Relationship between lactate dehydrogenase C chain and prostate cancer on male fertility

Hawraa Kadihm Abd ALHadii 1, Abdul Samad Aliwi Hassan2 and Murtada M Jawad3
1,2,3 Al-Furat Al-Awsat Technical University, Kufa, Iraq

email : hawraakazemal@gmail.com

Abstract

The main objective of this study was detected lactate dehydrogenase C chain in prostate cancer patients.

The case-control study consist of 90 subjects divided into two groups 45 patients with prostate cancer who attended the middle Euphrates oncology center (MEOC) and 45 healthy control individuals. The collections of samples were done from September 2019 till June 2020 with age ranged (45-80) year.

Inclusion Criteria age, occupation, smoking, social history, past medical and past surgical histories, and family history of cancer, especially for the prostate cancer. Exclusion Criteria the patient not suffering from any hemolytic diseases.

The result of study indicated a significant increase (p<0.05) in serum Lactate Dehydrogenase C chain level compared with the healthy group. The study indicated a significant increase (p<0.05) in serum Dehydrogenase C chain level in smokers, family history patients, but not significant with hypertension, diabetes patients compared with the healthy group.

Introduction

Lactate Dehydrogenase C chain (LDHC) belongs to the lactate dehydrogenase family that catalyzes the interconversion of pyruvate and L-lactate and plays important roles in aerobic glycolysis (Di Stefano et al., 2016).

The important of Lactate dehydrogenase C (LDHC) the first germ cell specific glycolytic isozyme found (Welch et al., 2000). It found to be expressed
only in spermatogenic cells, and in several glycolytic in male germ cells (Miki, 2007)

Lactate Dehydrogenase C chain encoded by the LDHC gene, assembles into a homotetramer of LDHC subunits, also known as the LDHC or LDHX iso-form (Andany et al., 2014).

Material and methods

Study samples were obtained from Middle Euphrates Oncology Center (MEOC) and from individuals with cancer of the prostate were obtained from the urology units of these hospitals. Patients of age (45-80) years histologically proved adenocarcinoma of the prostate. Controls were of age (45-70) years also ask the question; smoking, past medical and past surgical histories, and family history of cancer, especially for the prostate cancer, so the patient not suffering from any hemolytic diseases.

The collections of samples were done from September 2020 till June 2021. Three ml of peripheral blood were taken from each subject, transferred from the disposable syringe to plain tube without anticoagulant and then after 15 minutes blood is allowed to clot; the clot shrinks and serum can be obtained by centrifuging at 3000rpm for 10min the obtained serum 3ml is put in Eppendorf tubes and then labeled by number specific for each separated sample a total of 45 patients with prostate cancer and 45 healthy persons.

The levels of lactate dehydrogenase c chain levels were measurement for patients and healthy groups were using Enzyme-Linked Immunosorbent Assay.

Results
Figure 1. Compared to Lactate dehydrogenase C chain (LDHC) level between patients for prostate cancer and control group.

This figure indicates a significant difference in the level LDHC of in patients for Prostate cancer as (48.67 ng/ml) compared to control group as (10.72 ng/ml).

The result of Lactate dehydrogenase C (LDHC) the first germ cell specific glycolytic isozyme found, so subsequent studies noted (Welch et al., 2000) found to be expressed only in spermatogenic cells, and in several glycolytic in male germ cells according to (Miki, 2007) it very important in human men.

Reviewed in many studies have found that meiotic and post meiotic male germ cells prefer to use the lactate and the pyruvate over glucose as an energy substrate use lactate oxidation by the LDH isozymes has a significant role in energy metabolism during the middle and last stages of the spermatogenesis (Boussouar & Benahmed, 2004).

While noted that abundance of LDHC in these stages of spermatogenesis that glycolysable substrates are important for sperm motility (Mukai and Okuno, 2004) so essential for fertilization according to (Bone et al., 2000) This was proven when inactivation of the gene for the sperm-specific glycolysis pathway enzyme dehydrogenase when dramatically reduced the level of ATP in sperm,
caused severe defects in progressive sperm motility, and resulted in male
infertility result in LDHC important for lactate metabolism during
spermatogenesis and to the conversion of pyruvate to lactate accompanied by
the formed of reduced NAD$^+$ coenzyme important to activity in the spermatozoa
(Miki et al., 2004).

