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Original Article

The role of salivary caffeine clearance in the diagnosis of chronic liver disease

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ABSTRACT

Background: Chronic liver diseases (CLD) are quite prevalent throughout the globe. Its early and correct diagnosis is always a concern among physicians, especially the residual liver function. For this various substrates like caffeine are being investigated in body fluids like serum and saliva. Saliva as a study sample has its own advantages due to its non invasiveness; it can be very useful study sample.

Methods: 30 Subjects with CLD and 15 healthy controls were administered 200 mg of caffeine. Subjects classified into severity groups (class-A-mild-n = 9, B-moderate-n = 11, and C-severe-n = 10) based on "Child-pugh classification" of severity of liver disease. After 17 h of dietary caffeine restriction and before drug administration, 0 h salivary sample was taken. After the dose of caffeine, 4 and 16 h saliva sample was taken. Blood sample was taken from controls only at same time points. These samples were analyzed on semi automated analyzer using Enzyme Multiplied Immunoassay Technique (EMIT) by spectrophotometric method. Caffeine clearance values were calculated and results were statistically analyzed.

Results: Significant correlation was found between serum caffeine clearance and salivary caffeine clearance (SCC). Controls showed higher mean of SCC value of 1.6 ± 0.2 ml/min/kg while SCC values of subjects were less, with mean of 0.5 ± 0.2 ml/min/kg. Significant correlation was found between degree of hepatic dysfunction and SCC values.

Conclusion: Saliva can be used for diagnosis of CLD and assessment of residual liver function in CLD as alternative to serum.

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1. Introduction

The liver function assessment is important for estimation of the severity of liver disease, treatment efficacy and its prognosis. Conventional liver function tests, particularly various serum enzymes, provide important information on inflammation and cholestasis but give no indication of hepatic metabolic function.[1] The sensitivity and specificity of these tests are also a concern. Some of commonly tested enzymes which rise in liver diseases may be seen raised in other conditions as they are present in these tissues also.[2] Besides these, liver function tests may be normal in certain liver diseases also like congenital hepatic fibrosis, cirrhosis, non cirrhotic portal fibrosis etc. While serum albumin, which decreases in liver disease may decrease in nephritic syndrome and other chronic disease as well. Likewise it may be abnormal in persons with healthy liver; like aminotransferases which may be raised in cardiac diseases also. Thus researchers concluded that except for serum bile acids, the LFT are not specific for liver diseases and all the parameters may be elevated for pathological processes outside the liver.[3,4] It is also worthy to mention that these tests provide only static assessment of the degree of liver injury, but give little information about the residual liver function.

It has been emphasized that the assessment of residual liver function is most important factor to determine the severity of acute or chronic liver diseases; irrespective of its aetiology, long-term prognosis, step-by step disease progression, surgical risk and efficacy of treatment procedure.[5] It has been proposed that administration of a compound metabolized by the liver and study of its clearance from body affords a dynamic evaluation of residual metabolic capacity and thus the quantitative assessment of liver function.[6] The first quantitative liver function tests to assess residual liver function were suggested in 1962.[7] After that liver function test such as the galactose elimination, aminopyrine breath test and indocyanine green clearance have been developed and proved efficient by some studies.[8,9] Studies have been reported that these tests are not popular either because of technical difficulties or adverse effects, like breath tests are not feasible in patients with severe restrictive lung disease, and in elderly patients with chronic heart failure.[1,10]

Thus a quantitative liver function test is required which uses test substance that is completely absorbed, harmless and has exclusive hepatic elimination and excretion. It is further desired that the test material and its metabolites can be easily assessed in patient's body fluids with economical, widely available and accurate equipments and techniques. Caffeine 1, 3, 7 tri-methyl xanthine, an exogenous substance appears to be almost an ideal substance for the purpose.[11] This is due to its rapid and complete absorption[12] after oral ingestion and almost exclusive metabolism in liver,[13] caffeine clearance may show the residual metabolic capacity of liver in diseased patients giving quantitative assessment of liver function.

Blood serum is being used as standard diagnostic fluid for many body tests and clearance of caffeine can also be measured as the disappearance of the parent compound from the blood.[1,5] However saliva is emerging as efficient and feasible diagnostic fluid for many diseases and also being popular among patients and clinicians due to easy collection and less chances of cross contamination and can be used as sample for the study of larger group like country surveys. Saliva has been proposed as suitable diagnostic fluid for caffeine clearance assessment which is substantiated by a number of studies that confirmed an excellent correlation between caffeine elimination in saliva and liver function[14,15,16] In spite of these encouraging studies, the caffeine clearance test from saliva sample is not popular in clinical practice. This warrants further study to assess its feasibility as non invasive diagnostic modality for quantitative assessment of liver function and find out the possible shortcomings which is hindering its popularity.

Hence the study was aimed to validate the utility of saliva as study sample by evaluating the correlation of caffeine clearance in saliva and serum and then to correlate the salivary caffeine clearance with severity of chronic liver disease, using enzyme multiplied immunoassay technique (EMIT) with spectrophotometric method on a semi-automated analyzer.

2. Materials and method

2.1. *Patient selection*

Thirty hospitalized patients with chronic liver disease were selected. The diagnosis was confirmed on the basis of clinical findings and other relevant investigations. This group included twenty-five males and five females with age ranging from thirty-one to seventy-one years and mean age of forty-two years.

A detailed medical history of the patients was taken which included their presenting complaint and special attention was given on complications like malena, hematemesis, encephalopathy, esophageal varices and portal hypertension. Patients having such complications were not included in the study. Detailed drug history was also elicited. Personal history of indulgence in alcoholism, smoking, coffee and tea intakes were noted down and were asked to refrain from them during the study period. Along with chronic liver disease, a record of any other systemic illness like diabetes, hypertension, asthma, renal problems etc was also made. Permission was sought from the patient for the salivary caffeine clearance test and written informed consent was obtained from all the patients.

The chronic liver disease patients were classified into three severity groups based on child-pugh classification; as child-pugh class-A mild, B moderate, and C severe respectively.[17] 9 of the subjects belonged to child-pugh class-A, 11 belonged to child-pugh class B and 10 belonged to child-pugh class C. 15 healthy and young volunteers of either sex with age range of 20–35 years were selected as controls with no known history of chronic liver disease and were found normal on physical examination.

2.2. *Sample collection*

Study and control groups were individually informed in detail regarding the caffeine test protocol. They were instructed to follow exclusion of caffeine containing substance from their