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Elevation of Lactate Dehydrogenase & its Isoenzyme Pattern in Pregnancy induced Hypertension: Etiopathogenesis and Consequences

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Mini Review

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Abstract

Lactate dehydrogenase (LDH) is an intra cellular cytosolic enzyme, which play an important role in anaerobic Glycolysis. It is a tetramer having four subunits which may be all H type or all M type or it may be a mix of both these subunits. Preeclampsia is defined as a pregnancy-specific multi-systemic syndrome of widespread endothelial malfunction and vasospasm developing after 20 weeks of gestation. Analysis of Isoenzyme pattern of LDH is more important than Total LDH value, anaerobic form LDH is seen to be predominantly found in case of pre-eclampsia.

Keywords: Lactate Dehydrogenase; Pregnancy Induced Hypertension; Aerobic forms of LDH; LDH-A Gene; LDH-B Gene

Introduction

Lactate dehydrogenase (LDH) is an intra cellular cytosolic enzyme, which play an important role in anaerobic Glycolysis. During anaerobic glycolysis it converts pyruvate to lactate, where NADH acts as a donor of reducing equivalent. This reaction helps in regeneration of NAD+ which is required to sustain glycolysis in anaerobic media. Like any other non-functional plasma enzyme, LDH is also secreted in the plasma due to cell damage and acts as a marker of various diseases. LDH is a tetrameric enzyme which has got four subunits. It has two varieties of polypeptide chain, H type and M type.

The differential combination of the H and M subunits give rise to 5 types of isoenzyme of LDH, which are as follows: LDH1: HHHH; LDH2: HHHM; LDH3: HHMM; LDH4: HMMM; LDH5: MMMM

The gene coding the H type of protein is LDH-B Gene and the gene which codes for M type is LDH-A gene. LDH A gene is a well-characterised hypoxia-inducible gene and elevation/ineffective down regulation of HIF-1 alpha up regulates LDH A expression [1]. LDH is frequently used as a biochemical marker of cell damage and death in the management of cardiac or pulmonary infarction, muscular dystrophies, connective tissue diseases, among other diseases. Number of studies have shown the elevated LDH level in pre-eclampsia and also have shown the level of LDH Correlates with severity of preeclampsia [2-6].

Preeclampsia and its Latest Definition

Preeclampsia is defined as a pregnancy-specific multi-systemic syndrome of widespread endothelial malfunction and vasospasm developing after 20 weeks of gestation [7-9]. The ACOG revised guidelines define preeclampsia as a de-novo and abrupt onset persistent hypertension associated with proteinuria or pathological oedema or thrombocytopenia or impaired liver or kidney function or new onset of cerebral

or visual disturbances [7-10]. Eclampsia is defined as preeclampsia with sudden development of seizures or coma during the gestational or postpartum period, non-attributable to other neurological diseases that justify the convulsive state [11].

Approximately 10 million women develop preeclampsia each year worldwide. Globally, preeclampsia is a leading cause of maternal and infant illness and mortality claiming up to 76,000 maternal and 500,000 infant deaths per year [12]. In India, the incidence of preeclampsia is 8% to 10 % among pregnant women [13]. Multifactorial risk factors like nulliparity, multifetal gestations, obesity, diabetes mellitus, and maternal age above 35 years are associated with preeclampsia [14]. Delay in diagnosis often leads to severe maternal and neonatal complications encompassing intrauterine death, foetal growth restriction, preterm birth, placental abruption, HELLP syndrome, eclampsia, maternal coma and even death.

LDH as a Bio Marker for Pregnancy Induced Hypertension

Several biochemical markers have been proposed to establish a rapid diagnosis of preeclampsia. In these patients, 24-hour proteinuria (300 mg/24 hours), protein/creatinine ratio (0.3 mg/dl), serum uric acid (6.0 mg/dl), alkaline phosphatase (44 to 147 IU/L), lactate dehydrogenase-LDH-(420 U/l), and other assays are usable clinical tools of great use and prognosis [15-17]. Several studies have shown progressive higher value of LDH with increased severity of the disease [18-21]. Evaluation of total LDH value is only of limited significance to assess the specific cell damage. The isoenzyme pattern of LDH reflects the functional differences in LDH isoenzyme activity, which in turn is related to energy metabolism and oxygen availability and helps in the differential diagnosis of pathologic states [22].

