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TOTAL CREATINE KINASE AND ITS ISOENZYMES IN CORD BLOOD OF FULL TERM NEWBORNS

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ABSTRACT

Creatine kinase (CK) is a key enzyme of energy metabolism, especially in muscle tissue. CK has two polypeptide chains of M and B, and three isomers, CK-BB, CK-MB and CK- MM. In some conditions like acute myocardial infarction and Neuromuscular disorders, increased CK activity is used as a part of diagnosis. CK can also be elevated in absence of neuromuscular diseases or cardiac injury, such as strenuous exercise, intramuscular injections etc.Several reports indicate elevated activity of serum CK in the maternal blood during child birth.

Keyword: Creatine kinase, CK-Isoenzymes, High risk pregnancy

INTRODUCTION

Creatine kinase (CK) is an important enzyme in consumption and saving energy, especially in muscle tissue. It is required for regeneration of adenosine triphosphate (ATP) by reversible transfer of the phosphoryl group from phosphocreatine to adenosine diphosphate (ADP) [1]. CK has two polypeptide chains of M and B and three isomers of CK-BB, CK-MB and CK-MM. B chain is specific for brain tissue and M chain is specific for muscle tissue. CK is present in the blood in small amounts and it exists at high levels in cells with high energy requirements such as skeletal, cardiac and smooth muscles, it is also found in kidneys, brain, neuronal tissues, retinal photoreceptor cells, spermatozoa and sensory hair cells of the inner ear [2,3,4].

Increased CK activity has been reported with some physiological conditions like increased muscle activity and exercise yet some disorders such as myocardial necrosis, acute skeletal muscle atrophy, muscular dystrophy, burns, epilepsy, surgical procedures, streptococcus infections also result in a raised activity of this enzyme [5,6,7]. During labour, maternal serum CK activity show a several fold rise [8,9]. Surgical intervention during labour further increases the activity of CK in the serum [10,11,12]. Several studies demonstrated remarkable changes in CK activity during labour and its association with the type of delivery.

Pharmacological agents such as cocaine, ethanol and halothane are other factors responsible for increased CK activity [13,14]. Brain damage, low birth weight, term of delivery and skeletal injuries during delivery could be related to higher CK activity in cord blood[15,16]. Persistent high activity may implicate some conditions such as rhabdomyolysis and significant brain injuries [17,18,19]. On this basis, elevated serum activity of CK has been used as a sensitive but nonspecific test for myocardial infarction. The poor specificity reflects the ubiquity of CK in many tissues other than the myocardium.

Creatine kinase (CK), formerly known as creatine phosphokinase, is an intracellular enzyme present in greatest amounts in skeletal muscle, myocardium, and brain; smaller amounts occur in other visceral tissues. Disruption of cell membranes due to hypoxia or other injury releases CK from the cellular cytosol into the systemic circulation [20]. Creatine kinase has been localized at various locations in human body [21].

HISTORICAL PERSPECTIVE

The creatine kinase enzyme was discovered by Lehmann in 1934 and the creatine kinase reaction in 1936 [22]. Creatine Kinase (CK) was purified and partially crystallized the first time by the group of Kuby [23] and the majority of the early studies on the physical properties and structure of creatine kinase were carried out on enzymes isolated from rabbit muscle. Eppenberger [24] described that in 1962, Dance and Watts suggested that the active form of CK could be a dimeric molecule [25].

A full length cDNA for human M creatine kinase was isolated and sequenced by Perryman and colleagues in 1986 [26] and the human MCK gene isolated in laboratory in 1988 [27] by screening a phage human genomic DNA library with a canine BCK probe. The human MCK gene spans 17.5 kb of the genome and contains 8 exons separated by 7 introns [28]. The gene was located to human chromosome 19 and mapped to the 19q13.2-q13.3 site [29].

STRUCTURE AND FUNCTION

There are two isoforms of Creatine kinase:

1. Cytosolic Isoform

These are dimeric isoenzymes in cytosol (85 kDa). These comprise of two subunits M and B. They function as a temporay energy buffer. The combination of two subunits gives rise to three types, *viz.*

a) MM (Muscle type)
b) BB (Brain type)
c) MB (Hybrid)

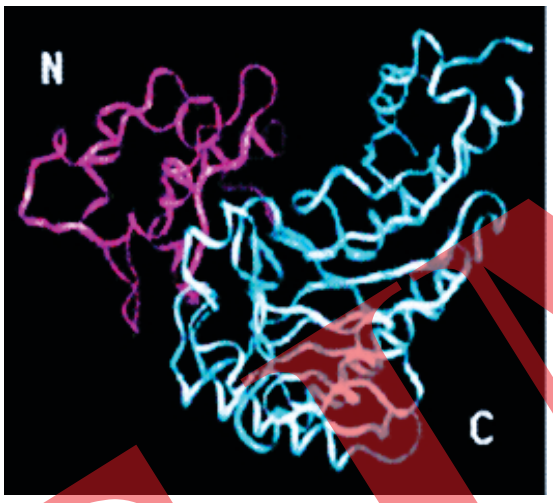

Fig.1. Muscle type CK: Monome Small Domain (N) Large Domain (C)

