Original Article

A Review: Association of Alpha-fetoprotein With Metabolic Syndrome

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Abstract

Cluster of Metabolic syndrome is closely associated with various types of cancer. Alpha feto-protein is still used as a biomarker for liver cancer 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 relationship between alpha feto-protein and various metabolic syndrome and alpha fetoprotein may be used as metabolic markers. Liver is major organ for the metabolism if any changes in the liver leads various metabolic diseases and also severe damage develops liver diseases, injure healthy liver cells, causing cell death and inflammation and alpha fetoprotein levels are important for the diagnosis of liver cancer. Alpha feto-protein may be help for diagnosis of metabolic syndrome or liver cells damage screening.

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

INTRODUCTION

Alpha fetoprotein (AFP) is a 70 kDa single standard glycoprotein that is produced by the fetal liver and yolk sac during the earliest stage of pregnancy. The normal physiology of Alpha fetoprotein decreased rapidly after birth and remains low levels throughout life. In 1980s reported that absolute size of the fetus as well as gestational age may be play a significant role in determining maternal and fetal alpha fetoprotein concentrations, and that there is a significant relationship between maternal, cord arterial and venous, decreased levels of serum alpha fetoprotein around 14 weeks pregnant afterwards shown to be associated with a very low risk of birth defects, potentially dangerous during pregnancy period complications characterized by high blood pressure and placental complications. Alpha fetoprotein expression is mainly regulated at the transcriptional level and the gene contains an upstream regulatory region consisting of a tissue-specific promoter, three independent enhancers, and two silencer regions that down regulate the expression of the AFP gene in the liver.

There Alpha-fetoprotein enhancers are normally blocked by the gene promoter during fetal liver development and instead act on transcription of the albumin gene. Alpha-fetoprotein is measured using a chemiluminescent immunoassay, which is very useful in diagnosing liver cirrhosis or cancer. Recent studies have shown that alpha-fetoprotein is associated with metabolic syndrome, liver cell damage, and other liver diseases (1).

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 (2).

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Cirrhotic liver parenchyma cells typically evolve into liver cancer (3). Alcoholic liver disease, non-alcoholic steatohepatitis, diabetes mellitus, obesity, and genetically inherited illnesses such hemochromatosis, -1 antitrypsin deficiency, and porphyrias have all been recognised as risk factors for the development of liver damage or cancer (4).

Diabetes mellitus affects people all around the world. According to data from the International Diabetes Federation (IDF), 380 million people have diabetes worldwide in 2013. (5). Higher incidences of liver cancer and lower survival rates are associated with diabetes mellitus, a separate risk factor for the development of liver cancer (6). According to a recent meta-analysis, people with diabetes mellitus had a 2.5-fold increased chance of developing liver cancer than people without the disease (7). Obesity and its effects The development of non-alcoholic steatohepatitis is a separate risk factor for liver cancer. According to data from the United States, liver cancer mortality rates were 1.7 times higher for women with BMI > 35 and 4.5 times higher in males with BMI > 35 (8,9,10).

1.1 Diagnostic criteria for Metabolic syndrome

According to the International Diabetes Federation guidelines (IDF), metabolic syndrome is defined as having three or more of the following components:

- WC >90 cm for Indian men and >80 cm for Indian women; BMI ≥22.9 kg/m2;
- TG ≥150 mg/dL, or taking specific treatment for lipid abnormality; HDL-c < 39.83 mg/dL for men and <49.88 mg/dL for women;
- Systolic blood pressure (SBP) ≥130 mmHg, or diastolic blood pressure (DBP) ≥85 mmHg, or treatment for previously diagnosed hypertension; Fasting Plasma Glucose (FPG) ≥100 mg/dL or previously diagnosed type 2 diabetes.

The recent study showed that serum alpha-fetoprotein value significantly correlated with age, waist circumference (WC), aspartate Aminotransferase, alanine Aminotransferase, gamma glutamyltransferase, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, and Total cholesterol in participants with Metabolic syndrome.

In participants without metabolic syndrome, alpha-fetoprotein significantly correlated with aspartate Aminotransferase, alanine Aminotransferase, gamma glutamyltransferase, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, and Total cholesterol. The components of metabolic syndrome included central obesity, elevated blood pressure, elevated triglycerides, reduced high-density lipoprotein cholesterol, and elevated Fasting Plasma Glucose. The association between the components of metabolic syndrome and serum alpha-fetoprotein levels in participants with and without metabolic syndrome. Alpha-fetoprotein levels in elevated triglycerides, reduced HDL-c, and elevated Fasting Plasma Glucose groups were significantly different compared with alpha-fetoprotein in normal triglycerides, high-density lipoprotein cholesterol, and Fasting Plasma Glucose groups in all subjects. The subjects were divided into 10 groups according to deciles of serum alpha-fetoprotein levels. Across increasing serum alpha-fetoprotein deciles, the prevalence of metabolic syndrome increased.

