be shuttled back to the uMtck, unlike what happens normally and the absence of creatine in UMtc removes the repressor effect of intracellular creatine on the synthesis of creatine by AGAT, as already seen above. Secondly, when the CrP is not hydrolyzed by the CK enzyme in the Sarcolemmal mitochondria, consequently, the spontaneous dissociation of the CrP results. (for reasons explained below.)
- The spontaneous dissociation of CrP iin turn has rwo consequences.

1. The ratio between the CrP and creatinine in the muscle cell is disturbed.
2. The total creatine content of the cytosol of the cell is increased.

This consequently, leads to the increased degradation of the creatine into creatinine, with consequent increase in the S. Creatinine.

The mechanism of spontaneous dissociation of CrP and its aftermath is explained below:

2.3 Spontaneous Dissociation of CrP and its aftermath

This requires a bit of recapitulation of the laws of thermodynamics, and also the concept of Gibbs Free energy and how it is related to the changes in enthalpy and entropy. For the detailed understanding of the same, the readers might consult a standard text book of Chemistry. However, a brief explanation is given, consistent with the scope of this article.

Under the sedentary life style conditions, with little scope for exercise, the hydrolysis of CrP, in the Sarcolemmal M line mitochondria (smMtck) does not take place, as the release of the product of the hydrolysis, the ATP, is coupled to the contraction of myofibrils.

- The high energy phosphate in the compound CrP, is responsible for the spontaneous dissociation of CrP, as its entropy is high. The high energy compounds (like CrP) spontaneously dissociate into low energy molecules, which are thermodynamically, more stable.
- The best indicator of spontaneity in a reaction is the change in Entropy (S orΔS)
- The Second Law of Thermodynamics states that for a reaction to be spontaneous, there must be an increase in entropy.
- It is known fact that, if the free energy of the reactants is greater than that of the products, the entropy will increase and hence, the reaction takes place in the forward direction, as is the case of dissociation of CrP.
- While entropy decides the spontaneity of the reaction, Gibbs free energy decides the direction of the reversible chemical reaction subject to the fulfilment of the following criteria.

A. $\Delta G<0$ The reaction will occur spontaneously to the right.
B. $\Delta G>0$: The reaction will occur spontaneously to the left.
C. $\Delta G=0$: The reaction is at equilibrium and will not proceed in either direction

- The Gibbs free energy, ($\Delta G°$) of hydrolysis of creatine phosphate reaction is –43.1 KJ/mol. The negative sign indicates, that the reaction is exergonic, (gives out energy) and that it spontaneously decomposes and proceeds in the forward direction only.
- The negative sign of Gibbs free energy is because the change in entropy is greater than the changes in enthalpy as per the following reaction (2)

$$\Delta G = \Delta H - T\Delta S, \text{ ----------} \quad (2)$$

where ΔG indicates change in free energy ΔH, Is change in the enthalpy and $T\Delta S$, indicates the product of absolute temperature and the change in the entropy.

Hence the decomposition reaction (3) of CrP might be written as follows

$$CrP \rightarrow Cr + Pi \text{ [free energy]} \quad (3)$$

- The spontaneous decomposition of the (as against the enzymatic hydrolysis of CrP by CK.) has two effects.

A. The Cr released is not available to be recycled for creatine shuttle, due to the Compartmentation of creatine, between the cytosol, Mitochondria and blood, as already seen above. As a result, the creatine released by the spontaneous decomposition of CrP is not available for creatine shuttle for resynthesis of CrP in uMtck, as against what happens during the enzymatic hydrolysis of CrP.
B. The creatine, thus formed, increases the creatine present in the
C. Un-phosphorylated form in the cytosol.

- Consequently, the total creatine content of the cytosol is increased. The normal average amount of total creatine (creatine and phosphocreatine, together) stored in the body is approximately 120 mmol/kg of dry muscle mass.
- With increased creatine in the cytosol, the normal ratio of CrP to Cr is disturbed.
- As a result, the Cr degradation rate, also is increased, the normal in humans being about 1.6% (2 g) per day to keep the Cr: CrP ratio in the cell.
- This increases the percentage of creatine degraded Per day, the normal being 1 % of creatine present in the Cell.
- Thus the total creatinine, the degradation product of creatine, is increased in the blood.

- Thus the proposed mechanism offers an answer to the observed inverse relationship between the Low HDL-C and raised S. Creatinine.

3. CONCLUSION

A possible molecular mechanism, underlying the inverse relationship between the raised Creatinine and Low HDL-C, in the backdrop of CKD and the sedentary life style, has bee proposed. This foresees, a competition between ABC1/ ABG1 transporters, that facilitate the efflux of excess/ unused cholesterol from the cells into the HDL-C and the synthesis by CK, of CrP in the uMtck, respectively and the role of the sedentary life-style behind the mechanism, is established. That, exercise increases the HDL-C levels and reduces the raised S creatinine levels, supports the contentions expressed in the proposed mechanism.The suggested mechanism has therapeutic implications also, as it shows the way to reduce the risk from the two individual risk factors (the low HDL-C and raised S. Creatinine), for the cardiovascular and renal morbidly and mortality. The take home message of this article is, that the low HDL-C could be a predictor, marker or indicator of disease progression, especially when associated with increased s. Creatinine. Also, this article focusses on the contributory effect of sedentary life style on CKD and at the same time stressing the benefit of exercise in improving the HDL-C as well as S. creatinine levels.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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