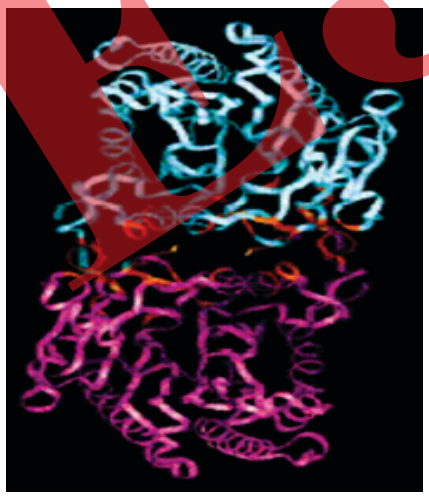

Fig.2. Muscle type CK:Dimer(Interface site highly conserved)

The functional expression of cytosolic isoforms can be depicted as:

ADP + Phosphocreatine (PCr)→ATP + Cr

They are coupled to glycolysis and actin-myosin system. CK maintains the high ATP concentration. Brain type CK has structure similar to muscle-type CK. High activity of BB type is found in brain, retina, and sperm. Brain type CK activity is associated with learning processes. CK over-expression has been observed in tumours. Lower CK activity generally indicate neurodegeneration [30,31].

2. Mitochondrial Isoform

These are bound to outside of inner membrane within cristae. The spatial energy buffering takes place through transphosphorylation wherein Creatine (Cr) enters through the pore and reacts with the ATP, as a result phosphorylated creatine is created and ADP is released:

Cr + ATP→PCr + ADP

Thus, PCr mediates between sites of ATP consumption and production.

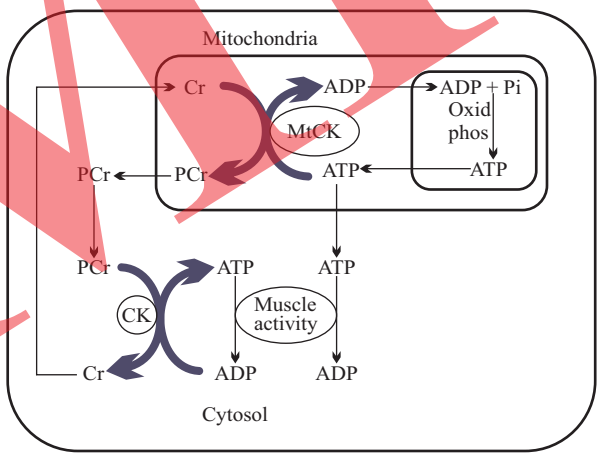

Fig.3. Diagrammatic Representation of Interaction between Cytosolic and Mitochondrial Creatine Kinase.

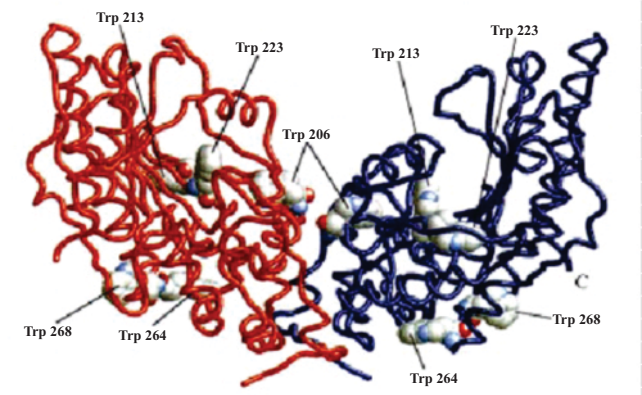

Fig.4. Mitochondrial CK Dimer

The mitochondrial CK monomers comprise of Small N-terminal domain and Large C-terminal domain. ATP binding site is located in the cleft between the two domains. The octamer form is stable against denaturation and is insensitive to proteolysis. Its dissociation to dimer takes hours to weeks [32,33].