Metabolic syndrome components according to the various guidelines as followings:

Table.1 Metabolic syndrome components and Guidelines:

World Health Organization (WHO)	**International Diabetes Federation guidelines (IDF)**	**National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III)**	**American Association of Clinical Endocrinologists (AACE)**	**European Group for the Study of Insulin Resistance (EGIR)**
Abdominal obesity: Waist-to-Hip Ratio: >0.9, BMI ≥30 kg/m², WC > 37 inches	WC >90 cm for Indian men and >80 cm for Indian women; BMI ≥22.9 kg/m2;	WC: >40 inches for men, >35 inches for women	fasting plasma glucose and two or more of the following:	Top 25% of the fasting insulin values among nondiabetic individuals and two of the following: WC: ≥94 cm for men, ≥80 cm for women
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, or treatment for previously diagnosed hypertension;	Systolic blood pressure (SBP) ≥130 mmHg, or diastolic blood pressure (DBP) ≥85 mmHg	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

Lipid Profile Triglycerides : >150 mg/dL HDL-C: <35.0 mg/dL	TG ≥150 mg/dL, HDL-c : Men: < 39.83 mg/dL, Women: <49.88 mg/dL	Triglycerides: ≥150 mg/dL HDL-C: Men: <40 mg/ dL, Women:<50 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
High Insulin Levels fasting plasma glucose : >110 mg/dL	Fasting Plasma Glucose (FPG) ≥100 mg/dL or previously diagnosed type 2 diabetes.	fasting plasma glucose : >110 mg/dL		Fasting glucose ≥6.1

The primary biomarker utilized and advised for early detection and screening of liver cancer worldwide is still alpha fetoprotein (AFP) (11). Although elevated alpha fetoprotein levels are seen in 33–65% of liver cancer patients, alpha fetoprotein is still employed as a tumour diagnostic for liver cancer. In patients with chronic hepatitis and in situations of cirrhosis, non-specific serum alpha fetoprotein increase is observed in 15 to 58% of patients (12). Numerous investigations have demonstrated a relationship between alpha fetoprotein and metabolic illness (liver cell damage, liver cancer and diabetes mellitus etc.). Studies examining the relationship between alpha fetoprotein and diabetes mellitus are few and far between.

The main goal of this review is to find out association of alpha-fetoprotein with various metabolic syndromes and to use as a biomarker for the early diagnosis for screening of liver cancer and diabetic with liver cirrhosis patients.

1.2 Prevalence of metabolic syndrome

Presence of metabolic disorder poses a risk of developing a metabolic disorder in the future and is likely to address the high lifetime risk of cardiovascular infections and other diseases.

The new report found that the overall prevalence of the metabolic condition was 4.8% (National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III), total number= 333/6889), 5.2% (American Heart Association and the National Heart, Lung, and Blood Institute (AHA/NHLBI), total number= 643/12473), 7.0% (International Diabetes Federation(IDF), total number = 971/13953) and 6.5%. % (stable, n = 430/6578).

Atherogenic dyslipidemia, characterized by low High density lipoprotein levels, was the most widely recognized part of the metabolic disorder regardless of the rules used (26.9–41.2%), followed by hypertension (16.6–26.6%), stomach fullness (6 .8–23.6%), atherogenic dyslipidemia, characterized by elevated cholesterol levels. fatty substances (8.6–15.6%) and elevated fasting glucose (2.8–15.4%) .Prevalence of metabolic disorder and parts of the metabolic condition in 26,609 children(33).

Table 2: Prevalence of metabolic disorders and metabolic status.

Country	Total (n)	Metabolic syndrome	Blood pressure	Waist circumference	Fasting plasma glucose	Triglycerides	HDL cholesterol	Author for Reference
Harmonized								
UAE	555	38 (6.8)	30 (5.4)	101 (18.2)	54 (9.7)	8 (1.4)	271 (48.8)	Al Dhaheri et al. (2016)
Brazil	2031	242 (9.0)	465 (22.9)	646 (31.8)	73 (3.6)	254 (12.5)	851 (41.9)	Martins et al. (2015)
Taiwan	355	24 (6.8)	123 (34.6)	63 (17.7)	4 (1.1)	32 (9.0)	46 (20.6)	Huang et al. (2015)
Jamaica	746	6 (0.8)	154 (20.6)	108 (14.5)	8 (1.1)	4 (0.5)	343 (46.0)	Bennett et al. (2014)

China	323	22 (6.8)	20 (6.2)	180 (55.7)	22 (6.8)	40 (12.4)	63 (19.5)	Lin et al. (2014)
Philippines	861	108 (12.5)	127 (14.8)	173 (20.1)	144 (16.7)	171 (19.9)	467 (54.2)	Sy et al. (2014)
Kenya	90	9 (10.0)	51 (56.7)	17 (18.9)	1 (1.1)	3 (3.3)	47 (52.2)	Kaduka et al. (2012)
Spain	292	18 (6.2)	48 (16.4)	81 (27.7)	11 (3.8)	24 (8.2)	49 (16.8)	Gavrila et al. (2011)
Jamaica	839	10 (1.2)	56 (6.7)	134 (16.0)	10 (1.2)	5 (0.6)	393 (46.8)	Ferguson et al. (2010)
India	486	12(2.5)	15 (3.1)	51 (10.5)	31 (6.4)	27 (5.6)	150 (30.9)	Gupta et al. (2009)
Overall	6578	430 (6.5%)	1089 (16.6%)	1554 (23.6%)	358 (5.4%)	568 (8.6%)	2707 (41.2%)	
National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III)								
India	2503	1004 (46.2%)	865 (39.8%)	362 (16.6%)	1116 (51.3%)	982 (45.1%)	982 (45.1%)	Jonas et al,.(2022)
Birbhum	9886	1035 (10.7%)	4810 (29.7%)	4810 (14.6%)	4810 (16.6%)	4810 (29.7%)	4810 (30.2%)	Anamitra et al. (2018)
India	473	41 (8.7)	123 (26.0)	76 (16.1)	42 (8.9)	37 (7.8)	184 (38.9)	Manjunath et al. (2014)
India	85	8 (9.4)	5 (5.9)	18 (21.2)	7 (8.2)	18 (21.2)	53 (62.4)	Sinha et al. (2013)
China	2532	101 (4.0)	519 (20.5)	79 (3.1)	58 (2.3)	241 (9.5)	742 (29.3)	Li et al. (2010)
Russia	862	23 (2.7)	149 (17.3)	19 (2.2)	6 (0.7)	83 (9.6)	266 (30.9)	Sidorenkov et al. (2010)
Turkey	84	10 (11.9)	20 (23.8)	25 (29.8)	11 (13.1)	24 (28.6)	19 (22.6)	Gündogan et al. (2009)a
Turkey	1306	93 (7.1)	424 (32.5)	182 (13.9)	25 (1.9)	183 (14.0)	318 (21.3)	Erem et al. (2008)
Finland	1099	38 (3.5)	565 (51.4)	51 (4.6)	25 (2.3)	31 (2.8)	212 (19.3)	Mikkola et al. (2007)
Turkey	285	18 (6.3)	25 (8.8)	14 (4.9)	13 (4.6)	115 (40.4)	40 (14.0)	Soysal et al. (2005)
USA	163	1 (0.6)	2 (1.2)	3 (1.8)	3 (1.8)	4 (2.5)	22 (13.5)	Huang et al. (2004)

