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Role of liver parameters in diabetes mellitus – a narrative review

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Diabetes mellitus is characterized by hyperglycemia and abnormalities in insulin secretion and function. This review article focuses on various liver parameters, including albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), alpha fetoprotein (AFP), alpha 1 antitrypsin (AAT), ammonia, bilirubin, bile acid, gamma-glutamyl transferase (GGT), immunoglobulin, lactate dehydrogenase (LDH), and total protein. These parameters play significant roles in the development of different types of diabetes such as type 1 diabetes (T1DM), type 2 diabetes (T2DM) and gestational diabetes (GDM). The article highlights that low albumin levels may indicate inflammation, while increased ALT and AST levels are associated with liver inflammation or injury, particularly in non-alcoholic fatty liver disease (NAFLD). Elevated ALP levels can be influenced by liver inflammation, biliary dysfunction, or bone metabolism changes. High bilirubin levels are independently linked to albuminuria in T1DM and an increased risk of T2DM. Elevated GGT levels are proposed as markers of oxidative stress and liver dysfunction in T2DM. In GDM, decreased serum AFP levels may indicate impaired embryo growth. Decreased AFP levels in T2DM can hinder the detection of hepatocellular carcinoma. Hyperammonemia can cause encephalopathy in diabetic ketoacidosis, and children with T1DM and attention deficit hyperactivity disorder often exhibit higher ammonia levels. T2DM disrupts the regulation of nitrogen-related metabolites, leading to increased blood ammonia levels. Bile acids affect glucose regulation by activating receptors on cell surfaces and nuclei, and changes in bile acid metabolism are observed in T2DM. Increased LDH activity reflects metabolic disturbances in glucose utilization and lactate production, contributing to diabetic complications. Poor glycemic management may be associated with elevated levels of IgA and IgG serum antibodies, and increased immunoglobulin levels are also associated with T2DM.

Key words: liver parameters, pathogenesis, diabetes mellitus, type 1 diabetes, type 2 diabetes, gestational diabetes

Diabetes mellitus (DM) is a group of metabolic disorders characterized by high blood sugar levels and disturbances in insulin production and function. It encompasses various forms, including type 1 diabetes (T1DM), type 2 diabetes (T2DM), gestational diabetes (GDM) as well as other subtypes like maturity-onset diabetes in the young and latent autoimmune diabetes in adults. Risk factors for diabetes include genetic predisposition, obesity, sedentary lifestyle, poor dietary habits, stress, urban living, impaired glucose tolerance, and hypertension. Individuals with diabetes and chronic hyperglycemia are at an increased risk of developing long-term complications that affect the functioning of multiple organs. These complications commonly involve the eyes (retinopathy), kidneys (nephropathy), nerves

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(neuropathy), heart (cardiovascular diseases), and blood vessels (vasculopathy). These diabetic complications can result in a significant damage to these organs and contribute to various health problems associated with diabetes (Rafaqat et al. 2023).

DM is a significant global health concern, contributing to high mortality and morbidity rates. The international diabetes federation estimates that approximately 1 in 11 adults worldwide are affected by DM. Low- and middle-income countries account for nearly 80% of the diabetic population with a particularly high burden in South-East Asian nations. Various liver conditions, including non-alcoholic fatty liver disease (NAFLD), hepatocellular carcinoma, and cirrhosis, have been associated with diabetes (Noroozi Karimabad et al. 2022).

The liver plays a crucial role in maintaining glucose homeostasis, insulin clearance, and the production of inflammatory cytokines. Common liver enzymes such as alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) are involved in these processes. In addition to their physiological functions, abnormal serum levels of these enzymes can indicate liver or bile duct injury (Kunutsor et al. 2014). Increased liver enzyme activity may also indicate inflammation, which can disrupt insulin signaling. NAFLD, which is associated with insulin resistance and the risk of diabetes, can be assessed through measures of liver enzymes (Noroozi Karimabad et al. 2022). Clinical and experimental studies have shown that an elevated influx of free fatty acids from visceral adipose tissue can lead to hepatic steatosis and insulin resistance (Cho et al. 2007). Furthermore, research has demonstrated that elevated levels of GGT and ALT enzymes are associated with an increased risk of developing T2DM in the future. These findings highlight the potential role of liver enzymes as markers for diabetes and its associated complications (Kunutsor et al. 2014).

The objective of this review was to assess the association between liver parameters and diabetes, considering recent advancements, notable research gaps, ongoing debates, and potential directions for future investigations. While there are numerous liver parameters, this review is specifically focused on albumin, ALT and AST, ALP, alpha fetoprotein (AFP), alpha 1 antitrypsin (AAT), ammonia, bilirubin, bile acid, GGT, immunoglobulin, lactate dehydrogenase (LDH), and total protein. These parameters are discussed in relation to their pathophysiological roles in various forms of DM, as depicted in Figures 1, 2, 3.

