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The validity of carbohydrate antigen 19-9 in serum and saliva as a new type for diagnosis in Iraqi kids having cystic fibrosis

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ABSTRACT

Cystic fibrosis is a life-limiting, recessive disease; it occurs due to mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Carbohydrate antigen 19-9 (CA19.9) is a tumour-associated, primarily occur in patients having biliary tract and pancreatic cancers but are also observed in patients having other malignancies. Conditions related to benign like cholestasis, cirrhosis, cholangitis, plus pancreatitis also result in CA 19-9 elevations. Raised levels of serum CA 19-9 seems in CF patient to be related to disease pulmonary exacerbation also in the lung the amount of sputum. Investigate whether serum and saliva (CA19.9) level may contribute to cystic fibrosis diagnosis establishment in patients. This "case-control study" consists of 80 individuals (30 patients and 50 healthy controls). Their age was range between one month and 18 years. Blood and saliva samples were taken from patients. Saliva level in patients was 1.775 ± 1.030 U/ml ($P < 0.001$) as compared to control group (0.956 ± 0.682 U/ml). A serum level of CA19.9 was found to be increased ($P < 0.001$) by 0.818 ± 0.601 U/ml in CF patients as compared to healthy (0.334 ± 0.101 U/ml) control. From this study, we can conclude that the salivary CA19.9 level can be diagnosed as a marker for cystic fibrosis.



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INTRODUCTION

Cystic fibrosis (CF) considered a recessive and life-limiting disease. It occurs from the chromosomal gene mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene (Uozumi *et al.*, 2010). It plays a central function in the ion transport regulation around the cell membrane,

like bicarbonate and chloride, through the epithelial cells apical membrane. Thus, any defect in this gene can cause upregulation of fluid and electrolyte in epithelial tissues in the body, like in the sweat gland, pancreas, lungs, reproductive system and sinuses (He *et al.*, 2009). The imbalance of electrolytes and fluid results in the thick sticky mucus in sinuses and lungs or secretions which are viscous in the reproductive tract, GI tract and pancreas to acquire (Moskowitz *et al.*, 2008; Kazmerski and Orenstein., 2012). Also, organ function also gets affected.

Carbohydrate antigen 19-9 (CA19.9) is associated with the tumor. It is a sialyl-lacto N-fucopentane radical containing polysaccharide. It showed epitope structural similarity with the A antigen of the Lewis blood group (Yue *et al.*, 2011). Carbohydrate antigen 19-9 is present on the liver, fetal stomach, pancreas and intestine epithelial cells. Detection of trace amounts can be done in an adult's normal lung tissue and gastrointestinal

tract while large amounts can be found in urine, duodenal secretion, saliva, bile, gastric secretion, seminal fluid, ovarian cyst fluid (Molina *et al.*, 2012).

CA 19-9 antigens is used originally as a marker of tumor in malignancies of the gastrointestinal tract. Serum CA 19-9 level was increased in CF patients, specifically in those having the progressive disease of pulmonary. However, it is not distinct in the patients having a borderline sweat test and mild disease also having upper levels (Augarten *et al.*, 2003). In the use of (CA 19-9) as a tumor marker clinically there is an important limitation that (5-10%) of the Caucasian population can't synthesize the antigen because of the fucosyltransferase enzyme deficiency (Uozumi *et al.*, 2010).

The molecular heterogeneity of (CA19-9) is necessary and involves variations, partial cleavage and deletion in the glycosylation degree and nature. The standard clinical assay for (CA 19-9) detects and captures all antigens of (CA 19-9), the tissue or carrier protein origin. Some glycoproteins of these are expressed normally at biliary duct and human pancreatic cells apical site also by salivary and endometrial epithelia, colon, gastric. Also, small amounts can be found in healthy patient serum (Uozumi *et al.*, 2010). They have shown that antigen is expressed in regenerating epithelial cells and bronchiolar epithelial cells which are covering septal remodeling structures and fibrosing alveolar septi surface in the lung fibrosis having patient's lungs. The secretion of antigens of carbohydrate is from the apical bronchial gland, into the lumen not basally (Obayashi *et al.*, 2000).

MATERIALS AND METHODS

Study design: This "case-control study" consisting of 80 subjects (30 patients and 50 healthy controls) were enrolled in this study, their age range between one month and 18 years, during the period from February 2018 to July 2018, Patients were chosen from two teaching hospital AL-Imamain AL Kadhmain city and children welfare hospital in Baghdad Medical city. The present study is approved via the Ethical Committee of the College of the Medicine / University of AL-Mustansiriyah.

Subject divided in two groups i.e cystic fibrosis patients group (n=30 (female=13 and male=17) and healthy control group (n = 50) (female=21 and male=29).

Inclusion criteria: Patients have cystic fibrosis from (1 month to 18 years), which were chosen from two teaching hospital AL-Imamain AL Kadhmain city and diagnosis by a physician.

Exclusion criteria

Patient with diarrhea disease, renal problem (chronic renal disease), diuretic therapy, abnormal lipid profile, IBD (inflammation bowel disease), cholestasis (gall stone disease) and age less than 18 years were excluded from the study.

Sample collection

Fasting blood samples were taken from patients. About 5ml of venous blood was withdrawn from control and healthy individuals, after getting oral consent. The samples were stored at -20°C until further analysis.

Saliva sample (unstimulated) was collected into a sterile 5ml tube. The participants were told to expectorate once per minute to 15 minutes. The samples are kept on ice and transferred to the laboratory. They are stored under temperature -20°C until further analysis.

