Association of Alpha-Fetoprotein With Metabolic Syndrome - A Hospital Based Study

Venkatesan Narasimman[1], Radha Saraswathy[2*]

[1,2]120TT Biomedical Genetics Research Lab (BMGRL), Department of Biomedical Sciences, School of Bioscience and Technology, VIT University, Vellore, Tamil Nadu, India

Abstract

Cluster of Metabolic syndrome is closely associated with various types of cancer, fatty liver disease, cardiovascular diseases, neurological dysfunction and neural tube defects. Alpha feto-protein is still used as a biomarker for liver cancer and neonatal screening worldwide but relation between metabolic syndrome and the exact role of alpha fetoprotein in adult is unclear. The recent study evidenced that there is a relationship with alpha feto-protein and cluster of metabolic syndrome. The aim of the study to analyze the relationship between alpha feto-protein and various metabolic syndrome and alpha fetoprotein may be used as metabolic markers through the following linkages: (i) The linkage of alpha-fetoprotein with demographic parameter (ii) The linkage of alpha-fetoprotein with Diabetes, Hypertension, Dyslipidemia Obesities, nonalcoholic steatohepatitis (NASH) (iii) The linkage of alpha-fetoprotein with Cancer, (iv) The linkage of alpha-fetoprotein with liver disease. The alpha feto-protein elevation which might be useful for early diagnosis and prevalence of liver disease, cancer, cluster of metabolic syndrome and neonatal defects.

Keywords: Alpha feto-protein, Diabetes mellitus, Liver Cancer, Liver Cirrhosis, Metabolic syndrome.

Introduction

Metabolic syndrome is characterized by a complex of metabolic risk factors, including abdominal obesity, impaired glucose metabolism, dyslipidemia, and arterial hypertension [1–3]. Metabolic syndrome is associated with the development of diabetes, cardiovascular disease, and non-alcoholic fatty liver disease [1, 4, 5]. The prevalence of metabolic syndrome is increasing worldwide. In the world, liver cancer is the ninth most prevalent cancer in women and the fifth most common disease in males. The second most frequent reason for cancer-related mortality is hepatocellular carcinoma, also known as liver cancer. Every year, around 80,000 new cases of cancer and liver injury are discovered worldwide. In China, Gu et al. [6] reported that in 2005 the prevalence of metabolic syndrome was 9.8% in men and 17.8% in women. Zhou et al. [7] conducted a cross-sectional study in 14 provinces of China and reported that the prevalence of metabolic syndrome was 22.1% in men and 25.8% in women in 2014.

Insulin resistance and chronic inflammation appear to be the central mechanisms underlying the pathophysiology of the metabolic syndrome [8].

Alpha-fetoprotein is a single-chain glycoprotein produced by the fetal liver and yolk sac. Alpha-fetoprotein ranges decline rapidly after birth and remain low throughout a person's life in a normal population [9–11]. Alpha-fetoprotein levels are reactivated during liver regeneration and hepatocarcinogenesis, which occur in hepatocellular carcinoma, acute or chronic viral hepatitis, chronic liver disease, and gonadal tumors [12–14].

Address for correspondence: Radha Saraswathy
Department of Biomedical Sciences, School of Bioscience and Technology, VIT University, Vellore, Tamil Nadu, India
Email: radhasaraswathy@vit.ac.in

How to cite this article: Venkatesan Narasimman, Radha Saraswathy, Association of Alpha-Fetoprotein With Metabolic Syndrome – A Hospital Based Study, J PHARM NEGATIVE RESULTS 2022;13: 945-957.

Access this article online

Quick Response Code:

Website: www.pnrjournal.com

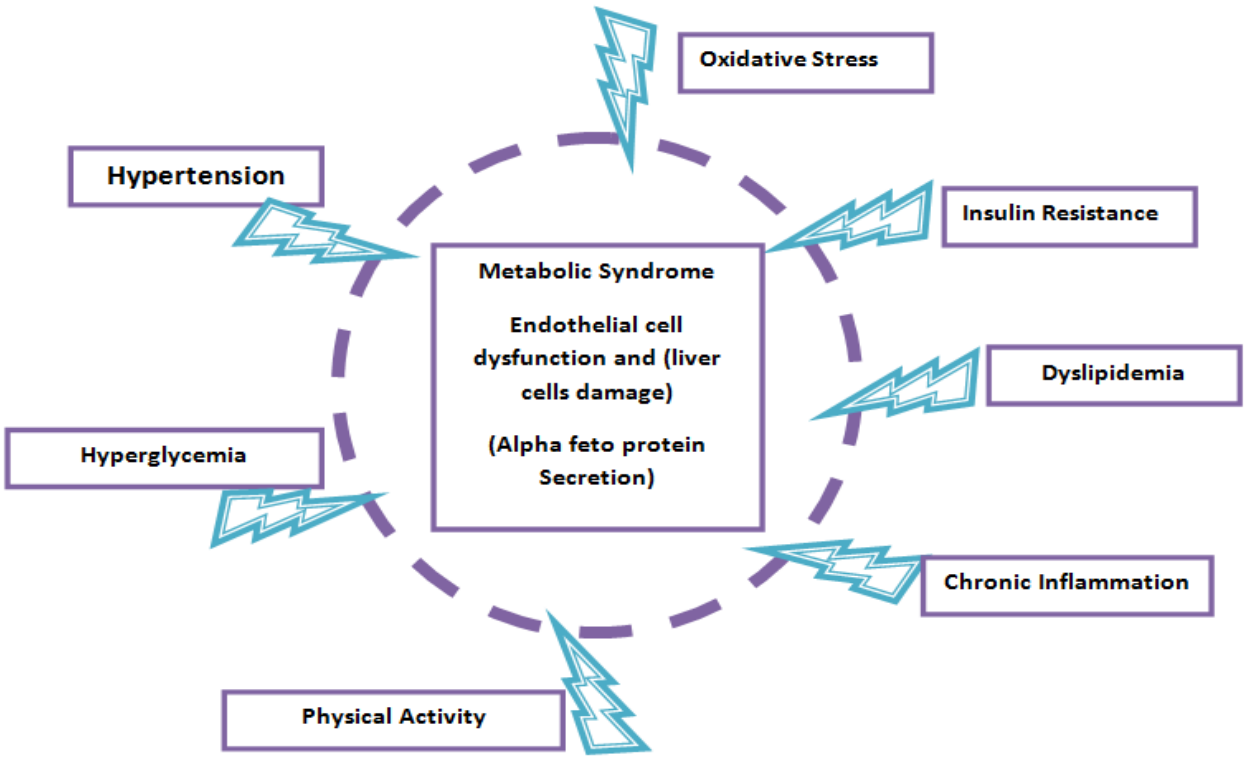
DOI: 10.47750/pnr.2022.13.04.128

Elevated serum alpha-fetoprotein levels have been used primarily to predict the development of hepatocellular carcinoma, including large tumor, advanced or metastatic stage, portal vein thrombosis, and postoperative recurrence [15]. Recently, Xu et al. [16] investigated the association between serum alpha-fetoprotein and fatty liver disease in a population of 9800 people who underwent medical examinations and found that participants with Fatty liver disease had higher levels of alpha-fetoprotein than those who did not have fatty liver disease. Additionally, Babali et al. [12] found that patients with non-alcoholic fatty liver disease had higher alpha-fetoprotein levels than those without. Alpha-fetoprotein levels become increasingly elevated as the grade of liver steatosis increases, which suggests that alpha-fetoprotein level monitoring might help clinicians to treat non-alcoholic fatty liver disease.

The presence of hepatic inflammation, steatosis and fibrosis may be the underlying cause of increased serum alpha-fetoprotein levels in fatty liver disease patients with severe fatty liver [12, 16]. Because metabolic syndrome is closely associated with an increased risk for fatty liver disease morbidity and mortality [16], Metabolic syndrome is a collection of pathological conditions associated with metabolic, pro-inflammatory and prothrombotic conditions. Metabolic syndrome play an important role in the process of atherosclerosis associated with the clustering of risk factors that can increase the risk of atherogenic damage. There is an association between the components of the metabolic syndrome and the progression of atherosclerosis, the leading cause of death from cardiovascular disease. This study was undertaken to evaluate the potential role of alpha feto-protein with metabolic syndrome components including oxidative stress, hypertension, hypoglycemia and insulin resistance, obesity, dyslipidemia, chronic inflammation, physical inactivity, and an atherogenic diet. We investigated the associations of serum alpha-fetoprotein with prevalence of metabolic syndrome in a Indian population with following linkages (i) The linkage of alpha-fetoprotein with cluster of metabolic syndrome (ii) The linkage of alpha-fetoprotein with Diabetes, Hypertension, Dyslipidemia Obesities, nonalcoholic steatohepatitis (NASH) (iii) The linkage of alpha-fetoprotein with Cancer, (iv) The linkage of alpha-fetoprotein with liver disease.

The important mechanisms oxidative stress leads to Insulin resistance is when muscle, fat, and hepatic cells do not respond to insulin because of excesses of body fat and lack of physical activity and have difficulty in absorbing glucose from the blood so it leads to various metabolic syndrome like diabetes, cancer, hepatosteatosis. Oxidative stress leads to changes in cellular macromolecules such as DNA, lipids and proteins, insulin plays an important role in glucose metabolism, lipid metabolism and reduces antioxidant protection, leading to hepatosteatosis, cell damage and leads to liver failure (Fig-1).

Fig-1. Association of alpha-fetoprotein with a component of the metabolic syndrome and the development of liver diseases.



MATERIALS AND METHODS

Materials

This study included 1000 participants (500 healthy groups and 500 metabolic syndrome groups) who underwent individual health examinations that included a physical examination and clinical laboratory tests at the apollo diagnostics Dec 2017 and October 2019.

The following were the criteria for exclusion: Subjects under medication that was known to alter lipid metabolism, participants who did not provide all of their information.

Informed consent was obtained from all participants and the study was approved by the ethics committee of the Apollo diagnostics, Bangalore.

Methods

Clinical parameters and anthropometric measurements

The study conducted anthropometric measurements Waist circumference, height, weight, systolic blood pressure, and diastolic blood pressure were measured. Weight list was determined as weight in kilograms isolated by tallness in meters squared.

Laboratory Techniques

Laboratory examinations were assessed in the morning after an overnight fasting (no caloric intake). Alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltransferase (GGT), triglycerides (TGL), total cholesterol (CHOL), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), fasting plasma glucose (FBS), and creatinine (CRE2) were conducted and analyzed using an automatic biochemical analyzer (Dimension Series Siemens/ Roche, Bangalore) with Siemens/Roche reagents. Hemoglobin A1c (HbA1c) was assessed using a high-performance liquid chromatography analyzer (BIORAD-D10, Bangalore) with BIORAD reagents. Alpha feto protein and Insulin performed using an automated chemiluminescence analyzer (Centaur CP/Architect- Bangalore) with Siemens/Abbott reagents.

Diagnostic criteria for metabolic syndrome

Diagnostics criteria used for metabolic syndrome according to the below mentioned International guidelines as follows.