To conduct this review, various databases, such as PubMed, Google Scholar, and Science Direct, were utilized to gather relevant literature. The search was conducted until December 01, 2022. Specific terms such as "pathophysiology", "diabetes", "type 1 diabetes", "type 2 diabetes", "gestational diabetes mellitus", and "liver parameters" were used to identify relevant published articles. Additionally, reference list of identified articles was examined to find additional related studies. It was focused on clinical studies published in the English language, without imposing any time limitations, although a preference was given to more recent research.

There are numerous liver parameters available, but this review is specifically focuses on albumin, ALT and AST, ALP, AFP, AAT, ammonia, bilirubin, bile acid, GGT, immunoglobulin, LDH, and total protein. These parameters are discussed in relation to their pathophysiological roles in various forms of DM, as depicted in Table 1.

Table 1
Role of liver parameters in different types of diabetes mellitus

Liver Parameters (Levels)	Type 1 Diabetes	Type 2 Diabetes	Gestational Diabetes
Albumin	↑	↑/↓	↑/↓
ALT and AST	↑	↑	↑
ALP	↑	↑	↑
AFP	?	↓	↓
AAT	Ø	′	↑
Ammonia	↑	↑	?
Bilirubin	↑	↑/↓	↑/↓
Bile Acid	↑	↑	↑
GGT	↑	↑	↑
Immunoglobulin	Ø/↓	↑	↑/↓
LDH	↑	↑	?
Total Protein	?	↑	?

Abbreviations: AAT – alpha1 antitrypsin; AFP – alpha fetoprotein; ALP – alkaline phosphatase; ALT – alanine aminotransferase; AST – aspartate aminotransferase; GGT – gamma-glutamyl transferase; LDH – lactate dehydrogenase. (↑ – increased level; ↓ – decreased level; ↑/↓ – increased/decreased level; **Ø** – absent; ′ – insufficient; **?** – unknown role; **Ø**/↓ – deficient/decreased level).

Albumin

Albumin, the most abundant soluble protein in plasma or serum, makes up approximately 50% to 60% of the total protein content. It is primarily synthesized by the liver and undergoes degradation in the muscles, liver, and kidneys. Apart from its role

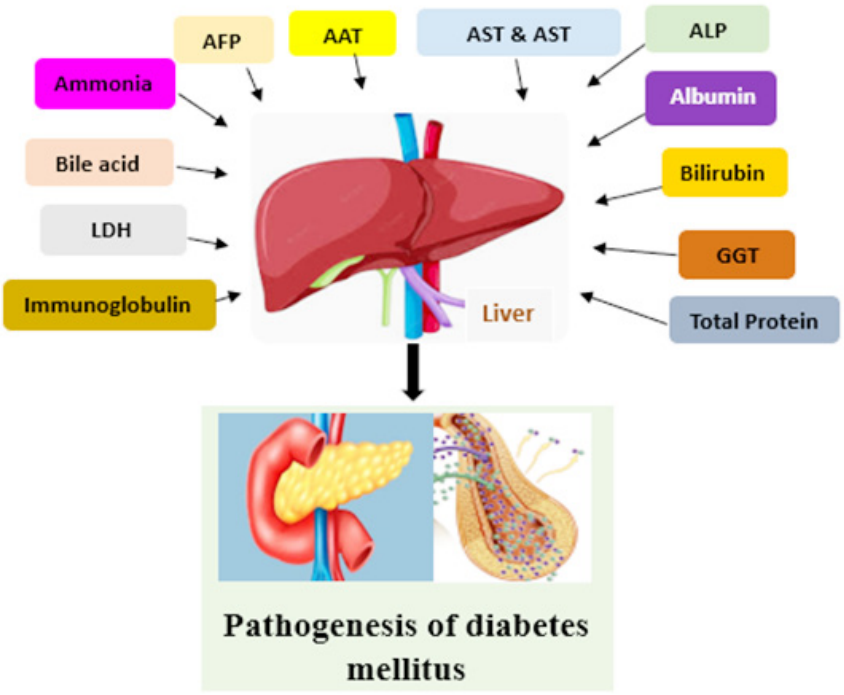


Figure 1. Overall presentation of liver parameters involved in the pathogenesis of diabetes mellitus. Abbreviations: AAT – alpha 1 antitrypsin; AFP – alpha fetoprotein; ALP – alkaline phosphatase; ALT – alanine aminotransferase; AST – aspartate aminotransferase; LDH – lactate dehydrogenase.