Biochemical estimation of carbohydrate antigen 19-9 (CA19.9)

Serum CA19.9 concentrations were measured using an (ELISA) method cancer antigen 19-9(CA19-9) test system code: 3925-300. The expected normal concentration is ≤ 40 U/ml.

Statistical analysis

Data were statistically analyzed by SPSS version 25. All data were presented as a mean \pm SD. Statistical differences between the value of patients and control groups were determined by "case-control study" between the variables was performed by correlation coefficient $P < 0.05$ is considered to be significant.

RESULTS

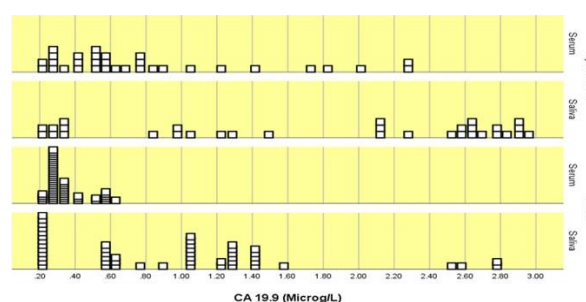


Figure 1: The distribution of CA 19.9 (U/ml) in patients having cystic fibrosis and in serum and saliva healthy controls

In the present study, the serum level of carbohydrate antigen 19-9 in cystic fibrosis patients (n=30) and a healthy control group (n=50) were compared.

Cystic fibrosis patients showed a significant ($P < 0.001$) increase in saliva CA 19.9 level (0.818 ± 0.60 U/ml) as compared to healthy control (0.334 ± 0.10 U/ml). Similarly, in serum CA 19.9

Table 1: Serum CA 19.9 levels in the cystic fibrosis patients and healthy control

	Cystic fibrosis (n= 30)	Controls (n=50)	P-value
Serum	1.775±1.030 (0.196-2.950)	0.956±0.682 (0.191-2.800)	0.0001

concentration was also found to be increased in the CF patients. Table 1 shows serum carbohydrate antigen 19-9 (CA19.9) healthy and CF patients.

The correlation of the saliva level and serum CA 19.9 level in cystic fibrosis and control was found to be 0.093 and 0.132. The correlation is depicted in Figure 2.

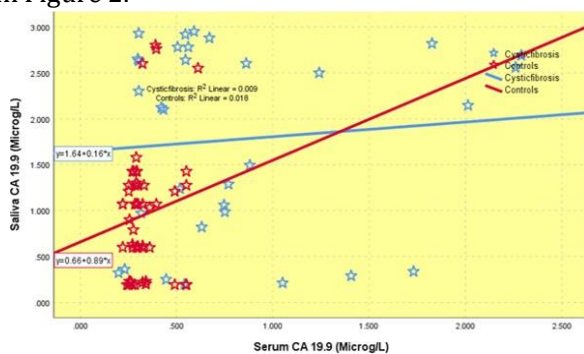


Figure 2: The correlation between saliva and serum CA 19.9 (U/ml) in healthy controls and patients

DISCUSSION

Cystic fibrosis (CF) considered as the autosomal recessive disease and life-shortening most common disease; it affects all epithelial surfaces which found in organs, the most affected organs are the eccrine sweat gland, lung, liver and the pancreas (Burgel *et al.*, 2015). Elevated levels of CA 19-9, an intracellular adhesion molecule, occur primarily in patients with pancreatic and biliary tract cancers but also have been reported in patients with other malignancies. Benign conditions such as cirrhosis, cholestasis, cholangitis, and pancreatitis also result in CA 19-9 elevations (Ben-Ishay *et al.*, 2016).

Increased serum concentrations of CA 19-9 seem in CF patient to be correlated with pulmonary disease exacerbation also with the sputum amount in the lung. Both cholangitis and pancreatitis are associated with important non-specific concentrations in serum of CA 19-9. Acute pancreatitis is present in (CF) but only in the insufficiency of pancrease case. The increased (CA 19-9) causes cholangitis and due to (CA 19-9) high concentrations in the bile, which in case of inflammation can translocate into the blood. Cholangitis infection is related to the translocation of bacteria from the reflux or digestive tract in the biliodigestive anastomosis can be possible in this case and may be supported by the characteristic of slowed intestinal transit of cystic fibrosis (Murai *et al.*, 2013; Esteghamati *et al.*, 2014).

For the detection of the clinical diseases, the saliva is an arising body fluid having various advantages for prognosis and diagnosis of disease. The salivary glands may be affected indirectly or directly by the systemic and oral diseases and may affect the composition and quantity of saliva which is produced (Rai *et al.*, 201). CA19-9 was observed to be increased in patient's serum with gastrointestinal tract cancers, and also found This tumor marker CA19.9 was elevated in other fluids of the body, e.g. urine and saliva and are described previously as potential markers for urothelial and parotid malignancies detection (Ben-Ishay *et al.*, 2016). The various test is employed for the monitoring the extent of CF disease such as gastrointestinal and respiratory tracts, nutritional status etc. (Moskowitz *et al.*, 2008). Respiratory tract evaluation frequently includes chest computed tomography, pulmonary function testing, chest x-ray etc. (Watson *et al.*, 2004; Blackman *et al.*, 2006; Vanscoy *et al.*, 2007). However, sputum culture in patients who can discharge a sputum sample or deep oropharyngeal swab cultures is reported to be a preliminary simple diagnostic approach.

CONCLUSION

In the present study, we trace on the oral swab diagnosis of the CA 19.9. We report significant elevation ($p \leq 0.001$) in salivary CA19.9 level in CF patient as compared to healthy control. So. We can conclude that the salivary CA19.9 level can be diagnosed as a marker for cystic fibrosis.

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