Many studies detect that this extreme subfertility was a consequence of a
disorder in sperm function Motility of LDHC sperm was impaired and their
progressive motility lowering over time mean that Ldhc null sperm are unable to
the swim through the tract of female (Odet et al., 2008).

Moreover, even if LDHC null sperm were able to reach the eggs, s indicated
that they were unable to fertilize oocytes, LDHC null sperm did not undergo the
protein tyrosine phosphorylation changes characteristic of capacitation and were
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Found that deficiency of the LDHC would stimulate an impairment in the
ATP production by inhibition of glycolysis the principal origin of ATP in the
sperm Consistent with this hypothesis, we found rapid lower in progressive
motility and ATP levels over time in LDHC null sperm than in sperm (Odet et
al., 2008)
In many of studies noted of the translational relevance to problems of male infertility and to the development of a male contraceptive (Goldberg et al., 2001; O’Hern et al., 1995)

In healthy group of study the level of lactate dehydrogenase C is (10.72) that mean apparently ectopic expression of LDHC present in the parental cells was lost with high passages by hypermethylation of the promoter it is not uncommon for a cell line to miss the expression of tissue-specific markers as crossing the number increases (Antequera et al., 1990).

Methylation could be a crucial factor in the suppression of gene expression, either directly or indirectly, by silencing the target gene's critical transcription regulators or by restricting access to transcriptionally relevant binding sites on the promoter.

In the patients the level of lactate dehydrogenase C is (48.67) that indicate hypomethylation in cancer cells is associated with activation by demethylation of metastasis associated genes (Jones and Baylin, 2002). In methylation status of the LDHC promoter was detected in the prostate cancer samples by offers the sensitive quantitative analysis of methylation in double sites of (Tost et al., 2003; Mirmohammads et al., 2006).

Mirmohammads et al noted that differential methylation patterns in fact exist in these prostate cancer samples with various degrees of malignancy that mean very pleasant observation was that the specimens with relatively higher methylation levels were examination to formally prove the results may supply a
lead to developing a biomarker based on the methylation status of the LDHC (Mirmohammads et al., 2006).

The preferred metabolism of lactate by LDHC provides pyruvate as the starting substrate for the citric acid cycle, spermatids use the citric acid cycle as the major source for energy production according to (Semenza et al., 2000), in cancer show increased rate of glycolysis, resulting in excessive lactic acid generation from glucose, energy demand is met by aerobic glycolysis rather than mitochondrial oxidative phosphorylation, In addition to mitochondrial dysfunction, overexpression of important glycolytic enzymes has been proposed as an underlying cause in cancer. In this sense, the substrate preferences of LDHC, which are unaffected by greater lactate concentrations, may be favorable for cancer cell metabolism and survival by offering a metabolic rescue pathway through the use of lactate for ATP delivery.

In this research seen the mechanism of LDHC activation in cancer also it has previously been shown that germ cell specific genes may get away transcriptional repression in the somatic tissues of adult in the course of malignant transformation by the promotor demethylation (Semenza et al., 2000)

Result increase of glucose pathway upon hypoxic conditions is present in the LDHC promotor region, a strong inductor did not outcome in expression of LDHC activation mechanisms of LDHC might be similarly sophisticated as regulate for its isoenzyme LDH for activation. The availability of LDHC-specific monoclonal antibodies so LDHC supply the basis to dissect whether LDHC has a biological significance in the specific metabolic method observed in patients cancer (Shim et al., 1997).

**Effect of different age on LDHC level**
We conclude from the data of Figure (4-4) that there are no differences between age groups with significant differences between prostate patients and controls groups.

