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Intradialytic creatine supplementation: A scientific rationale for improving the health and quality of life of dialysis patients

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ABSTRACT

The CK/PCr-system, with creatine (Cr) as an energy precursor, plays a crucial role in cellular physiology. In the kidney, as in other organs and cells with high and fluctuating energy requirements, energy-charged phospho-creatine (PCr) acts as an immediate high-energy source and energy buffer, and as an intracellular energy transport vehicle. A maximally filled total Cr (Cr plus PCr) pool is a prerequisite for optimal functioning of the body and its organs, and health. Skeletal- and cardiac muscles of dialysis patients with chronic kidney disease (CKD) are depleted of Cr in parallel with the duration of dialysis. The accompanying accumulation of cellular damage seen in CKD patients lead to a deterioration of musculo-skeletal and neurological functioning and poor quality of life (QOL). Therefore, to counteract Cr depletion, it is proposed to supplement CKD patients with Cr. The anticipated benefits include previously documented improvements in the musculo-skeletal system, brain and peripheral nervous system, as well as improvements in the common comorbidities of CKD patients (see below). Thus, with a relatively simple, safe and inexpensive Cr supplementation marked improvements in quality of life (QOL) and life span are likely reached. To avoid Cr and fluid overload by oral Cr administration, we propose intradialytic Cr supplementation, whereby a relatively small amount of Cr is added to the large volume of dialysis solution to a final concentration of 1–10 mM. From there, Cr enters the patient's circulation by back diffusion during dialysis. Because of the high affinity of the Cr transporter (CRT) for Cr affinity for Cr (Vmax of CRT for Cr = 20–40 μM Cr), Cr is actively transported from the blood stream into the target cells and organs, including skeletal and cardiac muscle, brain, proximal tubules of kidney epithelial cells, neurons, and leukocytes and erythrocytes, which all express CRT and depend on the CK/PCr system. By this intradialytic strategy, only as much Cr is taken up by the body as is needed to fill the tissue Cr pools and no excess Cr has to be excreted, as is the case with oral Cr. Because aqueous solutions of Cr are not very stable, Cr must be added immediately before dialysis either as solid Cr powder or from a frozen Cr stock solution to the dialysate,

Abbreviations: AGAT, arginine-glycine amidinotransferase (mostly in the kidney); AMPK, AMP-activated protein kinase; ANT, mitochondrial adenine nucleotide or ATP/ADP carrier of the inner mitochondrial membrane; ATP, adenosine-trisphosphate, the universal energy currency of living systems; CK, creatine kinase: MM-CK: cytosolic muscle-type MM-CK dimer, cytosolic non-muscle or brain-type BB-CK dimer: mtCK octameric mitochondrial CK; CKD patients, chronic kidney dialysis patients; CKD, chronic kidney disease patients; Cr, creatine, Crn: creatinine, total Cr: Cr plus PCr; CrT, creatine transporter or $2Na^+$:$1Cl^-$:1Cr-cotransporter belonging to the solute carrier family SLC6A8; ECs, erythrocytes; EPO, erythropoietin; GAMT, guanidino acetate methyl-transferase (mostly in the liver); GAT2, gamma-aminobutyric acid transporter-2; GFR, glomerular filtration rate; HCys, homocysteine; HIF, hypoxia-induced factor; mPTP, mitochondrial permeability transition pore; mtCK, mitochondrial octameric CK isoform, sandwiched between inner and outer mitochondrial membranes; NAFL, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; PCr, phosphoryl-creatine or phospho-creatine; QOL, quality of life; SAM, S-adenosyl-methionine; TBARS, thiobarbituric-acid-reactive substances; tHCys, total plasma homocysteine concentration; VDAC, voltage-dependent anion carrier of the outer mitochondrial membrane.

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Protection by creatine of erythrocytes and immune cells
Protection from oxidative damage and mechanical stress by creatine
Sparing of erythropoietin (EPO)
Diabetes mellitus type-2
Insulin sensitivity
Metabolic syndrome
Dyslipidemia
Fatty liver disease
NASH
NAFL
X-ray contrast media induced kidney failure

or alternatively, Cr could become an additional component of a novel dry dialysate mixture in a cartridge device.