LOCALISATION

Skeletal Muscles

Available data suggest that tissue levels of phosphocreatine are related to maximum potential rates of ATP turnover and oxidative capacity. In the case of muscle fibers, this is correlated with power output [34]. Several researchers have hypothesized that muscle soreness is more prevalent among those individuals with a predominance of type II muscle fibres [35,36]. Individuals with a greater percentage of type II muscle fibres experience a greater increase in serum creatine kinase activity after muscle-damaging exercise. Creatine kinase activity is not determined by muscle fibre types, especially when the intensity of the exercise is below a certain threshold [37]. Currently it is clear that there are differences in the rates of phosphocreatine resynthesis between the types of muscle fibers after phosphocreatine depletion induced by exercise. It appears that the rate of resynthesis is lower in type II muscle fibers during the initial minutes of recovery (possibly more lactic acidosis in this type of fiber), which can present an adverse effect on the production of energy and the performance during a subsequent exercise. However, after these initial minutes, the resynthesis of phosphocreatine in the muscle fibers is accelerated in type II fibers, so that after 15 minutes recovery, the creatine phosphate concentration is greater than that observed before exercise. So far we do not know the mechanism responsible for this excess of phosphocreatine in type II fibers. The MCK (muscle type) promoter is under the control of myogenic transcription factors, like MyoD-I, and thus parallels the upregulation of other muscle specific protein isoforms [38].

Cardiac Muscle

In cardiac muscle, the significance of the different isoforms of CK has been related to their intracellular localization rather than to kinetic differences[39]. The heart is characterized by having different CK isoenzymes (MBCK and mitochondrial (MtCK)) which are found specifically localized at sarcoplasmic reticulum, plasma membrane, myofilaments, mitochondria and glycolytic complexes [39,40].

Smooth Muscle

The creatine kinase content of smooth muscle is of similar magnitude to ATP. The reported creatine kinase of various smooth muscles is small, ranging from 0.5 to 4.4mM, and is about 0.5-2 times the content of ATP [41]. Since the early demonstration of CK in chicken gizzard smooth muscle [42], the isoforms BB, MB and MM-CK have also been detected in smooth muscle, BB-CK being the main isoform in most smooth muscles. Another important CK isoform in terms of energetics is mitochondrial CK (Mi-CK). An appreciable amount of CK activity has been detected in the enriched mitochondrial fraction of smooth muscles [43,44].

Kinetic differences nonetheless could have some significance to subcellular isoenzyme localization in smooth muscle. The multiple isoforms of CK may be localized within the cell to perform specific functions related to other localized proteins and metabolites [45].

Brain

The brain-type cytosolic isoform of creatine kinase, BB-CK, exists primarily in the brain and retina and is associated with ion transport pumps in the brain [46,47,48]. Comparatively high activity of CK were reported in the cerebellar cortex [49] consistent with findings which indicate that grey matter shows a higher flux through the CK reaction and higher Pcr concentrations when compared to white matter [50]. The ubiquitous form of Mt-CK is also present in contact sites of brain mitochondria.

The phosphocreatine values in brain is approximately 4.5mM [51], and most of this is intracellular. The PCr-dependent glutamate uptake system is present in synaptic vesicles [52]. Brain function appears to be linked with the creatine kinase/phosphocreatine system in several ways, which would explain the relationship between CK regulation and the development of neurodegenerative disease such as Alzheimer disease [53].

Other Tissues

The CK in non-muscle cells, such as spermatozoa, retina photoreceptors cells, brain cells, kidney, salt glands, myometrium, placenta, pancreas, thymus, thyroid, intestinal brush-border epithelial cells, endothelial cells, cartilage and bone cells, macrophages, blood platelets, tumor and cancer cells [54], are characterized by intermittently high and fluctuating energy requirements, has attracted interest, suggesting a spatial buffering or energy transport function for the CK/PCr system. For example the presence of high activity of CK (B-CK and Mi-CK) and total creatine (Cr) in spermatozoa seem to support this idea [55].

CK is also present in cartilage and bone cells, PCr is present in chondrocytes as it was demonstrated by 31P-NMR measurements of superfused resting zone

cartilage from the growth plates of bones from young animals [56]. Bone cells in culture also show B-CK activity when stimulated with Vitamin D metabolites, parathyroid hormone and prostaglandin E2 [57]. B-CK has also been shown to be directly and sex-specific stimulated by sex steroids in rat bone indicating that gonodal steroids may contribute to bone growth and to maintaining a balance bone-turnover, with CK being directly involved in the energetics of this process [58,59].

The adipose tissue contains PCr and CK with activity in brown fat tissue 50 times higher than in white fat [60]. In brown adipose tissue, which is responsible for heat generation, CK activity is in the same order of magnitude as that found in cardiac or nerve tissue. The invariable presence of significant activity of CK in the thyroid of several species, including man, suggests that this enzyme may also have a role in thyroid tissue metabolism or hormone biosynthesis.

CREATINE KINASE IN PREGNANCY

Creatine kinase and its isoenzyme activity show a great variation during pregnancy. In a study, McNeely and group measured serum CK activity of 28 women with normal pregnancy at six time intervals, *viz*., (a) during the third trimester, between 30 and 36 weeks of gestation, (b) on admission to hospital in labor, (c) within 30 min after delivery, (d) between 7 and 9 hrs after delivery, (e) on the fifth day postpartum, and (f) at the time of the routine six-week check-up. Mean CK activity were 29, 45,109, 132, 49 and 35 U/L at 1, 2, 3, 4, 5 and 6 time intervals. Thus, showing that there is a transient rise in CK activity as soon as the time of delivery approaches and peak activity are obtained between 7 to 9 hrs after the delivery. The CK activity tends to reach at normal levels within six-weeks after delivery. Similar trends were observed for the CK isoenzymes CK-MM, CK-MB and CK-BB activity [61].