In the figure 2 showed the ages of patients and control group Results appear no significant difference between ages groups with significant difference between patients and control group the age of patient were (45-80) the cause of Risk of prostate cancer also rising with age Prostate cancer incidence rising from 1 in 20,000 for men younger than 39 to 1 in 45 for men aged (40–59) and to 1 in 7 for men aged (60–79) (Crawford, 2003)

As 64% of prostate cancer detected are made in men over the age of 65 and the number of men in this age there will be a growing population requiring tretment (Bechis & Carroll, 2011) Understanding the molecular and cellular mechanisms that underlie age relation with changes in the prostate will be import to combat disease risk.
For prostate cancer found stem and progenitor cells are the favored cells of origin. The effects of aging on progenitor activity, the cause of age-related changes to prostate epithelium by profiling epithelial cells isolated from 3-month old and 24-month old prostate, aging in the prostate is associated with maintenance of progenitor activity, it is critical to evaluate the effects of aging on progenitor activity, the cause of age-related changes to prostate epithelium by profiling epithelial cells isolated from 3-month old and 24-month old prostate. Aging does not affect the ability of basal and luminal cells to form progenitor-like primary organoids, nor does it affect their ability to self-renew when reconnected to secondary organoid culture. These cells share features with human luminal progenitor cells, such as elevated prostate-specific mRNA expression. (Crowell, et al., 2019)

So numerous studies have detected overlap between the prostate stroma and adjacent epithelium (Levesque & Nelson, 2018), that age-related changes to the prostatic stroma induce the development of the prostatic epithelium (Bianchi-Frias, et al., 2010). Conditioned media from fibroblasts isolated from younger prostates, but not from the older prostates, has been shown to suppress prostate epithelial cell growth indicate that young fibroblasts produce various factors than aging fibroblasts (Begley et al., 2005).

According to Gomes et al found In the serum of older patients, there were increased levels of methylmalonic acid, a recognized tumor development mediator. Conversely, plasma ratios of NAD+:NADH and NADP+:NADPH, which are important for a variety of cellular processes (Gomes et al., 2020), decrease with age. A decrease in NAD+ has been linked to reduced mitochondrial and nuclear function, and increased age-related pathogenesis.
leads to an increase in lactate dehydrogenase LDH as has been shown in figure(4-4) (Clement et al., 2019).

**Effects of different diseases on LDHC level**

![Comparison of LDHC level with disease group.](image)

**Figure 3.** Comparison of LDHC level with disease group.

The data of figure 3 indicate no significant differences in the level of LDHC in a group of different diseases (Diabetes and hypertension).

The figure3 show no significant difference in diseases between groups. this were agreement with most studies they found no association between diabetes mellitus and prostate cancer risk As a result, findings of higher age and more advanced tumors among men with diabetes mellitus and prostate cancer could suggest that selection may play a role in the observed inverse relationship between diabetes mellitus and prostate cancer, with differences only observed among men with low risk prostate cancer. Changes in insulin, insulin-like
growth factor-1 (IGF-1), and testosterone levels have previously been indicated as a link between diabetes and prostate cancer, the incidence of low and intermediate risk prostate cancer reduced with increasing HbA1c concentrations, according to the study this may be related to higher androgenicity among men with decrease glucose levels, the influence of metabolic factors may further need a relatively well-differentiated target tissue for their action diabetes mellitus and long-term hyperglycemia frequently results in microvascular complications due to capillary dysfunction and change shape and size of intraprostatic microvessels have been linked to the danger of lethal prostate cancer, lower microcirculation might thus alternatively explain the decrease risk among the men with diabetes mellitus (Fall et al., 2013).

Other research on blood pressure (hypertension) and prostate cancer have found no evidence of a link between the two. These studies, however, contained far fewer individuals and cases than ours; the greatest previous study included both incident and fatal instances, the relationship between blood pressure and prostate cancer risk in our investigation revealed a progressive change as disease features changed. High blood pressure was linked to a lower risk of total incidence prostate cancer and non-aggressive disease, but not to a lower risk of prostate cancer that was fatal. research suggests that elevated hypertension associated with a lower the risk of incident prostate cancer, but is not significantly related to the danger of the prostate cancer death (Lund Haheim et al., 2006).

4. Effect of smoking on biomarker level:
Figure 4 Comparison of the LDHC level between groups of patients with prostate cancer, smokers and control non-smokers.