Table-1: Diagnostic criteria for metabolic syndrome

International Diabetes Federation guidelines (IDF)	**World Health Organization (WHO)**	**National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III)**	**European Group for the Study of Insulin Resistance (EGIR)**	**American Association of Clinical Endocrinologists (AACE)**
WC >90 cm for Indian men and >80 cm for Indian women; BMI ≥22.9 kg/m2;	Abdominal obesity: Waist-to-Hip Ratio: >0.9, BMI ≥30 kg/m^2, WC > 37 inches	WC: >40 inches for men, >35 inches for women	Top 25% of the fasting insulin values among nondiabetic individuals and two of the following: WC: ≥94 cm for men, ≥80 cm for women	fasting plasma glucose and two or more of the following:
Systolic blood pressure (SBP) ≥130 mmHg, or diastolic blood pressure (DBP) ≥85 mmHg, or treatment for previously diagnosed hypertension;	Systolic blood pressure (SBP) ≥140 mmHg, or diastolic blood pressure (DBP) ≥90 mmHg or antihypertensive medication	Systolic blood pressure (SBP) ≥130 mmHg, or diastolic blood pressure (DBP) ≥85 mmHg	Systolic blood pressure (SBP) ≥140 mmHg, or diastolic blood pressure (DBP) ≥90 mmHg or antihypertensive medication	Systolic blood pressure (SBP) ≥130 mmHg, or diastolic blood pressure (DBP) ≥85 mmHg,
TG ≥150 mg/dL, HDL-c : Men: < 39.83 mg/dL, Women: <49.88 mg/dL	Lipid Profile Triglycerides : >150 mg/dL HDL-C: <35.0 mg/dL	Triglycerides: ≥150 mg/dL HDL-C: Men: <40 mg/ dL, Women:<50 mg/dL	Triglycerides: ≥2.0 mmol/liter HDL-C <1.0 mg/dL	Triglycerides: ≥150 mg/dL HDL-C: Men: <40 mg/ dL, Women:<50 mg/dL
Fasting Plasma Glucose (FPG) ≥100 mg/dL or previously diagnosed type 2 diabetes.	High Insulin Levels fasting plasma glucose : >110 mg/dL	fasting plasma glucose : >110 mg/dL	Fasting glucose ≥6.1	

Statistical Analysis

The clinical parameters and anthropometric measurements statistical analysis(ANOVA) were performed and the data were normally distributed are reported as mean ± standard deviation and data that had a analysis of variance (ANOVA) are reported as median and range. Elevated alpha feto protein compared with metabolic and without metabolic syndrome, also correlations between serum AFP values and clinical and other laboratory parameters.

RESULTS

This study conducted with 1000 individuals including those with and without metabolic syndrome (Healthy People (n=500) and Metabolic syndrome n=500). Clinical details and follow-up clinical history of the subjects and their biochemical parameters were recorded. According to the evaluation there was 500 healthy group the alpha feto protein levels are the mean range is 3.31 ng/mL. Alpha feto-protein compared with healthy group metabolic syndrome groups minimum median range is 25.77 ng/mL and maximum median range is 141.1 ng/mL. Our study results are indicating that alpha feto protein levels are high in metabolic syndrome patients. Alpha feto protein levels compared with various metabolic syndromes shown in the table (Table-2).

Table 2: Confidence Interval for mean by metabolic Syndrome

Patient Status	Number	Mean	25%	50%	75%
Normal	500	3.418	2.1	3.10	4.6
Diabetes	74	28.09	3.4	4.60	20.5
Hyperbilirubinemia	100	46.76	2.2	4.45	16.9
Hyperlipidemia	100	28.63	2.1	4.00	22.6
Pre-Diabetes	26	25.77	4.8	9.25	48.3
Uremia	100	41.42	2.3	4.28	23.2
Hyperlipidemia with Diabetes	40	36.39	3.8	11.0	59.0
Uremia with Diabetes	40	33.23	2.1	4.10	41.3
Uremia- Hyperlipidemia-Diabetes	20	141.1	7.9	79.6	183.9

Alpha fetoprotein levels 95% confidence Interval the healthy group had the range between 3.03-3.79 ng/mL. The metabolic syndrome group minimum range between 7.40-40.78 ng/mL. Our study results in 95 % of confidence Interval showing that strong association of alpha feto protein with various metabolic syndromes (Table-3).

Table 3: Confidence Interval (95%) for mean by metabolic Syndrome

Patient Status	95% Confidence Interval for Mean by metabolic Syndrome (Alpha feto-protein (AFP) Levels in ng/mL)
Normal	3.03-3.79
Pre-Diabetes	10.75-40.78
Diabetes	14.25-41.93
Hyperbilirubinemia	13.24-80.28
Hyperlipidemia	10.06-47.19
Uremia	7.40-75.45
Uremia with Diabetes	9.50-56.96
Hyperlipidemia with Diabetes	13.11-59.66
Uremia- Hyperlipidemia-Diabetes	29.79-252.51

Alpha fetoprotein levels in other metabolic or diabetes mellitus group patients evaluated according to age and metabolic markers such as fasting plasma glucose, insulin level, glycosylated hemoglobin and insulin resistance. Alpha fetoprotein levels were tended to decrease with increasing age. When patients evaluated according to fasting plasma glucose levels, serum alpha fetoprotein levels decreased significantly as fasting blood glucose levels increased ($p<0.009$). Table 4 and 5 summarized relations between alpha fetoprotein and metabolic markers.

The mean body mass index was 21.70±4.56 in control group, 28.30±5.58 in metabolic syndrome groups. Mean alpha fetoprotein levels in metabolic syndrome group compared with Control group were significantly high. (Control, 3.10±3.31; cluster of metabolic syndrome, 4.60 ±0.41). When metabolic syndrome or diabetes mellitus patients were compared with control group alpha fetoprotein levels were significantly higher in metabolic syndrome group. ($p<0.05$) (Table 4 and Table-5).