A group of researchers evaluated creatine kinase (CK) estimations on 148 healthy teenage girls (of whom 38 were pre-menarchal and 110 post-menarchal), 133 healthy mature women, 124 pregnant women, and 37 postmenopausal women. The activity was highest in the pre-menarchal teenagers, and became successively lower in the postmenarchal teenagers, the mature women, and the pregnant women, so that the mean activity of the pregnant women was less than half that of the teenagers. The CK activity then observed elevated again after the menopause [62].

In another study conducted on Forty-nine normal pregnant women recruited late in the third trimester for serial determinations of creatine kinase (CK) and its MB isoenzyme fraction (CK-MB) at four different times: (a) on recruitment between 36 and 40 weeks gestation, (b) on admission in active labor, (c) immediately after delivery, and (d) on the first postpartum day. In the patients with vaginal delivery total CK was significantly elevated at time 4 compared with times 1, 2 and 3 (P value < 0.0001). CK-MB fraction was also significantly elevated at time 4 compared with times 1, 2 and 3 (P value < 0.0001). In 35.7% of the patients at time 4, CK-MB was sufficiently elevated to give the laboratory interpretation of "borderline" or "consistent with a myocardial infarction," even though none of the patients had cardiac symptoms or complications [63].

Abramov and his team determined serum creatine phosphokinase, lactate dehydrogenase and aspartate amino transferase activity in late pregnancy, and throughout labor and early puerperium. Fifty women having normal pregnancies followed by uneventful vaginal deliveries were prospectively studied for serum lactate dehydrogenase, aspartate amino transferase and creatine phosphokinase including its MB isoenzyme before, during and after labor. Cardiac status was evaluated in all women using serial electrocardiographic and physical examinations. All women were found to have low to normal antepartum serum enzymes activity. However, during labor total creatine phosphokinase increased markedly, reaching a peak of 2-4 fold baseline levels 24 hours postpartum. It then declined gradually back to baseline. Nulliparous women reached substantially higher levels than multiparous women. The MB, also called cardio-specific isoenzyme was found to be an important contributor to creatine phosphokinase surge in most women. Correlation was demonstrated between length of the active phase of labor and both total and MB creatine phosphokinase activity. There was no clinical or electrocardiographic evidence for cardiac muscle damage in any of the study patients. Serum lactate dehydrogenase and aspartate amino transferase were not altered during or after labor. It was concluded that serum total creatine phosphokinase and its MB isoenzyme increase substantially during normal vaginal labor without evidence of myocardial ischemia. The uterus and placenta, two organs which were reported to embody substantial amounts of these enzymes, and which participate actively in the process of labor, are thought to release these enzymes to the circulation during labor. Knowing the normal patterns of these enzymes in the serum during labor and puerperium may prevent erroneous diagnosis of myocardial ischemia or infarction. Lack of electrocardiographic abnormalities and low lactate dehydrogenase and aspartate amino transferase activity may assist in excluding such

diagnosis [8].

Researchers have also investigated the reliability of maternal serum Creatine Phosphokinase (CPK) in the diagnosis of ectopic pregnancy.100 consecutive women with documented tubal pregnancies and 50 women with normal intra-uterine pregnancy were prospectively studied. The mean CPK activity in the study group (103±50.3 IU/L) were significantly higher than the mean CPK activity of control group (52.4±10.9 IU/L). The mean CPK activity in the study group showed gradual increment with increase in the gestational age, unlike the control group. The positive predictive value was 99% and the negative predictive value 90.7% for the diagnosis of tubal pregnancy. Hence, serum CPK activity were reported significantly higher in women with tubal pregnancy that may or may not have ruptured and are reliable in the diagnosis of a tubal pregnancy [9].

One another study assessed the diagnostic value of creatine phosphokinase (CPK) and its isoenzyme CPK- muscle brain (MB) in ectopic pregnancy (EP) in order to locate a simpler diagnostic approach for EP. All pregnant patients in their first trimester of gestation that presented with complaints of vaginal bleeding, abdominal pain, or both were enrolled in this study. The results for CPK activity were recorded as follows: sensitivity (69.81%), specificity (64.15%), positive predictive value (PPV; 66.07%), negative predictive value (NPV; 68%), positive likelihood ratio (PLR) (1.95), and negative likelihood ratio (NLR) (0.49). The results for CPK-MB activity were recorded as: sensitivity (71.7%), specificity (56.6%), PPV (62.29%), NPV (66.7%), PLR (1.65), and NLR (0.5). They observed a significant elevation in CPK and CPK-MB serum activity in EP and concluded that transvaginal ultrasound (TVS) as better diagnostic tool for EP [66].