The smoking of patients with prostate cancer and control group show significant difference (P<0.05) as show in figure 4 the cause of smoking could accelerate the course of prostate cancer. Cadmium, male hormones, genetic abnormalities, and immunological function are among of the physiological factors most frequently thought to have a role in smoking-induced prostate cancer. Due to the usage of cadmium-containing phosphate fertilizers on tobacco plants, cadmium is assumed to be present in tobacco smoke. Laboratory research on human prostate cancer cells showed some evidence to support a role for cadmium in prostate cancer (Johansson et al., 2006).

Two assumptions appear to underpin the hormonal theory. Smoking has an anti-estrogen effect, and second, prostate cancer is hormone dependent. However, research on the effect of smoking on plasma testosterone were conflicting.

(Hickey et al., 2001).
Plasma estradiol, estrone and the adrenal hormones androstenedione and dehydro epianodosterone sulphate (DHEAS) smoking is antiestrogenic in males, which makes the hormonal hypothesis less likely (Hickey et al., 2001).

Studies found mutation in the tumor suppressor gene p53 may be a mechanism that explains the association between smoking and fatal prostate cancer that have associated p53 mutations with a subset of advanced prostate cancer (Hickey et al., 2001).

Studies have found that Smoking has been decrease the immune system. Studies have reported that smokers have lower the natural killer cell activity and impaired T lymphocyte suppressor cell function so smoking cessation has been connected with increased natural killer cell activity and lower white blood cell counts (Raddam et al., 2017).

The five isoforms of lactate dehydrogenase affect by smoking compound. Interestingly the isozyme of LDH will be in association and affected by smoke compounds results appear to detect many other studies findings, about the role of smoking in rising the LDH level in stream of blood that agree with our study as show in figure 4 Similar studies have observed rising level of LDHC in blood of smokers We think there is another reason help in explaining the rising LDH level and have the smoke compounds to formed free radicals and oxidative stress in many cell and tissues of the body (Raddam et al., 2017).

5. Effect of family history on LDHC level:
Figure 5: Comparison of the LDHC level between control group and patients with prostate cancer who have a family history.

Indicated the data of Figure 5 there were significant differences in LDHC level between the groups of patients who had a family history of prostate cancer as (45.56 ng/ml) with control group (9.00 ng/ml).

From history it has been found there is significant difference (p<0.05) between patients and control group in family history of prostate cancer as shown in figure 5 This finding which shows a high aggregation of family history in patients it’s agree with Fraumeni and Li they found Fraumeni and Li defined "cancer families" as families with a substantial genetic susceptibility to cancer. Fraumeni and Li's criteria include early age of illness onset in the family and an excess of other malignancies in the family. The average age of diagnosis of prostate cancer in these families was 54.9 years, which is much lower than the general population's average of 70 years (Love et al., 1985).
Cannon et al. analyzed 2,824 cases of prostate cancer and discovered that prostate cancer cases were more connected to one another on average than a group of age-matched controls, indicating that prostatic cancer is a family disease (Cannon et al., 1982).

Men with one affected first degree relative have a twofold increased risk of prostate cancer compared to men without a family history of the disease.

There is a trend of increasing prostate cancer risk with increasing numbers of affected first degree relatives, with men with two or three affected first degree relatives having a five and 11-fold increased risk of prostate cancer, respectively, compared to men without a family history of the disease (Lynch et al., 1974).

The familial aggregation of cancer does not imply any specific mechanism of genetic inheritance; aggregation can occur as result of both Mendelian and polygenic inheritance. Similarly, common environmental exposures, such as shared eating patterns among families, can also cause disease aggregation. Despite the fact that this study established familial aggregation of prostate cancer and identified families with prostate cancer clusters, no definitive evaluation of the relative role of genetic or environmental variables in the etiology of prostate cancer in these families has been made (Silverberg et al., 1989).

Other screening methods may be beneficial in the future (e.g., serial serum prostate-specific antigen determinations, transrectal ultrasound, or magnetic resonance imaging of the prostate). Furthermore, a subset of all men with prostate cancer may develop a family variant of the disease, similar to syndromes seen in other late-onset malignancies including breast or colon cancer additional genetic and linkage investigations of this group of individuals who may have a strong hereditary propensity to prostate cancer disease are currently being conducted (Steinberg et al., 1990).
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