Table 4: Multivariate Regression Model among Patient

Parameter	Coefficient of variation	Standard error	t	P Value	[0.025	0.975]
Age	-0.2568	0.276	-0.931	0.353	-0.799	0.285
Systolic Blood Pressure	0.3316	0.578	0.574	0.567	-0.804	1.468
Diastolic Blood Pressure	-0.2566	0.637	-0.403	0.687	-1.509	0.995
Body Mass Index (BMI)	-0.8455	0.866	-0.976	0.330	-2.548	0.857
Fasting Blood Sugar (FBS)	0.2384	0.282	0.844	0.009	-0.317	0.793
Post Prandial Blood Sugar (PPBS)	0.2151	0.149	1.441	0.150	-0.078	0.508
Glycated hemoglobin (HbA1c)	-11.0575	3.971	-2.785	0.006	-18.86	-3.255
Total cholesterol	0.1936	0.118	1.647	0.100	-0.037	0.425
High-density lipoprotein (HDL) cholesterol	-1.1408	0.41	-2.782	0.006	-1.947	-0.335
Triglycerides	-0.0401	0.046	-0.864	0.008	-0.131	0.051
Low-density lipoprotein(LDL) cholesterol	-0.2002	0.134	-1.492	0.136	-0.464	0.064
Lactate dehydrogenase (LDH)	-0.0235	0.035	-0.666	0.506	-0.093	0.046
Blood urea nitrogen (BUN)	0.0145	0.168	0.087	0.931	-0.315	0.344
Total Bilirubin (TBI)	13.4279	2.508	5.355	0.000	8.500	18.355
Direct Bilirubin (DBI)	-15.5193	3.477	-4.463	0.000	-22.352	-8.686
Creatinine	7.9971	6.705	1.193	0.234	-5.179	21.173
Aspartate transaminase (AST)	-0.0144	0.043	-0.332	0.740	-0.099	0.071
Alanine transaminase (ALT)	0.154	0.099	1.553	0.121	-0.041	0.349
Alkaline phosphatase (ALP)	0.0255	0.024	1.044	0.297	-0.023	0.074
Fasting Insulin (IRI)	-0.2183	0.418	-0.523	0.601	-1.039	0.602
Homeostatic Model Assessment for Insulin Resistance (HOMA-IR)	1.7468	1.432	1.22	0.223	-1.067	4.561
C-reactive protein (CRP)	0.0315	0.006	5.17	0.000	0.020	0.044
Interleukin-6 (IL-6)	0.0001	0.046	0.003	0.998	-0.090	0.090
Prostate-Specific Antigen (PSA)	0.0584	0.714	0.082	0.935	-1.344	1.461
Estradiol (Ee2)	-0.1184	0.713	-0.166	0.868	-1.519	1.282

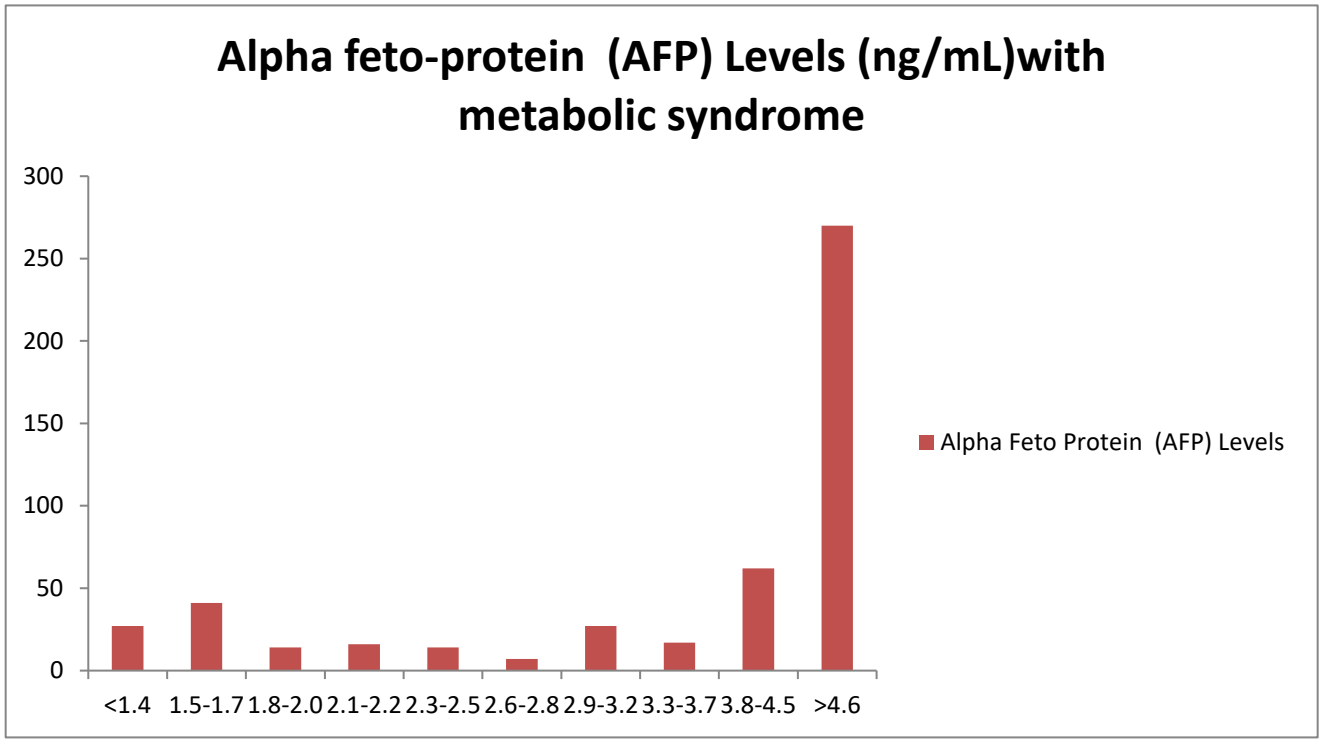
Table 5: Multivariate Regression Model among Control

Parameter	Coefficient of variation	Standard error	t	P Value	[0.025	0.975]
Age	0.0055	0.011	0.512	0.609	-0.016	0.027
Systolic Blood Pressure	-0.0118	0.031	-0.386	0.700	-0.072	0.048
Diastolic Blood Pressure	0.0173	0.034	0.501	0.617	-0.05	0.085
Body Mass Index (BMI)	0.0061	0.034	0.178	0.859	-0.062	0.074
Fasting Blood Sugar (FBS)	-0.08	0.093	-0.859	0.391	-0.263	0.103
Post Prandial Blood Sugar (PPBS)	0.0021	0.005	0.397	0.691	-0.008	0.012
Glycated hemoglobin (HbA1c)	-0.7112	0.32	-2.22	0.027	-1.341	-0.082
Total cholesterol	-0.0005	0.005	-0.102	0.919	-0.01	0.009
High-density lipoprotein (HDL) cholesterol	-0.0076	0.022	-0.345	0.730	-0.051	0.036
Triglycerides	-0.0021	0.002	-0.859	0.391	-0.007	0.003
Low-density lipoprotein(LDL) cholesterol	0.0003	0.009	0.036	0.971	-0.018	0.018
Lactate dehydrogenase (LDH)	0.0064	0.011	0.598	0.550	-0.015	0.027
Blood urea nitrogen (BUN)	-0.0009	0.012	-0.075	0.940	-0.024	0.022
Total Bilirubin (TBI)	0.0031	0.08	0.038	0.969	-0.155	0.161
Direct Bilirubin (DBI)	0.0093	0.083	0.113	0.910	-0.153	0.172
Creatinine	-0.0347	0.357	-0.097	0.923	-0.735	0.666
Aspartate transaminase (AST)	-0.0081	0.01	-0.78	0.436	-0.028	0.012
Alanine transaminase (ALT)	-0.0023	0.009	-0.26	0.795	-0.02	0.015
Alkaline phosphatase (ALP)	0.0005	0.002	0.313	0.754	-0.003	0.004
Fasting Insulin (IRI)	-0.9438	0.998	-0.946	0.345	-2.904	1.017
Homeostatic Model Assessment for Insulin Resistance (HOMA-IR)	4.2629	4.578	0.931	0.352	-4.732	13.258
C-reactive protein (CRP)	-0.1949	0.229	-0.849	0.396	-0.646	0.256
Interleukin-6 (IL-6)	-0.4628	0.545	-0.849	0.396	-1.534	0.608
Prostate-Specific Antigen (PSA)	0.0514	0.146	0.353	0.725	-0.235	0.338
Estradiol (Ee2)	-0.0002	0.001	-0.231	0.817	-0.002	0.002