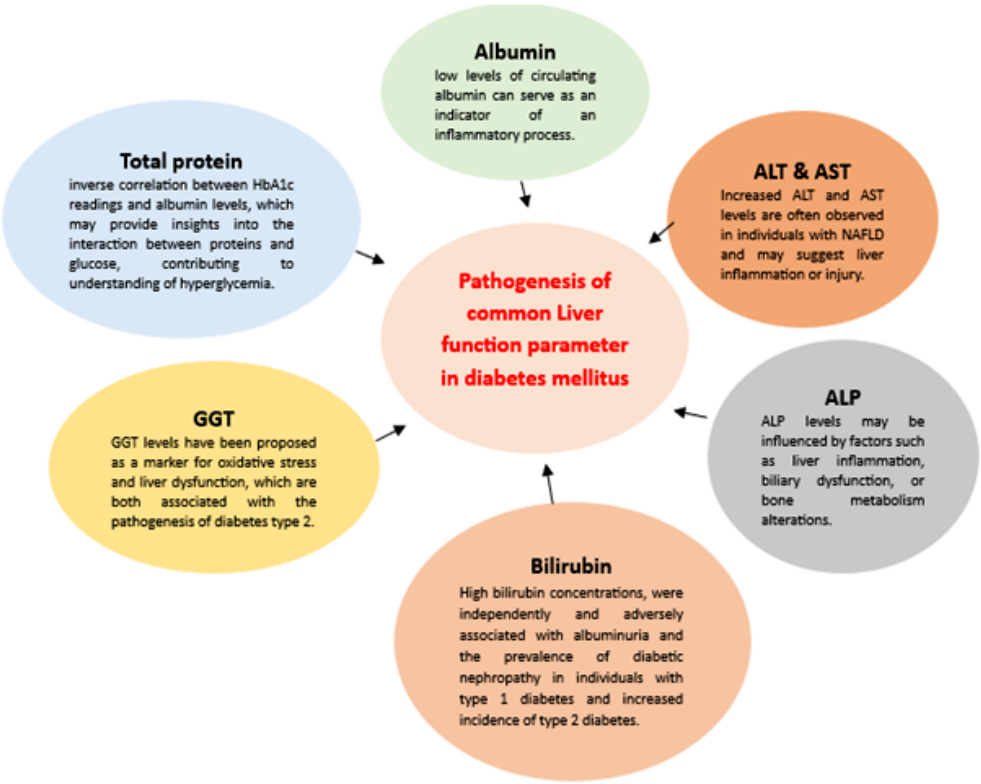


Figure 2. Pathogenesis of common liver function parameters in diabetes mellitus. Abbreviations: ALP – alkaline phosphatase; ALT – alanine aminotransferase; AST – aspartate aminotransferase; GGT – gamma-glutamyl transferase.

in maintaining plasma oncotic pressure, albumin exhibits versatility in various biological functions. For instance, it contributes to over 50% of the total antioxidant capacity in normal plasma and acts as the primary carrier protein for non-esterified fatty acids. Additionally, albumin binds and transports a range of other naturally occurring molecules, including metal ions, heme, thyroxine, and bilirubin. While it has traditionally been associated with malnutrition and protein intake, there is now substantial evidence indicating that low levels of circulating albumin can serve as an indicator of an inflammatory process (Chang et al. 2019).

Human serum albumin is a versatile protein that plays crucial roles in physiological processes. It is the most abundant protein in plasma and possesses the ability to bind to various ligands. As a result, it is susceptible to different post-translational modifications that can alter its structure and functions. One notable post-translational modification is glycation, which occurs through a non-enzymatic reaction between reducing sugars and proteins, leading to the formation of diverse advanced glycation end products (Bhat et al. 2017). DM leads to an increase in non-enzymatic glycation. Previous studies have mainly focused on advanced glycation end products and their impact on vascular complications. However, the role of early glycation Amadori-modified proteins, which are the most prevalent form of glycated proteins, has not been thoroughly investigated in humans. Schalkwijk et al. (1999) have found the increased level of Amadori albumin in patients with T1DM suggesting significant association with increased risk of nephropathy. These findings suggested pathophysiological involvement of Amadori albumin in microvascular complications among individuals with T1DM.

Inflammation leads to a decrease in the levels of albumin in the blood. Obesity, which is closely associated with inflammation in adipose tissue, is a major risk factor for T2DM. However, there are uncertainties regarding the connection between