Introduction

The creatine kinase/phosphocreatine (CK/PCr) system and the actions of creatine

Creatine (Cr) is a prominent guanidino component of skeletal, cardiac, and smooth muscle; brain and peripheral nervous tissues; and the kidney and other organs [1,2]. Cr can be charged to the high-energy compound, phosphoryl-creatine (PCr) by creatine kinase (CK) and ATP. PCr acts as an energy source and buffer and energy transporter, shuttling energy from subcellular sites (mitochondria) of energy production by glycolysis to sites of energy consumption where cellular ATPases (facilitating hydrolysis) and ATP-dependent ion pumps are located [1,3]. The main function of the CK-PCr circuit or shuttle (see Fig. 1) to optimize the free energy change of ATP hydrolysis ($\Delta G_{ATPhydrolysis} = \Delta G_{obs.} - RT \times \ln([ATP]/[ADP] \times [P_i])$, which is obviously strongly dependent on the local ATP/ADP ratio. That is, the CK/PCr system maintains high local levels of ATP in the vicinity of ATPases in resting and working cells and thus guarantees the highest work-output per ATP hydrolysed [1,4]. The prerequisite for this to happen is that cytosolic CK isoforms, either muscle-type MM-CK or brain-type BB-CK are forming functionally coupled microcompartments with various ATPases, such as the sarcoplasmatic reticulum Ca^{2+}-ATPase and the sarcolemmal Na^+/K^+-ATPase [4] (Fig. 1). At the mitochondrial site of ATP production, mitochondrial mtCK maintains a high ADP/ATP ratio and forms a functional microcompartment with the mitochondrial ATP/ADP-carrier (ANT), which is located in the inner membrane, and the voltage-dependent anion-selective channel (VDAC) in the outer membrane [5]. There, mtCK, sandwiched between ANT and VDAC, enables efficient high-energy export from the mitochondria to the cytosol in the form of PCr [1,3–5] (Fig. 1). Because PCr and Cr are present in cells at much higher concentrations relative to ATP and ADP (up to 10- and 100-fold higher, respectively) and have bigger diffusion coefficients compared to the bulky and charged adenosine nucleotides, ATP and ADP, PC and Cr are ideal molecules for shuttling energy equivalents from the sites of energy production either via mitochondrial oxidative phosphorylation or glycolysis to the sites of energy (ATP) consumption facilitated by ATPases. The action of the CK/PCr shuttle has been directly demonstrated in spermatozoa, where the distance from the sperm mitochondria in the midpiece to the distal

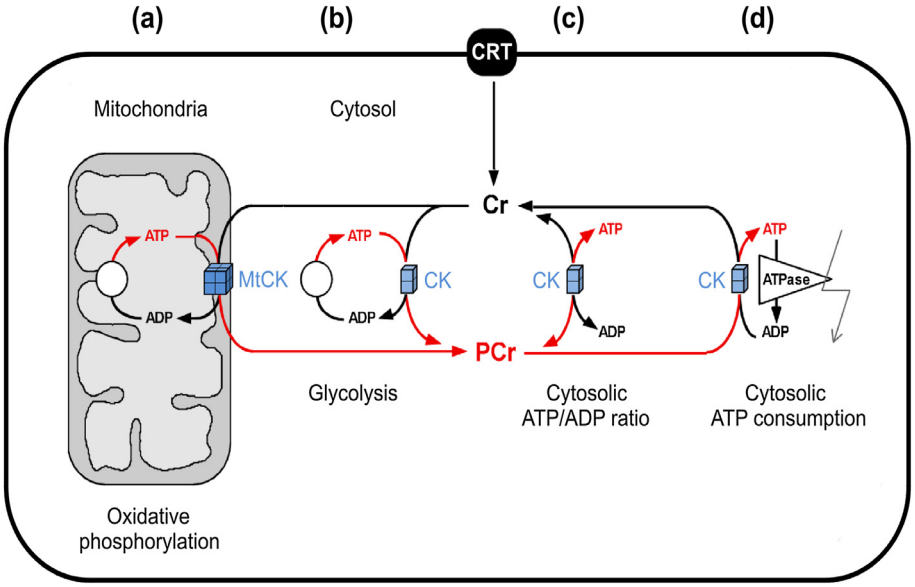

Fig. 1. The creatine kinase/phosphocreatine (CK/PCr)system. The CK/PCr shuttle or circuit [4] also functions in kidney epithelial cells. The model shows the compartment-specific localization of the isoenzymes of creatine kinase that are found in mitochondria (Mt) (**a**) (octameric MtCK, left) and in the cytosol (**b** and **c**) (dimeric MM-CK, BB-CK, MB-CK, right). In the kidney, the main CK players are the ubiquitous (u) uMtCK and BB-CK isoenzymes, which are highly expressed in this tissue. CK isoenzymes are either associated with ATP-delivery processes (mitochondrial oxidative phosphorylation [**a**] or glycolysis [**b**]) or ATP-consuming processes (ATPases [**d**] rightmost) to maintain local ATP/ADP ratios; or occur in soluble form (to maintain global cytosolic ATP/ADP ratios [**c**]). A large cytosolic PCr pool of up to 30 mM results from the action of CK on creatine plus ATP derived from oxidative phosphorylation (e.g., in aerobic skeletal or heart muscle) or glycolysis (e.g., in fast-twitch [anaerobic] skeletal muscle). The large PCr pool is then used as a temporal energy buffer to maintain constant global and local ATP/ADP ratios over a wide range of workloads. The higher diffusibility of PCr, as compared with ATP, together with localized CK isoenzymes, is used for spatial energy buffering, i.e., for an energy shuttle between ATP-providing and -consuming processes. This energy shuttle seems to be most important for cells that are polarized, e.g., spermatozoa, and/or have very high or localized ATP consumption, e.g., skeletal and cardiac muscle and neuronal cells (slightly modified figure and legend taken from Schlattner et al., 2006 [5]).