Risk factors for the presence of metabolic syndrome (MS)

Univariate and multivariate logistic regression analyses were used to analyze the risk factors for metabolic syndrome in these asymptomatic subjects. In the multivariate regression model, serum alpha-fetoprotein levels were associated with an increased risk for metabolic syndrome. After adjusting for age, waist circumference (WC), Body mass index (BMI), Systolic blood pressure (SBP), Diastolic blood pressure (DBP, Triglycerides (p Value-0.008), High-density lipoprotein (HDL) cholesterol(p Value-0.006), Fasting plasma glucose (p Value-0.009), HbA1c (p Value-0.006), prevalence of Fatty Liver disease using multivariate logistic analysis, Alpha feto protein levels were also associated with an increased risk for metabolic syndrome (MS). The association between Alpha fetoprotein and the presence of components of metabolic syndrome in the asymptomatic subjects was also analyzed. The results did not show an association between alpha feto protein levels and the presence of central obesity, elevated blood pressure. However, Alpha feto protein levels were associated with the presence of reduced HDL-Cholesterol and elevated Fasting plasma glucose. Analysis of the association between higher Alpha feto protein (AFP) (>4.6 ng/mL). These results suggest that the presence of reduced HDL-cholesterol and elevated Fasting plasma glucose may play a major role in the association between Alpha fetoprotein (AFP) and metabolic syndrome (MS), while elevated Blood pressure and elevated triglycerides may influence the association.

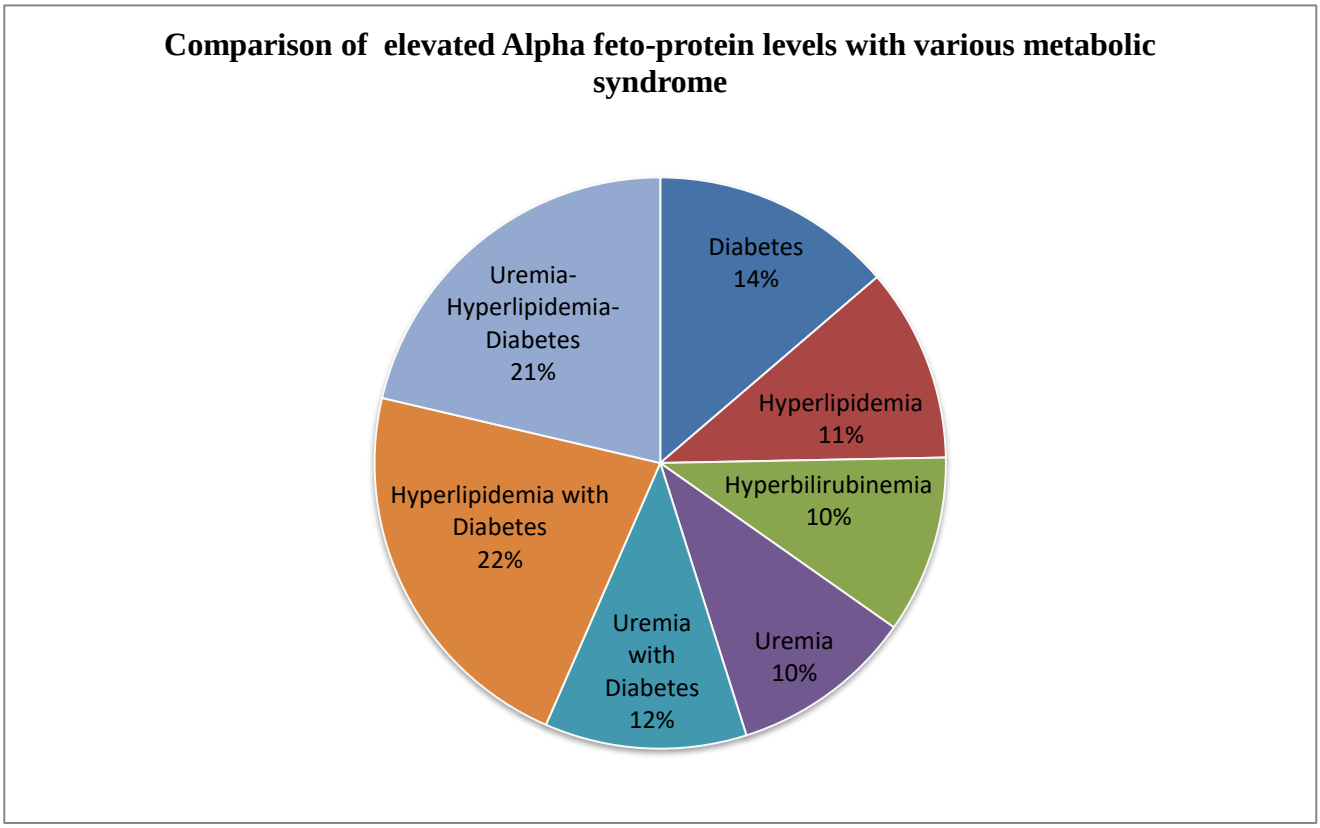
Fig-2: Alpha feto-protein (AFP) Levels with metabolic syndrome