CORD BLOOD CREATINE KINASE LEVELS

Total CK and CK isoenzyme activity in serum during pregnancy, labor and after delivery as well as in cord blood was estimated in a study by Chemnitz and others. Total CK was found decreased in the second trimester but increased in third trimester of pregnancy. Low serum CK-MB activity was found in patients with early labor pains. CK-BB activity could not be detected during pregnancy. Total CK and isoenzyme activity increased after delivery. The rise of total CK and CK-MB in maternal serum was directly correlated with the type of delivery, duration of labor, parity of the mother, and birth weight. It can be deduced that postpartum CK activity depends on skeletal muscle activity as well as on the activity of uterine muscle. Prematures and infants "small for date" had significantly lower total CK and slightly more elevated CK-BB activity in cord blood than children of normal maturity. CK-BB activity was much more pronounced in high risk patients with low Apgar score [67].

Some of the researchers measured isoenzymes of creatine kinase by electrophoresis in serum from cord blood and skin-puncture blood taken from 45 healthy full-term infants during the first three postnatal days. Mean total CK activities were 185 U/L in cord samples, 536 U/L in samples taken between 5-8 h postnatally, 494 U/L between 24-33 h, and 288 U/L in the 72-100 h samples. Values for all three isoenzymes increased to a peak over this period, with the highest activity generally being found in the samples taken 5-33 h after birth; the subsequent decline was most rapid for CK-BB. Serum CK isoenzymes in cord samples and those taken at 72-100 h in the 11 babies delivered by cesarean section did not differ significantly from those of babies delivered vaginally. However the postnatal increases in total CK, CK-MM, and CK-MB (but not in CK-BB) were significantly greater in those patients born by vaginal delivery. The reasons for the increases in CK isoenzymes after birth could not be explained, however, it was suggested that CK-MB should not be regarded as a "cardiac-specific" isoenzyme in the neonatal period [68].

Increased activity of creatine kinase BB (CK-BB) in umbilical cord serum with some normal babies and those with fetal distress was observed by Kumpel. Further investigations showed that the umbilical artery and vein tissue contained high CK-BB activity, indicating that some cord blood samples may not solely reflect CK-BB liberated from the brain [69].

Thirty two newborns were tested for umbilical cord blood CK-BB activity in a study. Fourteen of them had a superior to 7 Apgar score at first and fifth minutes, whereas 18 newborn infant Apgar score was inferior to 7. The CK-BB activity was significantly higher in newborn infants having a low Apgar score at birth. A low Apgar score at first and fifth minutes together with a high CK-BB activity must be considered a nervous trouble signal and a warning in order to look after children's psychomotor skills more strictly and individual neurological damage [71].

A study was conducted to observe the variations in the activity of total creatine kinase and CK-B in maternal and cord-blood samples, comparing data obtained for vaginal and cesarean births. In all cases, there was a significant postpartum increase in total CK and in CK-B activity in maternal sera, whereas cord-blood samples showed no significant differences between activities in arterial and venous blood for either

vaginal or cesarean births. Statistically significant differences were found in CK-B activity, but not in total CK, between cord-blood samples from vaginal births and those from cesareans [12].

CK isoenzymes (CK-MM, CK-MB and CK-BB) in umbilical cord blood sera of newborns in relation to their acid-base status was evaluated by Niklinski. The investigations were performed in a group of 75 newborns delivered after 37 weeks of pregnancy. Newborns were considered hypoxic if umbilical artery blood pH was under 7.2. Of 75 newly born infants 26 had features of perinatal hypoxia. They were unable to demonstrate significant differences in total CK, CK-MM and CK-MB activities in examined groups of newborns. They found a significant rise of CK-BB activity in cord sera of hypoxic infants. The results showed that the fetal brain is the most vulnerable to a hypoxic state [72].

Measurement of creatine kinase (CK) activity of cord blood and their evaluation in relation to the degree of maturity and distress in the newborn was done in a study of Japan. There was a positive correlation between the birth weight and CK, CK-MM, CK-MB and CK-BB activity of cord blood. The CK and CK-MM activity of cord blood in the neonates who were prematurely delivered and small-for-date were significantly lower than those in normal controls. The CK and CK-MM activity of cord blood in the neonates with low Apgar scores, 6-4 and 3-0, were 172 +/- 74, 145 +/- 73 and 104 +/- 63, 92 +/- 55 (U/l) respectively, which were significantly lower than those in the neonates with the high scores (10-7), 208 +/- 104, 183 +/- 92 (U/l). The neonates with distress showed the low CK and CK-MM activity, 76 +/- 12 and 61 +/- 8 (U/l). The CK and CK-MM activity of cord blood tended to decrease with prolongation of labor, but did not differ from each other among the neonates delivered by different modes. These results suggested that the CK and its isoenzyme activity are good indicators for the degree of maturity of neonates and the severity of neonatal distress [73].