Isoenzyme pattern of LDH is a more significant predictor of pre-eclampsia in comparison to total value of serum LDH. At times the total value of LDH is inconclusive , as it may not be significantly raised in case of pre-eclampsia. In such cases the isoenzyme pattern of LDH helps in understanding the shift of LDH towards anaerobic isoenzyme pattern. In aerobic metabolism, it is aerobic isoenzyme [LDH1] and in anaerobic metabolism, it is anaerobic isoenzyme [LDH5] whichis seen predominantly

Isoenzyme Pattern of LDH in Preeclampsia

In a study conducted by Fazal, et al. [23], the isoenzyme profile of the maternal serum from the normotensive term control showed predominant contributions of LDH 1 (22.1%) and LDH 2 (25.9%) forms with LDH 3, LDH 4 and LDH 5 contributing 19.8%, 16.8% and 15.4% respectively. In one another study by Neal, et al. [24] on serum LDH profile and uterine preparedness for labour, reports an almost similar serum isoenzyme distribution pattern with LDH 1 contributing 29.66%, LDH 2 of 30.33%, LDH 3 of 19.21%, and LDH 4 of 8.74% and LDH 5 of 12.07% at labour.

Many researchers have found that isoenzyme profiles of LDH suggests decreased levels of aerobic forms of LDH in preeclampsia when compared to normotensive pregnancy and also hints that the distribution changes in maternal serum are concordant with the changes in the cord blood, indicating the maternal isoenzyme pattern to be a specific and reliable predictor of the developing hypoxia even when total LDH values seem inconclusive. A study by Tsoi, et al. concludes that expression of LDH A gene is increased in the endothelial cells of the placenta and hence increased LDH 5 isoenzyme activity is a marker of endothelial pathology in preeclampsia. The study further explains that LDH – A gene is a well-characterised hypoxia- inducible gene and the up regulation of its expression combined with the shift of LDH profile to a more anaerobic side supports the proposed role of hypoxia in preeclampsia placenta and up regulation of HIF-1 alpha [25]. Makkonen, et al. Indicated that LDH 2 was decreased while LDH 3 was elevated in severe preeclampsia [26]. In yet another study conducted by Sammour, et al. [27], LDH 5 was significantly increased in both serum and placental extracts in severe preeclampsia when compared to normal pregnancy.

The most plausible explanations of the pathogenesis of preeclampsia focus on the placenta. The initial event of placentation involves the formation of the non-invasive trophoblastic shell, which progresses into an invasive phenotype, causing an exponential rise in the entry of oxygenated maternal blood into the intervillous space. The opening of inter- villous space and the consequent increase in PO2, reduces HIF-1 alpha expression, augmenting trophoblastic differentiation along the invasive pathway [28]. Preeclampsia progresses through a proposed two-stage model that includes poorly perfused placentation (Stage 1) arresting trophoblastic invasion, increasing vascular resistance and subsequent nutrient deprivation which modifies maternal metabolism to increase nutrient availability; inability to tolerate this modification leads to the clinical manifestations of preeclampsia (Stage 2). The central mechanism of pre- eclampsia revolves around placental under perfusion, associated hypoxia and cellular death, emphasising the pivotal role of lactate dehydrogenase.

Conclusion

Isoenzyme pattern of LDH is a more significant predictor of pre-eclampsia in comparison to total value of serum LDH. At times the total value of LDH is inconclusive , as it may not

be significantly raised in case of pre-eclampsia. In such cases the isoenzyme pattern of LDH helps in understanding the shift of LDH towards anaerobic isoenzyme pattern.

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