The linkage of alpha-fetoprotein with cluster of Metabolic Syndrome

Recent study Correlation between liver biomarkers and other variables, both groups had some correlations of liver biomarkers to inflammatory (amylase and RA Factor) and cardiac Biomarkers (LDH and CK), or alpha feto protein, indicating that elevated levels in liver Biomarkers may be associated with inflammation, cardiovascular disease or liver disorders. In clinical practice, alpha feto protein levels are elevated in various clinical situations, which include hepatocellular carcinoma, acute, or chronic viral hepatitis, chronic liver disease, and gonadal tumors (Collier and Sherman, 1998). Recently, Babali et al. (2009) have reported that subjects with nonalcoholic fatty liver disease (having increased obesity, AST, ALT, cholesterol, triglyceride and glucose levels,Increased Insulin Levels) have higher alpha feto protein levels than those without nonalcoholic fatty liver disease and that alpha feto protein levels rise as the grade of liver steatosis increases [48].

Fig-3: Comparison of Alpha feto-protein with various metabolic syndromes



The linkage of alpha-fetoprotein with Diabetes, Hypertension, Dyslipidemia Obesities, nonalcoholic steatohepatitis (NASH)

Obesity is a common risk factor for Non Alcoholic fatty Liver Diseases as well as Type 2 Diabetes Mellitus due to the development of insulin Resistance. The risk of developing diabetes mellitus even at a lower Body mass index is peculiar to the Asians where normal weight individuals with a higher prevalence of central obesity (without generalized obesity) have increased predisposition to develop Type 2 Diabetes Mellitus. Recent Study shows association of obesity with Non Alcoholic fatty Liver Diseases emerges from studies on patients undergoing bariatric or gastric bypass surgery where the prevalence of Non Alcoholic fatty Liver Diseases and Nonalcoholic steatohepatitis (NASH) ranges from 85 to 98 per cent and 24 to 98 per cent, respectively. The study on morbidly obese patients of south India, Non Alcoholic fatty Liver Diseases and Nonalcoholic steatohepatitis were diagnosed in 65.7 and 33.6 per cent, respectively and 14.1 per cent of these had advanced fibrosis on histopathological examination study. The study based on, in non-obese Asians, Non Alcoholic fatty Liver Diseases cases were lower (15-21%). The other study also shows meta analysis conducted Europe Excessive deposition of triglycerides in the liver interferes with the metabolism of glucose and fatty acids, leading to adverse effects of developing cancers [49].

The linkage of alpha-fetoprotein with Cancer

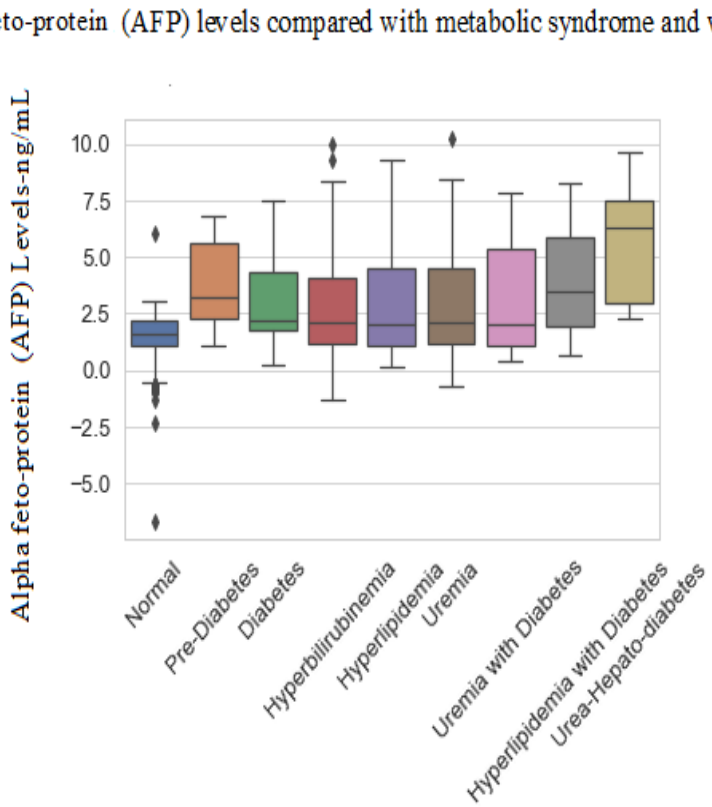
Recent study investigated 6237 French men, hyperinsulinemia was associated with an approximately 3-fold increased risk for Cancer. In the other role in glucose and lipid metabolism, insulin has pleotropic effects that regulate inflammatory and other pathways. Insulin-like growth factor-1 and insulin receptor substrate-1 an important substrate of Insulin-like growth factor-1, are downstream targets of insulin that are crucial to cellular proliferation. Cancer cells overexpress both Insulin-like growth factor and insulin receptor substrate-1–mediatd signals may act as survival factors and protect against transforming growth factor induced apoptosis in cancer, which may contribute to hepatic oncogenesis. In other state Insulin resistance is also associated with increased oxidative stress. The generation of reactive oxygen species leads to upregulation of proinflammatory cytokines such as tumor necrosis factor and one of the upregulation can be promote tumor growth via both anti-apoptotic action and leads to upregulation of proinflammatory cytokines through activation of nuclear factor-kappa B. Oxidative stress may be the influencing factor for tumorigenesis via inflammation and dysregulated cell proliferation; however, it may also directly induce cancer-promoting gene mutations. Trans-4-hydroxy-2-nonenal, a product of lipid peroxidation, is important in cancers that are caused by mutations of the p53 gene. The p53 pathway targets include wild-type p53 activated fragment, a cyclin-dependent kinase inhibitor and cell growth arrest or DNA damage gene,a p53-regulated and DNA damage-inducible protein, and the protein, which plays a role in G2/M

phase arrest insulin receptor substrate-1 can promote hepatocyte proliferation via mitogen-activated protein kinase and phosphatidylinositol–3 kinase, important pathways in cancer development.In a way that arouses curiosity or interest cirrhotic patients with cancer and impaired glucose metabolism that causes postprandial hyperinsulinemia have accelerated cancer growth. The PI3K/phosphatase and tensin homo-log (PTEN)/Akt axis is a key regulator of critical cellular functions such as insulin and other growth factor signaling, glucose and lipid homeostasis, and apoptosis. PTEN (tensin homo-log) acts as a phosphoinositide phosphatase which terminates PI3K-propagated cell signaling. The homo-log is a tumor suppressor that is dysregulated in obesity, insulin resistance, and Type 2 diabetes, it leads to another mechanism through which Non Alcoholic fatty Liver Diseases, Type 2 diabetes and insulin resistance could promote tumor growth in the cancer [50].