Amato and group studied the serum activity of creatine phosphokinase isoenzyme pattern (CPK MM, MB, BB) in cord blood and capillary blood samples of 20 healthy term infants. Total CPK activity was recorded high but similar in all samples. The CPK-MB fraction was found absent in cord blood. Moreover, CPK-BB activity was significantly higher in capillary blood than in cord blood. These results suggest specific organ involvement in the production of CPK fractions [74].

An investigation was done over the relationship of creatine kinase (CK) and its isoenzymes activity in the newborn to the mode of delivery, time interval from birth (divided in four 6-hour time periods without the involvement of cord blood in this study), parity and sex of the neonates. During the first postpartum day, serum activity of CK and its isoenzymes (CK-MM, CK-MB, CK-BB) were determined from 115 healthy full-term neonates born consecutively either by spontaneous vaginal delivery (VD, n = 85) or by elective cesarean section (CS, n = 30). The multiple regression analysis was applied. Total CK levels were positively correlated with VD ($p < 0.0003$). This was mainly attributed to a rise in the CK-MM activity which presented a similar pattern to CK. CK-MB activity was also positively correlated with VD. In contrast, CK-BB was negatively correlated to the postpartum time period. Neonatal sex and parity did not influence CK and its isoenzyme activity significantly. In conclusion, VD contributes significantly to an increase in CK activity during the first day of extrauterine life [65].

Fonseca and coworkers investigated the relationship of creatine phosphokinase and its isoenzymes with fetal asphyxia and risk at birth. Thirty-five pregnant women with high-risk pregnancy were studied. In 21 patients, fetal distress was diagnosed by interpretation of the fetal heart rate tracing (FHR). The remaining 14 women, having normal fetal cardiotocography, were considered as the control group. Total CK and its isoenzymes activity was measured in cord sera and 24 h after birth in peripheral blood. Abnormal FHR patterns correlate well with elevated enzyme activities. Total CK and its isoenzymes (CK-MM, CK-MB, and CK-BB) exhibited higher activity in asphyxiated infants as compared to normal neonates. Electrocardiographic ischemia occurred in seven newborns who had elevated CK-MB and CK-BB activity, both at birth and within 24 h postpartum. Chromatographic study showed in normal neonates that the predominant isoenzyme was CK-MM, whereas CK-BB activity was negligible. In the newborns with abnormal FHR, CK-MB and CK-BB were increased with predominance of CK-MB. It was concluded that antepartum fetal distress is associated with release of CK-BB, and particularly CK-MB; therefore, these biochemical markers may indicate either brain or myocardial damage [18].

One study was conducted over twenty-six normal newborns (13 male, 13 female) with normal prenatal histories, no perinatal stress, and normal vaginal deliveries for creatine phosphokinase (CPK) activity and isoenzyme activities in cord blood and in 24-hour postpartum serum. Total CPK activity was measured high in cord blood when compared with adult control values. Whereas , total CPK was significantly higher

in serum at 24 hours of age compared with cord blood. There was a significant increase in both the skeletal muscle isoenzyme and the cardiac muscle isoenzyme from birth to 24 hours of age was noted. There was a decrease in the brain isoenzyme at 24 hours of age which was not statistically significant. These results were compared with values obtained in a group of 10 neonates with severe cardiac problems. Three of the ill neonates had significant elevation of total serum CPK and the skeletal muscle isoenzyme when compared with the normal newborns. There were no significant differences between the normal infants and the ill neonates for the cardiac isoenzyme and the brain isoenzyme. These data suggest that caution should be used in the diagnosis of certain neonatal cardiac syndromes based on serum CPK activity and isoenzyme alone [70].

A few researchers examined brain-specific creatine kinase (CK-BB) in cord blood and 2, 6, 12, and 24 h after birth in 29 asphyxiated and 20 control infants. At 2 h after birth, median (quartiles) serum CK-BB activity was 10.0 U/L (6.0-13.0 U/L) in control infants, 16.0 U/L (13.0-23.5 U/L) in infants with no or mild HIE, and 46.5 U/L (21.4-83.0 U/L) in infants with moderate or severe HIE. Cord blood pH (cutoff value, <6.9) and cord blood base deficit (cutoff value, >17 mM) increase the predictive values of CK-BB. They concluded that elevated serum activity of CK-BB reliably indicates moderate and severe HIE as early as 2 h after birth [75].

The activity of creatine kinase MB in the umbilical cord blood of healthy term infants was measured by Trevisanuto and coinvestigators. The samples include umbilical cord blood of 85 healthy term neonates and the blood samples of their respective mothers at birth. Median (interquartile range) umbilical cord activity was 4.90 microgram/L (3.90-6.61) for creatine kinase MB. No association between maternal and cord blood activity was observed [76].