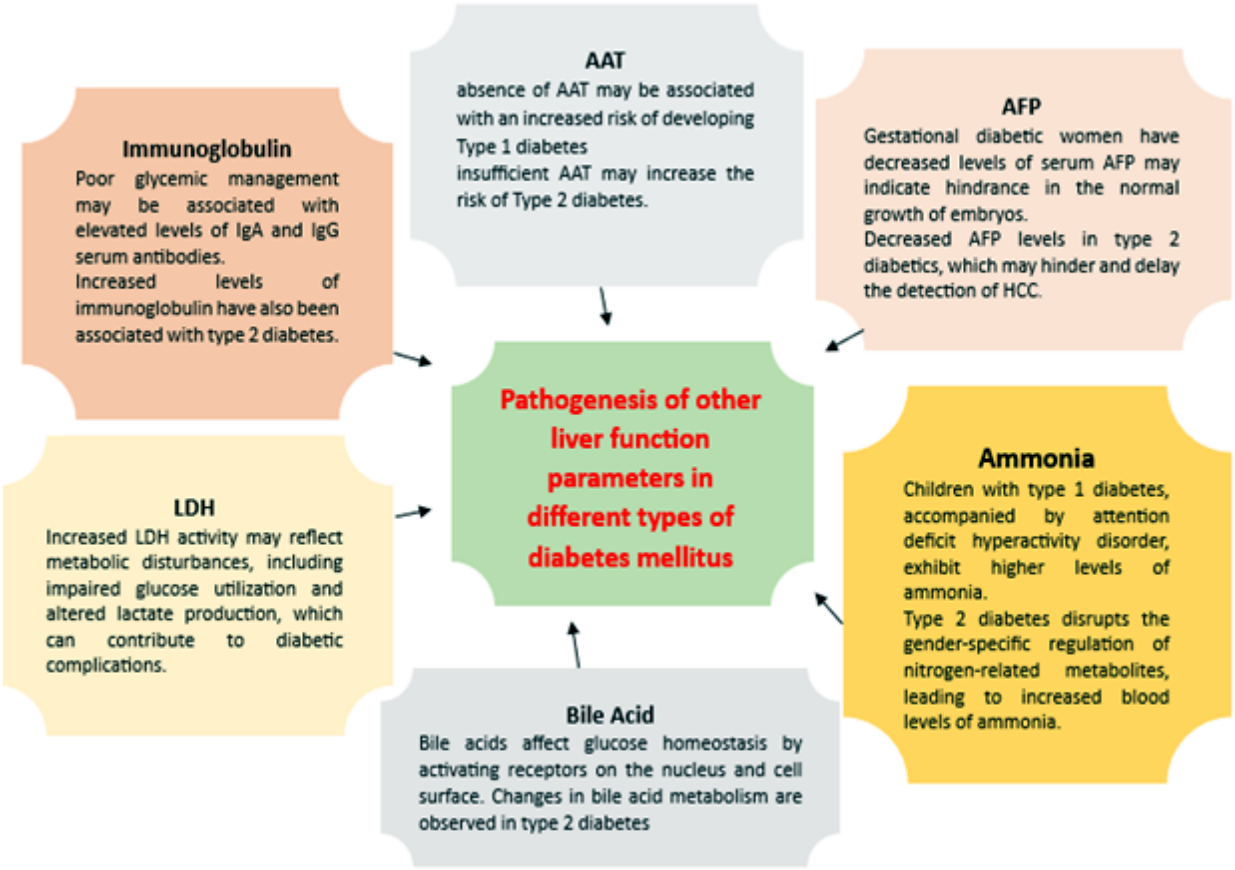


Figure 3. Pathogenesis of other liver parameters in different types of diabetes mellitus. Abbreviations: AAT – alpha 1 antitrypsin; AFP – alpha fetoprotein; LDH – lactate dehydrogenase.

albumin, adipose tissue inflammation, and its ability to predict T2DM. A study conducted by Chang et al. (2019) has found that individuals with a metabolic profile characterized by high levels of adipose tissue inflammation, obesity, hyperglycemia, and an increased risk of T2DM also exhibited lower levels of albumin. However, Bae et al. (2013) have investigated the relationship between insulin resistance and blood albumin levels, finding a correlation between higher serum albumin levels and insulin resistance. However, serum albumin did not independently influence the onset of T2DM. Furthermore, Hu et al. (2022) have investigated the association between blood albumin levels and diabetic peripheral neuropathy in individuals with T2DM. The authors have found a significant inverse relationship between serum albumin level and risk of diabetic peripheral neuropathy suggesting that blood albumin levels in patients with T2DM and higher BMIs may represent a distinct risk factor for diabetic peripheral neuropathy.

On the other hand, Cheng et al. (2016) have explored the connection between serum albumin levels and the risk of ketosis in hospitalized patients with T2DM. The authors have found a negative correlation between serum albumin concentration and the likelihood of developing ketosis in these patients. Recently, it has been found that albumin is among the non-glycemic and glycemic factors that can impact glycated hemoglobin (HbA1c), a commonly used marker for diagnosing and assessing glycemic control in T2DM. Therefore, Feng et al. (2021) have conducted a retrospective study examining the influence of albumin on HbA1c levels and the glycemic status indicated by HbA1c. The authors observed an inverse correlation between albumin levels and HbA1c in all participants, with a stronger correlation in individuals with T2DM. It is reported that lower albumin levels in T2DM patients were associated with a higher risk of inaccurate identification and management of glycemic status based on HbA1c. In addition, Tiwari et al. (2015) conducted a study investigating the association between albumin levels and HbA1c in the Asian Indian population. The findings indicated a negative relationship between serum albumin and HbA1c in Asian Indians, suggesting the potential for using HbA1c to predict diabetes and its complications in this population.

Gestational diabetes mellitus (GDM) is characterized by impaired glucose tolerance and is a prevalent complication that can occur during pregnancy. However, the precise association between the development of GDM and factors, such as advanced maternal age and a family history of diabetes, has yet to be fully established. Huang et al. (2015) have investigated the clinical relevance of detecting glycated albumin in pregnant women diagnosed with GDM. As a result, the fasting blood glucose levels and glycated albumin-L value exhibited a gradual decrease among pregnant women in the normal control group with the progression of gestational weeks. Conversely, pregnant women diagnosed with GDM experienced a significant increase in glycated albumin. In summary, various factors can impact pregnant women with GDM, and glycated albumin can be utilized to assess the recent blood glucose control in these individuals (Huang et al. 2015).