Overall	19278	333 (4.8%)	1832 (26.6%)	467 (6.8%)	190 (2.8%)	736 (10.7%)	1856 (26.9%)	
International Diabetes Federation(IDF)								
India	250	55 (22.0)	21 (8.4)	139 (55.6)	44 (17.6)	71 (29.2)	93 (37.2)	Kanitkar et al. (2015)
Brazil	2031	242 (11.9)	465 (22.9)	646 (31.8)	73 (3.6)	254 (12.5)	851 (41.9)	Martins et al. (2015)
Philippines	861	108 (9.1)	127 (14.8)	173 (20.1)	144 (16.7)	171 (19.9)	467 (54.2)	Sy et al. (2014)
USA	376	35 (9.3)	38 (10.1)	43 (11.4)	42(11.2)	21 (5.6)	73 (19.4)	Tope et al. (2013)
Brazil	711	28 (3.9)	71 (10.0)	90 (12.7)	35 (1.4)	35 (4.9)	313 (44.0)	da Costa et al. (2011)
Spain	292	18 (6.2)	48 (16.4)	81 (27.7)	11 (3.8)	24 (8.2)	49 (16.8)	Gavrila et al. (2011)
Brazil	3599	240 (6.7)	883 (24.5)	618 (17.2)	1322 (36.7)	598 (16.6)	694 (19.3)	da Silveira et al. (2010)a
China	2532	147 (5.8)	519 (20.5)	79 (3.1)	58 (2.3)	241 (9.5)	742 (29.3)	Li et al. (2010)
Qatar	203	16 (7.9)	34 (16.7)	16 (7.9)	8 (3.9)	30 (14.8)	43 (21.2)	Bener et al. (2009)
Turkey	84	16 (19.0)	20 (23.8)	25 (29.8)	11 (13.1)	24 (28.6)	19 (22.6)	Gündogan et al. (2009)a
Finland	1099	75 (6.8)	565 (51.4)	134 (12.2)	221 (20.1)	31 (2.8)	212 (19.3)	Mikkola et al. (2007)
Norway	1615	19 (1.2)	499 (30.9)	414 (25.6)	179 (11.1)	221 (13.7)	459 (28.4)	Hildrum et al. (2007)
USA	300	2 (0.7)	11 (3.7)	8 (2.7)	27 (9.0)	27 (9.0)	73 (24.3)	Huang et al. (2007)
Overall	13,953	971 (7.0%)	3301 (23.7%)	2466 (17.7%)	2150 (15.4%)	1750 (12.5%)	4088 (29.3%)	
American Heart Association and the National Heart, Lung, and Blood Institute (AHA/NHLBI)								
China	200	1 (0.5)	24 (12.0)	4 (2.0)	6 (3.0)	13 (6.5)	19 (9.5)	Cheserek et al. (2014)
USA	1610	81 (5.0)	403 (25.0)	209 (130)	64 (4.0)	258 (16.0)	467 (29.0)	Morrell et al. (2013)

Iran	203	13 (6.4)	1 (0.5)	26 (12.8)	35 (17.2)	47 (23.2)	85 (41.9)	Shahbazian et al. (2013)
USA	376	45 (12.0)	38 (10.1)	43 (11.4)	42 (11.2)	21 (5.6)	73 (19.4)	Tope et al. (2013)
USA	2103	103 (4.9)	681 (32.4)	94 (4.5)	177 (8.4)	350 (16.6)	538 (25.6)	Morrell et al. (2012)
USA	207	14 (6.8)	34 (16.4)	12 (5.8)	15 (7.2)	28 (13.5)	98 (47.3)	Dalleck and Kjelland (2012)
Spain	292	10 (3.4)	48 (16.4)	31 (10.6)	11 (3.8)	24 (8.2)	49 (16.8)	Gavrila et al. (2011)
USA	189	7 (3.7)	4 (2.1)	14 (7.4)	14 (7.4)	33 (17.5)	38 (20.1)	Fernandes and Lofgren (2011)
Brazil	3599	213 (5.9)	883 (24.5)	269 (7.5)	610 (16.9)	598 (16.6)	694 (19.3)	da Silveira et al. (2010)
Iran	934	70 (7.5)	56 (6.0)	31 (9.7)	74 (7.9)	246 (26.3)	714 (76.4)	Sharifi et al. (2009)
Qatar	203	15 (7.4)	34 (16.7)	16 (7.9)	8 (3.9)	30 (14.8)	43 (21.2)	Bener et al. (2009)
Netherlands	642	48 (7.5)	274 (42.7)	78 (12.1)	75 (11.7)	50 (7.8)	187 (29.1)	de Kroon et al. (2008)
Norway	1615	19 (1.2)	499 (30.9)	414 (25.6)	179 (11.1)	221 (13.7)	459 (28.4)	Hildrum et al. (2007)
USA	300	4 (1.3)	11 (3.7)	8 (2.7)	27 (9.0)	27 (9.0)	73 (24.3)	Huang et al. (2007)
Overall	12,473	643 (5.2%)	2990 (24.0%)	1309 (10.5%)	1337 (10.7%)	1946 (15.6%)	3537 (28.4%)	