The effect of Apgar score, cord blood gas, gestational age, and creatine kinase (CK) and creatine kinase MB (CK-MB) activity on cord blood cTnI levels were investigated in one another study. 112 perinatal hypoxic and 84 control newborns without perinatal hypoxia were enrolled in this study. Cord blood samples were collected from the babies for arterial blood gas analysis, cTnI, CK and CK-MB measurements. Gestational age, birth weight, sex, Apgar score and history of fetal distress were recorded. Hypoxic ischemic encephalopathy (HIE) group, hypoxic but without HIE group and control groups were identified according to clinical observations during the first 72 h in the newborn unit. HIE and perinatal hypoxic without HIE groups had a significantly higher cord blood cTnI level. Cord blood cTnI level did not have a correlation with birth weight and gestational age ($r = -0.02$, $p > 0.05$ and $r = 0.08$, $p > 0.05$ respectively). Cord blood cTnI level also had a negative correlation with pH, bicarbonate, base deficit, and Apgar score ($r = -0.40$, $p < 0.001$; $r = -0.39$ $p < 0.001$; $r = -0.45$ $p < 0.001$; $r = -0.41$, $p < 0.001$) respectively). Cord blood cTnI level showed a positive correlation with CK and CK-MB activity ($r = 0.45$, $p < 0.001$ and $r = 0.37$, $p < 0.001$ respectively). Receiver operator curve analysis revealed that the most sensitive factor for prediction of perinatal hypoxia is cord cTnI value [area under curve = 0.929]. The optimal cut-off value of cord cTnI was 0.35 ng/ml for hypoxia. The authors were of the view that cTnI levels in the cord blood are not affected by gestational age and birth weight. cTnI together with CK and CK-MB has been found to be elevated in hypoxic infants compared to normal infants. Therefore cTnI may be an indicator for perinatal hypoxia in neonates [77].

Elshal and Abdel-Hameed investigated the postnatal levels of markers of brain injury, which are CK BB and Protein S-100B in serum and to determine whether hypoxic-ischemic brain damage alters these markers and whether HIE can be predicted by elevated serum concentrations soon after birth. They included 20 neonates with HIE together with 15 control neonates in the study. Serum concentrations of CK BB and protein S-100B were determined after birth and 24 hours of age. The results demonstrated that cases with HIE had higher values of cord and 24 hours blood activity of CK BB, and higher values of cord and 24 hours levels of protein S-100B, and when doing statistical analysis to compare these results with those of control group, this difference was significant in all except cord level of protein S-100B. They concluded that CK BB and protein S-100B are predictive of HIE in full term neonates when measured soon after birth, yet the decision as to which infants could be candidates for postasphyxial measures should probably be based on several findings, which include cord blood pH, Apgar score, and serum protein S- 100 and CK-BB. Future work to establish the predictive value of these markers in long-term brain injury in neonates is recommended [78].

A study was done to determine CK changes among newborns delivered by vaginal and Cesarean section by Sakha and his group. A total of 180 term newborns were divided into three groups of 60 neonates upon their method of delivery including vaginal, elective and urgent Cesarean Section, and every group was divided in two subgroups upon their Apgar score as being low or high each containing 30 newborns. The study was performed on the cord blood of newborns,

collected at one hour after delivery. The titers of CK were analyzed by spectrophotometer method. The results showed that the activity of CK was higher in neonates with low Apgar score regardless of the method of delivery and probably this finding was the results of brain, cardiac and muscles hypoxia of the newborns. Also total CK was elevated in neonates born via Cesarean section (elective and urgent), this alteration may be the result of anesthesia and or mother tissue injury by surgical procedure and that was transferred to the neonates [37].

Kocylowski and co investigators tested the hypothesis that biochemical tissue-specific markers for the heart in umbilical cord blood of newborns with cardiac defects and intrauterine growth restriction (IUGR) are abnormal. A prospective study was conducted. Serum samples of the umbilical vein and artery from 599 healthy newborns at 37- 42 weeks of gestation were collected. Total creatine kinase (CK), CK-MB heart type (CK-MB), cardiac troponin T (cTnT), myoglobin, N-terminal pro-B-type natriuretic peptide (NT-proBNP), and S100 were measured. Reference ranges for each marker were constructed. Concentrations of tissue-specific markers from umbilical cord blood of neonates with cardiac defects (n = 10) and IUGR (n = 41) were plotted against the established reference ranges. Reference ranges for each studied marker were established for both umbilical artery and vein. In fetuses with cardiac defects, both NT-proBNP (66% in the artery, 70% in the vein) and cTnT (20% in the vein) were increased. In fetuses with IUGR in the vein, NT-proBNP (24%) and cTnT (12%) were increased, whereas S100 was decreased. In a subset of neonates with cardiac defects or growth restriction, irrespective of the pH at birth, tissue-specific injury markers for the heart in umbilical cord blood were abnormal [79].