The linkage of alpha-fetoprotein with liver disease

Fatty liver disease is a most common liver disease that may progress to cirrhosis and hepatocellular carcinoma. Recent and our study, observed that serum alpha-fetoprotein levels are significantly increased in subjects with fatty liver disease, and that Alpha feto protein levels are significantly associated with different metabolic biomarkers. The Statistics Univariate logistic analysis showed that elevated serum AFP levels are associated with an increased risk of fatty liver and other disease. The Statistics multivariate logistic regression analysis showed that alpha-fetoprotein is not independently associated with the risk factors for fatty liver diseases [51]. Our results suggest a significant association between Alpha feto protein and Fatty liver disease, as well as suggesting that Alpha feto protein acts as a cofactor, but not as an independent factor, for Fatty liver disease and useful for monitoring the liver damage.

Fig-4. Alpha feto-protein (AFP) levels compared with metabolic syndrome and without Metabolic Syndrome



Discussion

In this study, serum Alpha fetoprotein (AFP) levels significantly correlated with waist circumference (WC), HDL-cholesterol, and Triglycerides, in participants with metabolic syndrome (MS).

Participants with metabolic syndrome (MS) had significantly higher alpha-fetoprotein (AFP), levels ($p < 0.001$) than those without metabolic syndrome (MS), although all alpha-fetoprotein (AFP), levels were within the reference interval. We evaluated the association between the components of metabolic syndrome (MS) (central obesity, elevated Blood pressure, elevated Triglycerides, reduced HDL-cholesterol, and elevated Fasting plasma glucose) and alpha-fetoprotein (AFP), levels, and found that AFP levels in the elevated Triglycerides, reduced HDL- cholesterol, and

elevated Fasting plasma glucose groups were significantly different compared with alpha-fetoprotein (AFP) in the normal Triglycerides, HDL- cholesterol, and Fasting plasma glucose groups. Furthermore, we found that in the higher AFP group (>4.6 ng/mL), there was a higher prevalence of metabolic syndrome (MS), elevated Blood pressure, elevated Triglycerides, and elevated Fasting plasma glucose. Logistic regression analyses showed an association between alpha-fetoprotein (AFP) levels and increased risk for metabolic syndrome, reduced HDL- cholesterol, and elevated Fasting plasma glucose, but no association between obesity, elevated Blood pressure, or Triglycerides. These results suggest a significant association between alpha-fetoprotein and metabolic syndrome. Impaired glucose metabolism and dyslipidemia may play a major role in the association between alpha-fetoprotein and metabolic syndrome.

Verhagen et al. [18] found that the prevalence of metabolic syndrome was highest in the Insulin resistance (IR) group, and Insulin resistance increased with the number of metabolic syndrome components. Insulin resistance is associated with excessive fat accumulation in ectopic tissues, such as the liver, and plays a crucial role in the pathologic manifestations of metabolic syndrome, and is accompanied by elevated blood pressure, elevated Triglycerides, reduced HDL-cholesterol, and impaired Fasting plasma glucose [2, 19]. Some studies previously reported that Fatty liver disease (FLD) was more prevalent in patients with metabolic syndrome than in the general population, and Fatty liver disease may be the hepatic component of metabolic syndrome because metabolic syndrome and Fatty liver disease have a particularly close relationship [20–23].

The main potential mechanisms accounting for the association between metabolic syndrome and high alpha-fetoprotein levels may be Insulin resistance and hepatic steatosis. Hepatocytes play major roles in glucose homeostasis and can store or produce glucose depending on physical requirements (necessary condition) [19]. Insulin resistance impacts the hepatic glucose homeostatic pathways and leads to the release of free fatty acids from adipose tissue, elevates hepatic production of very low-density lipoproteins (VLDL), reduces high-density lipoproteins (HDL), and promotes inflammation and endoplasmic reticulum stress [18, 19]. Recent other study with a large cohort, Porepa et al. [24] found newly diagnosed diabetes in adults with or without pre-existing hypertension, dyslipidemia, or obesity who appeared to be at higher risk for advanced liver disease and lower hepatic insulin sensitivity leads to elevated hepatic glucose production, hyperinsulinemia, increased β-cell mass and hyperglycemia than isolated hypertension, dyslipidemia, or obesity. In a study by Matsuzaka et al. [25], in which hepatic steatosis was associated with the development of Insulin resistance, it was remained unclear whether IR leads to hepatic steatosis or whether steatosis enhances Insulin resistance and additionally, hepatic steatosis is associated with dyslipidemia and provocative markers [20, 21, 25]. Other studies have reported that increased chronic inflammation and oxidative stress in accumulated adipose tissue is an important pathogenic mechanism of obesity-associated metabolic syndrome [26–29]. Another potential mechanism accounting for the association between metabolic syndrome and high alpha-fetoprotein levels may be a state of chronic low-level inflammation and oxidative stress.

The serum Alpha feto protein is generally recognized as an important tumor marker and has specific diagnostic utilities [30]. Continuous increases of Alpha feto protein levels up to the pathological range in adults has been associated with hepato-cellular carcinoma, gastric cancer, hepatic necrosis, hepatic cirrhosis, acute hepatitis, chronic active hepatitis, Wiskott–Aldrich syndrome, ataxia telangiectasia and pregnancy [30, 31]. Continuous elevation of serum Alpha feto protein has rarely been found in participants with no obvious pathology [30, 32].