1.3 Association of Alpha fetoprotein in Metabolic Pathway and Cell Signal Pathway

Oxidative stress, which causes the oxidation of lipids, proteins, and nucleic acids, has been shown to play a significant role in chronic metabolic diseases, according to a recent study. Unexpectedly, oxidative DNA damage is connected to the pathological changes that occur in the liver as well as the various stages of fibrosis. Serum alpha fetoprotein levels that are high can indicate cell damage, ballooning, inflammatory infiltration, and the accumulation of oxidative DNA damage in the cells. Adipocytokine production is reduced as a result of elevated oxidative stress, and elevated reactive oxygen species (ROS) production from adipose tissue raises blood levels of oxidative stress, causing toxicity in metabolic syndrome subjects' liver, skeletal muscle, and main artery. In contrast to alpha fetoprotein expression in hepatocytes, oval cell proliferation during liver regeneration is associated with increased alpha fetoprotein expression. Alpha-fetoprotein levels are elevated in patients with metabolic syndrome as a result of oxidative stress and oval cell proliferation. Several metabolic pathways and enzymes, including NAD kinase (NADH), pentose phosphate pathway, folate-mediated one-carbon metabolism, malic enzymes (ME), nicotinamide nucleotide transhydrogenase, cytosolic or mitochondrial NADP-dependent isocitrate

dehydrogenase, glutamine metabolism, and fatty acid oxidation are primarily responsible for maintaining homeostasis of nicotinamide adenine dinucleotide phosphate. The relative contribution of these pathways and enzymes to the overall production of nicotinamide adenine dinucleotide phosphate in cells is still at a satisfactory level. produce nicotinamide adenine dinucleotide phosphate in cancer and proliferating cells. For cancer nicotinamide adenine dinucleotide phosphate homeostasis, the various processes and enzymes work together.For instance, fatty acid oxidation accelerates the citric acid cycle to produce citrate, which is exported to the cytosol by Malic Enzyme 1 and Isocitrate dehydrogenase 1 to participate in the production of nicotinamide adenine dinucleotide phosphate. The pathways by which nicotinamide adenine dinucleotide phosphate homeostasis and its de novo synthesis functions, and the relative roles that related enzymes and pathways play in cancer. Through the regulation of cell proliferation and apoptosis, the Hippo signaling pathway plays an important role in the regulation of organ size. in multicellular organisms. Suppression of this pathway promotes significant and extensive tissue growth. By phosphorylation and inhibition of the y-associated protein (YAP) transcription coactivators and the PDZ-binding motif (TAZ) transcription coactivator, which are important regulators of proliferation and apoptosis in mammals, the Hippo signaling pathway, which is highly conserved, limits organ size.As a link and integrator for numerous known pathways, including the Wnt pathway, G protein-coupled receptor (GPCR), epidermal growth factor (EGF), bone morphogenetic protein/transforming growth factor beta, and the Notch pathway, yes-associated protein (YAP) and a transcription coactivator with a PDZ-binding motif (TAZ) play an important role in cell fate control and tissue regeneration (30).

Alpha fetoprotein will bind to alpha fetoprotein receptors and activate the cyclic nucleoside 3',5'-monophosphate (cAMP)-enzyme A (PKA) protein pathway and induce Ca2+ influx, which will increase intracellular nucleoside 3',5'-cyclic monophosphate, enhances DNA synthesis, promotes the expression of c-fos, c-jun and ras oncogenes and stimulates the proliferation of carcinoma cells, in addition, when bound to alpha fetoprotein receptors, it triggers growth-stimulating signals and promotes alpha fetoprotein endocytosis. The endocytosed alpha fetoprotein then binds to specific proteins in the cytoplasm, causing activation or inhibition of signaling pathways. Endocytated alpha-fetoprotein has the ability to interact with phosphatase and tensin homologue (PTEN) and activate the PI3K/AKT/mTOR pathway, which promotes cancer cell development by increasing expression of the mammalian target of rapamycin (mTOR) protein.

Alpha fetoprotein receptors that bind to membrane bilayers and are then packaged into endosomal and vesicular bodies, which are transported by cells via endocytosis along the Golgi pathway. Finally, the vesicles release alpha fetoprotein and alpha fetoprotein receptors, which have been found in the nucleus and cytoplasm and has been involved in recycling and lysosomal degradation, as well as in signal transduction pathways. Scavenging alpha fetoprotein has also been identified as a member of the scavenger family that included the mannose receptor, and was found in small amounts on various cell membranes by various receptors (30).