Comparison of albumin levels between patients diagnosed with GDM and normal pregnant women. The findings revealed a significant decrease in serum albumin levels among patients with GDM suggesting that albumin can serve as valuable indicators for predicting metabolic changes in both GDM patients and their fetuses. It is crucial to identify and effectively manage complications associated with GDM, while also considering modifiable risk factors, as women with a history of GDM are likely to have a higher risk of developing the condition in future pregnancies (Nagalakshmi et al. 2012). In another study, glycated albumin has been used as an alternative marker for assessing glycemic control during pregnancy, a period characterized by significant physiological changes. The reference intervals of glycated albumin in healthy Chinese pregnant women were established and evaluate its ability to predict adverse pregnancy outcomes. The study findings revealed a consistent decline in glycated albumin levels with increasing gestational age. However, limited utility of glycated albumin testing was observed in diagnosing GDM and predicting unfavorable pregnancy outcomes (Dong et al. 2020).

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST)

ALT is primarily found in liver cells and AST is an enzyme present in liver cells, but it is also found in other tissues, such as the heart, muscles, and kidneys. Elevated levels of ALT in the blood can indicate liver damage or disease, such as hepatitis, liver cirrhosis, or liver cancer. Elevated AST levels can indicate liver damage, but it is less specific to the liver compared to ALT. AST levels are often evaluated in conjunction with ALT levels. In the context of diabetes, NAFLD is commonly associated with insulin resistance and T2DM. Increased ALT and AST levels are often observed in individuals with NAFLD and may suggest

liver inflammation or injury, which can contribute to insulin resistance and impair glucose metabolism.

The prevalence of elevated ALT levels in a large group of patients diagnosed with T1DM was assessed and investigated the clinical correlations and potential causes. The study findings indicated that elevated ALT levels are not uncommon in individuals with T1DM and are associated with risk factors related to NAFLD. Therefore, patients with T1DM and elevated ALT levels should be further investigated, as significant abnormalities that can be addressed with interventions may be identified (Leeds et al. 2009). In addition, glycogenic hepatopathy is an uncommon complication that arises from inadequate management of T1DM. It is characterized by elevated liver enzymes ALT and AST, hepatomegaly (enlarged liver), and the accumulation of glycogen (Asada et al. 2018).

Insufficient insulin or insulin resistance can result in the development of DM, a non-communicable metabolic disorder. Liver enzymes such as ALT and AST are commonly used as indicators of the liver health. Elevated levels of liver enzymes indicate damage to liver cells and are associated with T2DM and insulin resistance. Although the contribution of hepatic gluconeogenesis from amino acids to diabetes-related hyperglycemia is significant, the specific molecular pathways involved are not well understood. The conversion of alanine to pyruvate, which is crucial for gluconeogenesis from alanine, is facilitated by enzymes called alanine transaminases (ALT1 and ALT2). A study conducted by Martino et al. (2022) have revealed that ALT2 significantly influences hepatic gluconeogenesis from amino acids in diabetes.

Independent of traditional risk factors, elevated liver enzyme activity, particularly ALT, has been associated with a twofold increase in the risk of T2DM. This suggests that ALT may be a useful marker for identifying individuals at high risk of developing T2DM, especially in Asian populations (Cho et al. 2007). West et al. (2006) have demonstrated that diabetes raises the risk of chronic liver disease, and blood alanine transaminase levels serve as a sensitive indicator of liver-related mortality. Patients with T1DM or T2DM had a significantly higher prevalence of elevated ALT levels, three to four times higher than that of the general population.

Further research investigating the underlying causes and mechanisms of this elevation could lead to recommendations for effective early interventions (West et al. 2006). Wang et al. (2016) have examined the relationship between liver enzymes and the risk of T2DM in the Chinese population. They have found that higher levels of ALT were associated with an increased risk of T2DM. In the Chinese population, ALT levels of 21 IU/L may be considered at higher risk for developing T2DM (Wang et al. 2016). Similarly, Li et al. (2019a) have reported that elevated levels of ALT or AST increased the risk of developing T2DM. However, incorporating ALT levels into the prediction model did not improve the ability to distinguish T2DM cases.

Additionally, the study by Vozarova et al. (2002) have confirmed that elevated ALT levels were a risk factor for T2DM, suggesting a potential role of the liver in the development of the disease. Recently, the Rafsanjan cohort study assessed the relationship between ALT, AST, GGT, ALP, and diabetes. It has been found that increased levels of these liver enzymes were associated with a higher risk of developing diabetes. These findings suggest that elevated liver enzymes could serve as indicators for the likelihood of having diabetes (Noroozi Karimabad et al. 2022). Ghaznavi and Yasmin (2015) have conducted a study on individuals with a history of diabetes, who are two to three times more likely to develop type T2DM. They measured ALT levels in these individuals and found that first-degree relatives of diabetics with normal blood sugar levels had higher serum ALT levels, which could indicate future disease. Patients with T2DM exhibited higher levels of liver enzyme activity compared to those without T2DM and found a significant correlation between liver parameters and DM, indicating that early detection and treatment of abnormal liver parameters could potentially reduce liver-related complications and mortality among individuals with diabetes (Jha et al. 2021). Previous studies have also indicated a strong association between elevated levels of ALT, AST, GGT, and ALP and an increased risk of developing diabetes.