Adult hepatocytes re-express Alpha feto protein mainly through three mechanisms:

(i) The Adult hepatocytes are regarded as functional stem cells have the inherent capacity for regeneration [33]. When hepatocytes regenerate, Alpha feto protein levels increase [34]. Hepatocyte proliferation during reparative and regenerating growth is associated with progenitor cell activation and is revealed by observation of rising serum Alpha feto protein levels, cellular Alpha feto protein immune expression, and AFP gene expression during hepatocyte division in liver regeneration after chemical injury/damage or partial hepatectomy [33–36].

(ii) The DNA damage to hepatocytes induced by oxidative stress results in the activation of transcription factors and induces the expression of proto-oncogenes by DNA methylation, leading to genomic lack of stability and the result of hepatocarcinogenesis. Additionally, hepatomas that originate from spontaneously retro-differentiated hepatocytes can express alpha feto-protein [27, 37, 38].

(iii) In very extensive or chronic inflammation liver injury models, when the regenerative capacity of hepatocytes is impeded, reconstitution of the liver occurs through biliary epithelial cells (oval cells) that possess regenerative capacity with multilinear differentiation potential. Biliary epithelial cell proliferation leads to in- creases in Alpha feto protein-specific immune expression [34, 39, 40].

The Recent large sample cross-sectional study by Xu et al. [16] found that participants with Fatty liver disease had higher alpha feto protein levels than those without Fatty liver disease, and suggested that hepatocyte necrosis and subsequent hepatic regeneration may be responsible for the elevation of serum alpha feto protein levels. Babali et al. [12] found that patients with Non-alcoholic Fatty liver disease had higher Alpha feto protein levels, and suggested that hepatic inflammation, regeneration and/or fibrosis may be responsible for the elevation of serum alpha feto protein

levels in patients with severe fatty liver. We also considered it possible that hepatocyte steatosis and subsequent hepatic regeneration are responsible for the elevation of serum Alpha feto protein levels in patients with metabolic syndrome. Hepatic steatosis has been reported to be a common histological feature of hepatitis C viral (HCV) infection [41], and Goldstein et al. [42] found altered hepatocyte–hepatocyte interaction and loss of normal architectural arrangements leading to the elevation of serum Alpha feto protein levels in patients with chronic hepatitis.

Metabolic syndrome is a lifestyle and diet-related chronic non-communicable disease that has become a major burden on global healthcare [38, 43, 44]. Epidemiological studies indicate that nutrition plays a very important role in the development and progression of metabolic syndrome. A diet high in fat, cholesterol and sugar promotes the redistribution of body fat from peripheral to visceral adipose tissue and affects total (absolute) body weight [43, 44].

Recent animal experiments have been reported in which liver tissue sections from rats with diet-induced metabolic syndrome showed increased wet weight, hepatocyte damage (hepatocyte injury), fat vacuoles, fibrosis, collagen deposition, ballooning (cell size rise quickly) and inflammatory cell infiltration. Body fat mass was found to increase in these studies and impaired glucose tolerance (IGT), plasma lipid abnormalities, hyperinsulinemia and increased liver enzyme activity were observed [45, 46].

Recent study reported as Oxidative stress has emerged as a central player in some chronic metabolic diseases and leads to the oxidation of lipids, proteins, and nucleic acids. The above mentioned pathological liver changes and stages of fibrosis were also found to be associated with oxidative DNA damage [27, 38]. Nishida N et al. found that patients with high serum alpha fetoprotein levels and high degrees of ballooning and inflammatory infiltration had an accumulation of oxidative DNA damage [38]. Furukawa et al. [29] found that in- creased oxidative stress led to dysregulated production of adipocytokines, and that increased reactive oxygen species (ROS) production from adipose tissue led to increased oxidative stress in the blood, which hazardously affected the liver, skeletal muscle, and the aorta in metabolic syndrome subjects. Previous study observed oval cell proliferation during liver regeneration concomitant with increased alpha feto protein expression, with the mechanism being different from alpha feto protein expression in hepatocytes [34, 39, 47]. The recent research and our study observations, we considered that oxidative stress and oval cell proliferation were responsible for the elevation of serum alpha feto protein levels in patients with metabolic syndrome.

Recent study showed that whole-body insulin resistance, an elevated Aspartate transaminase level and advanced fibrosis are independently and directly correlated with an elevated alpha feto protein level in patients with chronic hepatitis C and also found that lifestyle modification can reduce the Alpha feto protein level and whole-body Insulin resistance. To our knowledge, this is the first report to examine the relationship between the serum alpha feto-protein level and systemic IR and to show that lifestyle modification can reduce the serum alpha feto-protein level. Further prospective studies are needed to confirm whether the reduction in the serum alpha-feto protein level achieved via lifestyle modification can prevent hepatocarcinogenesis in hepatitis C virus infected patients [58].

Our study serum insulin levels were analyzed and homeostasis model of assessment-insulin resistance calculated there was relationship with alpha-feto protein elevation. Our study indicates a relationship between serum alpha feto protein levels and insulin resistance, hepatic inflammation is an important factor in the progression of chronic liver disease and is regulated by chemokines.

Conclusion

In conclusion, the results from this study suggest that participants with metabolic syndrome have significantly higher alpha feto-protein levels than those without metabolic syndrome. Serum Alpha feto-protein levels were significantly associated with the prevalence of metabolic syndrome; these study results suggest that significant association between alpha-fetoprotein and metabolic syndrome (fatty liver, cardiovascular diseases, neurological dysfunction and neural tube defects). This study showing in the following linkages particularly in the female subjects (45.6%) compared to male subjects (37.6 %). (i) The linkage of alpha-fetoprotein with cluster of Metabolic Syndrome (ii) The linkage of alpha-fetoprotein with Diabetes, Hypertension, Dyslipidemia Obesities, nonalcoholic steatohepatitis (NASH) (iii) The linkage of alpha-fetoprotein with Cancer, (iv) The linkage of alpha-fetoprotein with liver disease. The important play role in the oxidative stress induces insulin resistance one of the factor for the alpha feto protein elevation. Though the linking of serum Alpha feto protein levels and the prevalence of metabolic syndrome, The alpha feto protein elevation which might be useful for early diagnosis and prevalence of liver disease, cancer and Cluster of metabolic syndrome in Indian population.

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