In addition to being used as a clinical biomarker for cancer diagnosis, alpha-fetoprotein (AFP) regulates cell proliferation, migration, apoptosis and immune response evasion, and induces malignant transformation of cancer cells. Much of the malignant behavior of alpha fetoprotein is mediated by its receptors (AFPR), which are found on the cell surface and are expressed in cells when alpha fetoprotein is present.These results suggest that alpha fetoprotein receptor expression not only accompanies alpha fetoprotein expression, but also has the potential to mediate extracellular alpha fetoprotein endocytosis, thereby inducing cell growth and differentiation and promoting carcinogenesis.The ability of alpha fetoprotein to bind to alpha fetoprotein receptors leads to activation of cyclic adenosine monophosphate (cAMP) protein kinase A (PKA) and induction of Ca2+ influx. This, in turn, increases intracellular levels of cAMP and PKA, increases DNA synthesis, increases oncogene expression, and increases the growth of liver cancer cells. The receptors for endocytosed AFP, which we also refer to as cytoplasmic alpha fetoprotein, then bind to a number of cytoplasmic proteins causing either activation or inhibition of signaling pathways. Endocytated alpha-fetoprotein is able to interact with phosphatase and tensin. Homolog (PTEN) and activates the PI3K/AKT/mTOR pathway, which enhances mTOR protein expression and promotes malignant behavior in hepatocellular carcinoma (liver cancer) cells. By altering the TGF- and p53/Bax/caspase-3 signaling pathways, cytoplasmic alpha-fetoprotein may increase resistance to apoptosis factors. acids (ATRA), thereby promoting Bcl-2 expression and preventing apoptosis. In addition, alpha-fetoprotein has the ability to bind to caspase-3 and prevent tumor cell apoptosis induced by the apoptosis-inducing ligand associated with tumor necrosis factor. Elucidation of the structure and function of alpha fetoprotein receptors will help scientific research. Knowledge about the transformation, proliferation, progression, migration and invasion of cancer cells, since many tumor cells express alpha fetoprotein receptors and these cells can take up alpha fetoprotein and have a malignant effect. In addition, alpha-fetoprotein has the ability to bind to caspase-3 and prevent tumor cell apoptosis induced by the apoptosis-inducing ligand associated with tumor necrosis factor. Elucidation of the structure and function of alpha fetoprotein receptors will help scientific research. knowledge about the transformation, proliferation, progression, migration and invasion of cancer cells, since many tumor cells express alpha fetoprotein receptors and these cells can take up alpha fetoprotein and have a malignant effect (34-37).

Initially, alpha fetoprotein receptors were found to bind to AFP in depressions in membrane bilayers, where they were then packaged into endosomal vesicles and vesicular bodies, which cells transported into the Golgi network via endocytosis. Finally, the vesicles released alpha-fetoprotein. fetoprotein and alpha-fetoprotein receptors, which have been found in the nucleus and cytoplasm and are involved in recycling and lysosomal degradation, as well as signal transduction (38-9).

The mannose receptor differentiation cluster 206 (CD206), the differentiation cluster 36 (CD36), the oxidized low-density lipoprotein receptor 1 (LOX1), the steroid receptor activator RNA 1 (SRA1), and the type B scavenger receptor type 1 (SRB1) have all been identified as members families of scavengers in subsequent studies.

In addition, in 1994 Laderoute et al. successfully isolated and partially identified additional alpha fetoprotein receptors that exhibited peanut agglutinin (PNA) lectin reactivity on epithelial tumor cells. Human adenocarcinoma cells, macrophages, dendritic cells, thymocytes, and leukemic cells, all of which express cell surface proteins, also contain these highly glycosylated proteins. The growth and development of tumor cells are often mentioned in reports of glycoproteins on these cells.

Recent studies have confirmed the existence of multiple alpha fetoprotein cell surface receptors, including but not limited to the following: a) chemokine receptors, b) cation channel proteins, c) cell cycle-associated proteins, d) extracellular matrix proteins, e) G-linked lysolipid receptors, f) proteins in the cytoplasm, and g) binding of serum IgM. that two families of binding proteins or receptors, the mucin family and the scavenger receptor family, have been identified as potential alpha fetoprotein receptors.Binding of a mucin or junk receptor to alpha fetoprotein has been the focus of a recent study that discussed in detail the processes involved in alpha fetoprotein uptake, cytoplasmic transport, signal transduction, and molecular crosstalk. These processes influence cell function and fate, promote malignant transformation of tumors, and provide additional evidence to support their designation as tumor alpha fetoprotein receptors.

According to a recent study, oxidative stress, which causes oxidation of lipids, proteins, and nucleic acids, plays an important role in chronic metabolic diseases. Pathological changes in the liver, as well as various stages of fibrosis, are unexpectedly associated with oxidative DNA damage. High serum alpha-fetoprotein levels may indicate cellular damage, bloating, inflammatory infiltration, and accumulation of oxidative DNA damage in cells. The production of adipocytokines is reduced as a result of increased oxidative stress, and increased production of reactive oxygen species (ROS) from adipose tissue increases the level of oxidative stress in the blood, causing toxicity in the liver, skeletal muscle and main arteries in patients with metabolic syndrome (40-49).

According to the results of a recent study, subjects with metabolic syndrome, diabetes mellitus, and damaged liver cells had significantly higher levels of alpha-fetoprotein than healthy subjects without metabolic syndrome. glucose levels had significantly higher levels of alpha-fetoprotein in their serum. According to numerous studies, diabetes mellitus is associated with an increased risk of many cancers, including liver, gallbladder, kidney, breast, endometrial, pancreatic, and colorectal cancers (13-18).

Worldwide, the prevalence of liver cancer is rising rapidly, and this is probably related to the rising prevalence of diabetes mellitus (18–20). It is still unclear what molecular pathophysiological mechanisms link liver cancer and diabetes mellitus. Numerous molecular pathways, including platelet growth factor, c-Jun N-terminal kinase, vascular endothelial growth factor, and PPAR-, AMP-activated protein kinase, are considered important in the development of liver cancer in diabetic patients (18).