Chen et al. (2017) have found that ALT, AST, GGT, and ALP were independent predictors of incident diabetes in both men and women. Abnormal levels of ALT have been associated with T2DM, but it is unclear whether higher ALT levels within the normal range can predict the risk. Wang et al. (2012) have found a dose-response relationship, indicating that higher ALT levels, even within the normal range, are reliable indicators of T2DM regardless of body mass index levels. In another study, Ogbodo et al. (2021) has found that ALT and AST were positively correlated, suggesting transaminase abnormalities in the livers of individuals with T2DM. The most prevalent chronic liver condition, known as NAFLD, is strongly associated with T2DM. Approximately

70% of individuals with T2DM have fatty livers, and the risk of developing cirrhosis and hepatocellular carcinoma increases significantly when NAFLD progresses to non-alcoholic steatohepatitis. Mandal et al. (2018) have conducted a study evaluating liver enzyme profiles in individuals with T2DM and NAFLD. The authors have found that serum levels of AST, GGT, and ALP did not significantly increase in NAFLD subjects, but ALT levels did increase in diabetes patients.

Higher risks of GDM have been observed among Chinese pregnant women who had elevated liver enzymes (ALT and AST) and a hepatic steatosis index (HSI) during early pregnancy, even when their levels were within the normal range. The association between HSI and GDM was largely influenced by changes in lipid metabolism, suggesting a potential link between altered lipid processing and the development of GDM in this population (Wu et al. 2023a, b). Increased and unexplained levels of ALT during early pregnancy have been found to be connected with a higher risk of developing GDM and preeclampsia during late pregnancy (Lee et al. 2017a). The correlation between the ALT/AST ratio and the occurrence of GDM has been investigated and the ALT/AST ratio was found to be higher in the GDM group compared to the normal glucose tolerance group. Additionally, the ALT/AST ratio demonstrated positive correlations with fasting blood glucose levels. Elevated levels of ALT/AST during early pregnancy were identified as independent risk factors for GDM. The predictive capability of ALT/AST was found to be comparable to that of triglyceride/high-density lipoprotein cholesterol (TG/HDL-C) for GDM (Song et al. 2022). However, there was an inverse correlation observed between the early ratio of AST/ALT levels in pregnant women and the risk of GDM. The inclusion of AST/ALT in a nomogram during early pregnancy demonstrated strong predictive capability for identifying the occurrence of GDM (An et al. 2022).

Alkaline phosphatase (ALP)

ALP is an enzyme found in various tissues, including the liver, bile ducts, bones, and intestines. Elevated ALP levels can indicate liver or bile duct problems, as well as bone disorders or certain types of cancer. While the direct relationship between ALP and diabetes is less established, elevated ALP levels have been observed in individuals with diabetes, particularly those with advanced liver disease or complications. ALP levels may be influenced by factors such as liver inflammation, biliary dysfunction, or bone metabolism alterations, which can all be associated with diabetes-related complications.

The presence of NAFLD is linked to a higher prevalence of chronic kidney disease in individuals diagnosed with T1DM. The association between markers of NAFLD, such as ALP in patients with T1DM has been investigated. There was a significant elevation in ALP levels among individuals in the highest quartile of urinary albumin excretion rate compared to those in the lowest quartile. Additionally, ALP levels were higher in individuals with hyperfiltration compared to those with normal or mildly impaired estimated glomerular filtration rate (eGFR). It has been shown that markers associated with NAFLD, specifically ALP, show a correlation with renal function in T1DM patients without albuminuria (Bulum et al. 2014). Individuals diagnosed with T1DM have shown indications of inflammation in the intestines. In comparison to the control group, diabetes patients had reduced fecal intestinal ALP activity. In mouse models, oral supplementation of intestinal alkaline phosphatase (IAP) significantly increased intestinal IgA levels (Lassenius et al. 2017).

In context of diabetes, Moshtaghie et al. (2000) have investigated the potential mechanisms underlying bone abnormalities in T2DM patients with different serum glucose levels, as there has been a debate regarding the connection between hyperglycemia and bone damage in diabetic patients. Similarly, Maxwell et al. (1986) have conducted a study on a group of diabetic individuals with higher ALP levels and found a significant correlation with higher mean fasting serum glucose levels, establishing a link between the severity of diabetes and diabetic bone damage. In relation to ALP, it has been identified as a predictor of mortality and cardiovascular events, including vascular calcification and insulin resistance. However, there is no apparent connection between insulin resistance and ALP. Cheung and Cheung (2013) have investigated the association between insulin resistance-related characteristics and ALP (total and bone-specific). They found that serum levels of bone-specific ALP were highly and independently correlated with insulin resistance-related characteristics, but not overall ALP levels. This novel correlation between insulin resistance and bone-specific ALP establishes a mechanistic link between insulin resistance and vascular calcification, while the association between insulin resistance and hepatic inflammation was predicted. It has been suggested that ALP inhibitors may be beneficial in preventing vascular calcification in T2DM.