A study done by Almeida and others on biochemical markers cTnI, CK-MB and NT-proBNP in normal neonates. These biomarkers were measured in both the cord blood and the venous blood. CK-MB remains constant from cord blood to the first day, declining thereafter to almost half the values (81.5 vs 52.0 U/l); cTnI increases from 0.004 to 0.058 ng/ml by 72 h falling to 0.030 by day 10; NT-proBNP peaks by 24 h (5085.5 pg/ml), subsiding to 3388.5 pg/ml by day 3, falling to 1316.0 pg/ml by day 10. They concluded that CK-MB, mostly of muscle origin and reflecting labor stress or injury, is not to recommend as a measure of myocardial damage in the neonate. The rise in cTnI may be explained by a degree of myocardial involvement. The initial rise and subsequent fall of NT-proBNP represents the physiological ventricular overload of transient birth adaptation [64].

Nakajima and Masaoka determined whether the tocolytic therapy affects CK activity in the umbilical blood. This study included 215 preterm infants born to women treated with and without ritodrine hydrochloride. CK activity in the umbilical blood at delivery were determined. Infants were divided according to the ritodrine tocolysis, as follows: Group A (n = 91), not exposed to ritodrine; Group B (n = 44), IV ritodrine for <1 week; Group C (n = 80), IV ritodrine for ≥1 week. The CK activity in cord blood of Group C (198.8 ± 14.2 IU/L) was significantly higher in comparison with Group A (155.0 ± 7.3 IU/L, $P < 0.05$). The CK significantly correlated with gestational age ($P < 0.01$) and birth weight ($P < 0.01$). They concluded that long-term ritodrine tocolysis leads to increased umbilical blood CK activity [15].

A comparative study on the cord blood activity of total Creatine kinase (CK) and Creatine kinase MB isoenzyme (CK-MB) in newborns delivered by vaginal delivery and cesarean section was done by Torabi and his companions. Total cord blood CK (CK) and MB isoenzyme (CK-MB) was measured immediately after delivery. Route of delivery and APGAR (Appearance, Pulse, Grimace, Activity, and Respiration) Score were also assessed. One hundred and seventy six newborns were recruited (57.4% male and 42.6% female). They found significant association between serum CK-MB activity and route of delivery. There was no significant association of serum activity of total CK and CK-MB with APGAR score ($p>0.05$). This study showed that newborns who were vaginally delivered had elevated CK-MB activity [10].

We also conducted an eighteen months hospital based descriptive study by using a structured data collecting tool. Our study aimed to correlate total CK activity with mode of delivery and APGAR score in newborns. The data were analyzed using SPSS software. Our study showed that out of 100 newborns, 51 were delivered by full term normal vaginal delivery (FTND) and 49 by lower segment cesarean section (LSCS). Maximum mothers were in the age group of 21 to 30 years. Birth weight of most of the newborns ranged between 2.5-3.0 kgs. We also observed elevated total CK activity in both the modes of delivery. Significantly higher total CK activity ($p<0.001$) was observed in LSCS cases as compared to FTND cases. With decreasing APGAR score, a significant increase ($p<0.001$) in total CK activity was observed at both 1min and 5 min. Our study revealed that LSCS mode of delivery and lower APGAR scores are associated with increased CK activity[80].

We also aimed to correlate total CK and its isoenzymes activitiy in the cord blood with high risk pregnancies. This was a Prospective observational study conducted

in our hospital. Cord blood of 100 full term newborns was collected and serum was analyzed for total CK and its isoenzymes activity by modified IFCC method. In this study, CK-total and its isoenzymes(CK-MB, CK-BB) activities were observed higher in cases with risk as compared to those without risk. Total CK activity was observed independent while CK-MB and CK-BB were found dependent on different risk factors like pregnancy induced hypertension and fetal distress. Our study revealed that high risk pregnancies are associated with increased total CK, CK-MB as well as CK-BB activity[81].

CONCLUSION

Creatine kinase (CK) is a key enzyme of energy metabolism, especially in muscle tissue. CK has two polypeptide chains of M and B, and three isomers, CK-BB, CK-MB and CK- MM. In some conditions like acute myocardial infarction and Neuromuscular disorders, increased CK activity is used as a part of diagnosis. CK can also be elevated in absence of neuromuscular diseases or cardiac injury, such as strenuous exercise, intramuscular injections etc. Several reports indicate elevated activity of serum CK in the maternal blood during child birth. In our studies, we also observed a significant decrease in total CK activity with increasing APGAR scores, and high risk pregnancies are associated with increased total CK, CK-MB as well as CK-BB activity.

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