In diabetic patients, insulin-like growth factor-I can be activated as a result of hyperglycemia, elevated blood insulin levels, and increased insulin resistance. In the liver, insulin-like growth factor I inhibits apoptosis and promotes cell proliferation. Is free. radical production can be increased as a result of cell proliferation induced by insulin-like growth factor I. This increase can lead to the development of liver cancer in liver tissue due to free radical-associated DNA damage and gene mutations. For early detection of liver cancer, biomarkers such as alpha-fetoprotein can be used. Alpha-fetoprotein is the most commonly used liver cancer marker. It is generally accepted that a serum alpha-fetoprotein level above 400 ng/mL is diagnostic of liver cancer, especially in patients at high risk of developing liver cirrhosis. However, in many cases of liver cancer, alpha fetoprotein levels are often normal at the time of diagnosis. According to the literature, the relationship between alpha fetoprotein and metabolic syndrome has been the subject of recent research. The first study looked at the diagnostic value of alpha fetoprotein levels in people with diabetes who had liver cancer. This is the third study to investigate the diagnostic value of serum alpha-fetoprotein levels in patients with diabetic liver cancer. Patients with liver cancer who also had diabetes mellitus had significantly lower serum alpha-fetoprotein levels than people without diabetes. People with diabetes may have lower levels of alpha-fetoprotein, which can delay the diagnosis of liver cancer and increase the chance of malignant liver cancer. Another study found that subjects in the control group had significantly higher serum levels of alpha fetoprotein than those in the diabetic group. However, they also found that serum alpha fetoprotein levels in the diabetic group were significantly lower than those in healthy individuals group (22).

The recent study reported that serum alpha-fetoprotein levels were higher in the diabetic group compared with the control group. Differences in the results of the two studies may be

due to differences in sample size, statistical methods, and study design (32).

Decreased alpha fetoprotein levels in patients with liver cancer who also have diabetes mellitus do not have a specific pathophysiological cause. Others have suggested that decreased serum alpha fetoprotein levels may result from increased urinary protein loss in patients with diabetic nephropathy (23).

This theory could explain the low levels of alpha fetoprotein in people with diabetes, but there is not enough evidence to support it. Proteinuria levels in patients with diabetes and liver cancer could not be measured retrospectively due to the retrospective design of our study. As a result, statistical analysis of this topic was not possible. Elsayed et al. reported that, insulin resistance, body mass index (BMI), alpha-fetoprotein, insulin, fasting plasma glucose, and low-density lipoprotein (LDL) cholesterol were found to be positively correlated with patients with liver cancer associated with infection (26).In addition, a negative correlation was observed between alpha fetoprotein levels, age, and fasting plasma glucose levels. In our study, there was no positive correlation between alpha fetoprotein levels and any metabolic marker. In our study, there were no cases of liver cancer caused by a viral infection. In this study, the liver cancer group had almost all etiological factors, including viral infection. Through various metabolic pathways, chronic viral infection is associated with diabetes mellitus and increased insulin resistance (27-29).

The positive correlation between alpha fetoprotein, insulin resistance, and other metabolic markers may be primarily due to the fact that this study was only done on people infected with the virus. Numerous studies have shown that obesity is a separate risk factor for the development of liver cancer. In cases of liver cancer, alpha fetoprotein levels also significantly negatively correlated with age and fasting serum glucose levels in our study. Alpha fetoprotein levels did not correlate with insulin resistance, BMI, HgA1c, or fasting serum insulin levels in patients with diabetes or non-diabetic liver cancer. Compared to the control group, the subjects in our study had a significantly higher BMI in both the diabetic and diabetic groups. Despite this, our study found no significant correlation between BMI and alpha fetoprotein levels (24, 25).