The relationship between plasma ALP and survival in T2DM individuals with myocardial infarction has been explored. Elevated ALP served as a predictive indicator of poor survival in diabetic patients with acute myocardial infarction, particularly when combined with impaired renal function. This observation was specific to male patients, suggesting that phosphatase activity may have a different role in cardiovascular disease in male and female with T2DM individuals (Nunes et al. 2016). Zhang et al. (2020) examined the potential impact modifiers and the prospective relationship between serum ALP and the likelihood of developing new-onset T2DM in hypertensive individuals. Their findings have indicated that higher serum ALP was significantly associated with an increased risk of new-onset diabetes in this hypertensive, non-diabetic group, especially in those with reduced total homocysteine or higher fasting glucose levels (Zhang et al. 2020). Furthermore, IAP, an anti-inflammatory enzyme released by enterocytes, has been shown to have a preventive effect against T2DM in previous studies. Malo et al. (2022) have investigated the long-term implications of IAP deficiency on the pathogenesis of T2DM. They found that IAP deficiency increased the risk of developing T2DM, and regular stool alkaline phosphatase (STAP) tests could indicate a patient's susceptibility to T2DM. Taking oral IAP supplements could potentially prevent T2DM. In another study, it has been observed that T2DM develops in mice deficient in IAP. High levels of IAP appeared to protect against diabetes regardless of obesity, and monitoring temporal IAP profiles may be a useful tool for predicting the onset of metabolic syndrome, including incipient diabetes (Malo et al. 2015).

Severe elevation of ALP was observed in a pregnancy that had complications of GDM and an infant diagnosed with neonatal alloimmune thrombocytopenia (Lozo et al. 2016). Even when maternal ALP levels were within the upper limit of normal, higher levels during early pregnancy were associated with an increased risk of GDM. Additionally, elevated early maternal ALP levels were correlated with higher fasting blood glucose and postprandial blood glucose levels (Xiong et al. 2019). A case of a 25-year-old pregnant woman diagnosed with GDM who exhibited a significant increase (25-fold) in the activity of the placental isozyme of ALP. An abdominal ultrasonographic scan showed no signs of hepatobiliary disease. Following delivery, the ALP level decreased, but did not fully return to the reference range. Similar abnormalities in ALP were observed in the patient's first-degree relatives, including her mother and sister (Wojcicka-Bentyn et al. 2004).

Alpha-fetoprotein (AFP)

AFP is a type of glycoprotein that is primarily synthesized by the fetal liver and yolk sac. After birth, the amount of AFP decreases quickly and remains consistently low throughout an individual's lifespan in the general population (Chen et al. 2016). Wald et al. (1979) have performed a study involving 27 singleton pregnancies in women with T1DM (insulin-dependent DM) and 90 controls without diabetes, matched for gestational age, maternal serum AFP levels were measured from 12 to 24 weeks of gestation, and discovered that the mean AFP level among the diabetic pregnancies was 60% lower than that in the controls. The difference in AFP level between diabetic patients and controls was particularly significant in sera taken before 21 weeks of gestation (Wald et al. 1979).

In another study, a decrease in maternal serum AFP has been observed in pregnant women with diabetes linked to the effectiveness of diabetic treatment rather than the presence of diabetes itself. Baumgarten et al. (1988) have found that women with poor glycemic control should have their maternal serum AFP corrected. The reduced synthesis of other fetal proteins, which could be associated with fetal growth retardation and the occurrence of malformations, may be indicated by decreased maternal serum AFP in poorly managed diabetics. Similar to other studies, the levels of maternal serum AFP might decrease in pregnancies affected by diabetes, but the link between this decrease and increased levels of glycosylated hemoglobin has been a topic of debate. Martin et al. (1990) have investigated that reductions in maternal serum AFP may indicate the same factors that can hinder the normal growth of embryos when maternal diabetes is not well controlled. The above-mentioned authors have found a trend in pregnancies with lower maternal blood AFP levels and higher glycosylated hemoglobin values to indicate early fetal development delay as assessed by ultrasonography.

Despite AFP role in fetus development, the levels of AFP become active again during the process of liver regeneration and the development of hepatocarcinogenesis. This reactivation has been observed in conditions such as hepatocellular carcinoma, chronic liver disease, acute or chronic viral hepatitis, and gonadal tumors (Chen et al. 2016). Several studies have investigated the relationship between T2DM, hepatocellular cancer (HCC), and AFP. It has been shown that lower levels of AFP, impaired liver function, and an increased risk of high-grade HCC were found to be associated with T2DM. Yang et al.

(2018) have conducted a study on the decreased AFP levels in T2DM, which may hinder and delay the detection of HCC, leading to more severe malignant HCC suggesting that AFP levels are important biomarker for diagnosing HCC, an aggressive tumor that commonly occurs in cirrhotic livers. In contrast, Sahin and Kocak (2021) have found that AFP cannot be reliably used to screen or diagnose cirrhosis and the presence of HCC in individuals with T2DM.