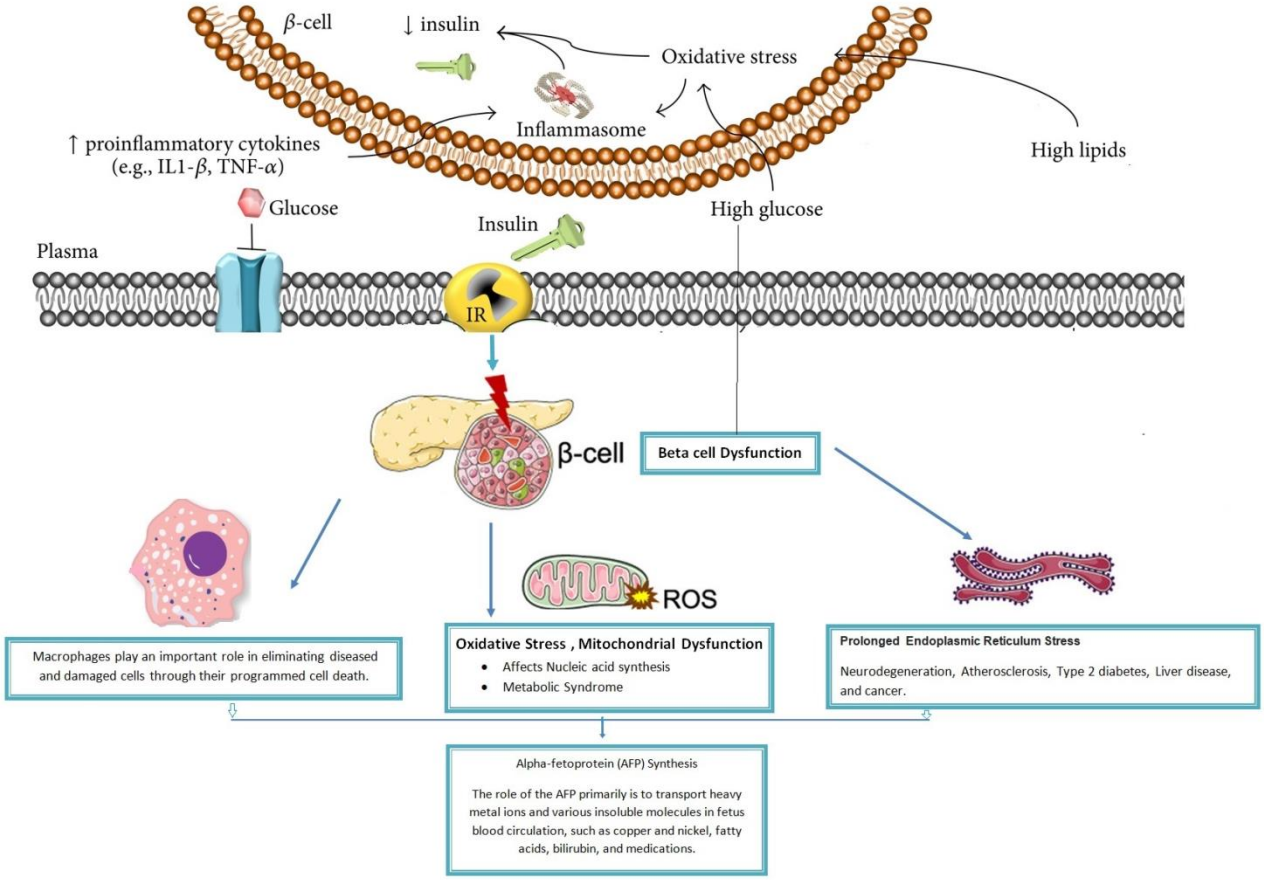
Hepatocarcinogenesis is largely dependent on the insulin resistance (IR) pathway. Both the level of insulin-like growth factors binding protein 1 (IGF BP-1) and the synthesis of insulin-like growth factors (IGF)-1 can be reduced in hyperinsulinemia. Plasma levels of total insulin-like growth factor-1 are also elevated when IGF BP-1 is suppressed. It is possible that an elevated level of insulin-like growth factor-1 is a major factor in the development of liver cancer. As a result, insulin resistance and hyperinsulinemia may indirectly contribute to hepatocarcinogenesis. There are many studies that have found a strong link between insulin resistance and the development of liver cancer, but very few studies have looked at the relationship between insulin resistance and alpha-alpha resistance. fetoprotein. A recent study found no correlation between alpha-fetoprotein levels and insulin resistance. Another study found specific diagnostic capabilities and widespread acceptance of serum AFP as a significant tumor marker. Adults with hepatocellular carcinoma, gastric cancer, hepatic necrosis, cirrhosis, acute hepatitis, chronic active hepatitis, Wiskott-Aldrich syndrome, ataxia-telangiectasia, and pregnancy have been found to have alpha-feto protein levels consistently above the pathological range. Serum Alpha-fetoprotein elevations were rarely seen in participants without overt pathology. Alpha-fetoprotein is primarily re-expressed in adult hepatocytes through three mechanisms.

(i) Adult hepatocytes are considered functional stem cells capable of regeneration by definition [33]. Alpha-feto protein levels rise as hepatocytes regenerate [34]. Increased serum alpha-feto protein, cellular immune expression of alpha-feto protein and alpha-fetoprotein gene expression during hepatocyte division during liver regeneration after chemical injury/damage or partial hepatectomy shows that hepatocyte proliferation during repair and regenerative growth is associated with cell activation -predecessors.

(ii) Oxidative stress causes DNA damage in hepatocytes, which activates transcription factors and induces DNA methylation, causing the expression of proto-oncogenes, leading to genomic instability and hepatocarcinogenesis. differentiated hepatocytes.

(iii) Biliary epithelial cells (oval cells) have regenerative capacity with multilinear differentiation potential when hepatocyte regenerative capacity is hampered in models of very extensive or chronic inflammatory liver injury. proliferation [50-60].

Figure 1 : Insulin resistance and alpha feto-protein Synthesis



1.4. Alpha-fetoprotein with genetic Disorder:

Niemann-Pick disease type C is a rare neuro-visceral lipid storage disease that is autosomal recessive. 9 cases of infantile-onset Niemann-Pick disease type C with various genetic mutations in the NPC1 gene that presented with neonatal cholestasis, For the first 4 months of life, serum alpha-fetoprotein levels were measured as part of their examination there was alpha-fetoprotein levels were elevated in 8 of 9 patients (89 %). Seven infants showed a significant increase, which ranged from four to three hundred times the upper limit for age. In most patients, alpha-feto protein levels peaked during the initial test and decreased as cholestasis improved and elevated alpha-feto protein levels are a common but non-specific indicator of Niemann-Pick disease type C -associated liver disease. These results indicate that the inclusion of alpha-feto protein levels in the diagnosis of neonatal liver disease is useful, especially if co-morbid cholestasis and Niemann-Pick disease type C are suspected patients. Alpha-fetoprotein is the embryonic precursor of albumin, which is produced in the intestine and liver during development. In pediatric and adult oncology, it is used as a tumor marker and in prenatal diagnosis of various congenital malformations such as abdominal wall defects and neural tube defects. (61).

Several metabolic conditions, most notably type 1 tyrosinemia, have well-documented levels of alpha-fetoprotein. Other metabolic disorders such as galactosemia, defects in bile acid synthesis, and gestational alloimmune liver disease (GALD, formerly known as neonatal hemochromatosis) have been associated with case reports of elevated alpha-fetoprotein levels. Another lysosomal storage disorder with liver damage, type 1 Gaucher patient who developed gocheroma, also had elevated alpha-fetoprotein levels (62-63).

The yolk sac and fetal hepatocytes produce alpha-fetoprotein. It is known that during oncogenesis or regeneration, the adult liver produces alpha-fetoprotein. We suggested that the regenerative activity of the damaged liver may be reflected in the presence of alpha-fetoprotein in metabolic diseases with liver damage. This idea is also supported by the fact that elevated alpha-fetoprotein levels were associated with liver damage in the current cohort. Other metabolic hepatopathy and possibly other lysosomal storage disorders may also have elevated alpha-fetoprotein levels. However, the current cohort is the largest of its kind to document consistently elevated alpha-fetoprotein levels regardless of metabolic state. Conditions that do not involve the liver, such as ataxia-telangiectasia and Finnish-type nephrotic syndrome, can also increase serum alpha-fetoprotein levels. Although alpha-fetoprotein levels are slightly elevated (less than 100 ng/mL) in patients, hereditary alpha-fetoprotein persistence is a rare

autosomal dominant trait (64,65,66).

Patterson et al., reported that maternal serum alpha-fetoprotein levels, which were taken as part of a routine pregnancy test, were within normal limits and suggests that NPC1 liver disease likely begins after the baby is born. As a result, a prenatal diagnosis cannot be made with this readily available test. There are two potential clinical implications of this clinical observation: 1) it demonstrates that elevated alpha-fetoprotein levels are a common but non-specific indicator of NPC-associated liver disease. 2) This highlights the importance of considering alpha-fetoprotein levels when diagnosing neonatal liver disease. In the appropriate clinical setting, this simple and accessible test may provide clinicians with an early indication to consider the diagnosis of Niemann-Pick disease type C. In light of new drugs being developed to treat diseases, timely diagnosis of Niemann-Pick disease type C is becoming increasingly important (67).

Table.3. Role of Alpha feto-protein in genetic disease patients.

Disease	**Effects of Metabolic activity**	**Clinical Characteristics**	**Genetic Mutations**	**Role of Alpah feto-protein**
Niemann-Pick disease type C	Lipid storage disease	Hepatomegaly , Hepatosplenomegaly , Cholestasis,Splenomegaly	R404Q *, R404Q *, R404Q *, R404Q * R404Q *, L1248fs/A1054T, P166H/R1077Q, F760del *, F760del/S940L	Transport of metal ions, proteins molecules into the cells and cell proliferation and regeneration
Galactosemia	Mitochondrial DNA (mtDNA) depletion	infantile-onset spinocerebellar ataxia, and early-onset encephalopathy	C10orf2 gene	
Tyrosinemia Type-1	lack of fumarylacetoacetate hydrolase	Hypertension,growth failure, renal tubulopathy , thrombocytopenia, rickets	heterozygous mutation in chromosome 15q25	
Citrullinemia Type-2	Citrin Deficiency	Neonatal intrahepatic cholestasis, Aminoacidemia, cholestatic jaundice	SLC25A13 gene (Heterozygous 851del4/S225X mutation)	
Ataxia telangiectasia (AT) (Twinkle variants)	Oxidative Phosphorylation	Polyneuropathy	Senataxin (SETX) Mutation	
Gestational Alloimmune Liver Disease (GALD)	Extrahepatic iron deposition	Hypoglycemia, coagulopathy, hypoalbuminemia ascites, jaundice, respiratory distress, hepatomegaly, and edema	Giant cell transformation of hepatocytes along with extramedullary hematopoiesis	
Down's syndrome	Non disjunction during Meiotic division	congenital malformations and mental retardation	Trisomy 21	

Multiple forms of cancer, including liver cancer, are closely associated with metabolic syndrome and diabetes. Because liver cancer is an extremely aggressive tumor with a poor prognosis, early detection is more important than ever. Worldwide, alpha-fetoprotein continues to be an important biomarker for the screening and diagnosis of liver cancer. In patients with diabetes and cirrhosis, lower levels of alpha-fetoprotein may delay the diagnosis of liver cancer, which can lead to a significant reduction in the effectiveness of treatment.

Recent research has been somewhat limited. First, there were insufficient numbers of diabetic and non-diabetic groups in the retrospective single center study. Diabetic patients could not be included in the study design, hindering the study of the potential role of antidiabetic drugs in the development of liver cancer. In addition, because the study was retrospective, it was not possible to determine whether the low alpha-fetoprotein levels in patients with diabetic liver cancer were due to urinary protein loss due to diabetic nephropathy. Secondly, no molecular analysis was performed, the recent study did not look at insulin resistance index or insulin levels. Normal liver cells can become cancerous or be damaged as a result of metabolic syndromes. More research is needed to determine the cause of the increase in alpha-fetoprotein levels and changes in individual genes or alleles. An indirect correlation between serum alpha-fetoprotein levels and insulin resistance needs to be investigated, but there is no direct correlation. In diabetic patients with cirrhosis, alpha-fetoprotein may be useful as a

biomarker for diagnosing various metabolic syndromes and screening for liver cancer, according to a recent study. As a result, normal liver cells can become cancerous or damaged due to changes in the liver metabolism. To determine whether alpha-fetoprotein is the cause of a metabolic disorder or metabolic disease, more research is needed to determine the cause of the increase in alpha-fetoprotein levels and changes in specific genes or alleles.

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