Alpha1 antitrypsin (AAT)

Human AAT, also known as α1 proteinase inhibitor (α1-Pi) and SERPINA1 (serine protease inhibitor, group A, member 1), is a medium-sized circulating glycoprotein (molecular weight of 52 kDa) that is soluble in water and diffuses through tissues. In the bloodstream, it has a half-life of around 4 to 5 days. The majority of AAT, accounting for over 80%, is produced and released by hepatocytes (liver cells), while additional amounts are synthesized by monocytes, macrophages, pancreatic cells, lung alveolar cells, enterocytes (intestinal cells), endothelial cells, and certain types of cancers (De Serres and Blanco 2014). Zhang et al. (2007) have proposed a novel biological role for AAT and suggested that it could be a promising candidate for the prevention or treatment of T1DM. Sandstrom et al. (2008) have conducted an investigation to assess whether the levels of AAT in plasma are altered in individuals with T2DM and found evidence supporting the idea that insufficient AAT may increase the risk of T2DM. AAT may serve as a potential anti-inflammatory drug to protect cells from immune attack in T1DM and as a therapeutic approach to enhance insulin secretion in T2DM (Kalis et al. 2010).

AAT has a protective role in diabetic retinopathy by preventing processes like apoptosis, extracellular matrix modification, and vascular damage. Its anti-inflammatory properties make it a promising treatment option. Mouse models of T1DM have been used to study the effects of AAT on retinal neurodegeneration and inflammation. Investigating the molecular mechanisms of AAT could provide valuable insights into its function in diabetic retinopathy and its potential application in other retinal diseases. Previous studies have identified expression profiles and mRNA associated with the proteins involved, indicating that AAT may hinder the progression of diabetic retinopathy through diverse signaling pathways (Potilinski et al. 2020).

AAT is involved in inflammatory and immune-related conditions, including diabetes mellitus. It has anti-inflammatory and immunomodulatory effects in chronic obstructive pulmonary disease. AAT activity is affected in both T1DM and T2DM. In T1DM mouse models, AAT therapy has positive effects, and in humans with T1DM, it influences inflammation and cell function. The role of AAT in T2DM is uncertain, but its activity is decreased in this condition. Park et al. (2021) have explored these connections and new therapeutic approaches using AAT for treating DM. In addition, Ghoreishi et al. (2022) have found that the absence of AAT may be associated with an increased risk of developing T1DM. Whereas, both normal and diabetic pregnancies have shown an elevation in serum AAT concentration, but with different regression line slopes. The highest AAT concentration was observed during the third trimester of diabetic pregnancy. Importantly, the increase in AAT concentration in the serum of pregnant women with diabetes was independent of the level of glycemic control (Lisowska-Myjak et al. 2001).

Ammonia

Physiologically, serum ammonia levels are a result of protein breakdown, primarily occurring in the gastrointestinal system. The liver and muscles play a role in removing ammonia from the body. Hyperammonemia can be caused by various factors, including urea cycle disorders, medications, infections, gastrointestinal bleeding, and liver or kidney failure. Undetected hyperammonemia, whether acute or chronic, can lead to irreversible neurological damage. Insulin promotes protein synthesis, but deficiencies or resistance in insulin, as seen in T1DM and T2DM respectively, increase protein breakdown and ammonia production. In such cases, aggressive resuscitation and treatment of diabetic ketoacidosis are crucial for management (Kenari et al. 2021). This study has highlighted the importance of considering hyperammonemia as a cause of encephalopathy in patients with uncontrolled diabetes and diabetic ketoacidosis. In addition, encephalopathy caused by hyperammonemia is a common occurrence in patients with liver disease. However, hyperammonemia without cirrhosis is rare.

Uncontrolled diabetes can lead to elevated ammonia levels and complications like diabetic ketoacidosis can be life-threatening. Manappallil et al. (2019) have presented a case study of a middle-aged man with developed encephalopathy, hyperammonemia, and diabetic ketoacidosis, suggesting a possible link between hyperammonemia and diabetes

mellitus-induced encephalopathy. In another study, diabetic encephalopathy has been characterized by a motor impairment and cognitive decline and the recent research has explored the metabolic changes and the relationship between metabolic organs and the brain in the etiology of neurological diseases (Cheon and Song 2021). Research by Sakhr et al. (2020) have found that children with T1DM and poor glycemic control, accompanied by attention deficit hyperactivity disorder, exhibit higher levels of ammonia and altered copper/zinc ratios. Additionally, T2DM disrupted the gender-specific regulation of nitrogen-related metabolites, leading to increased blood levels of ammonia, citrulline, and malondialdehyde (Contreras-Zentella et al. 2019).

Previously, Goldstein et al. (1980) have demonstrated that renal ammonia production is significantly increased in diabetic ketoacidosis and ketone bodies do not appear to limit renal ammonia production *in vivo*, contrary to previous findings in acidotic dogs. In a study involving non-diabetic adults, the administration of insulin had an hour-long effect on urea and ammonia metabolism, as well as an impact on glutamine metabolism. This has been observed through the measurement of 15N enrichment in urine samples during an infusion of labeled glycine, ammonium chloride, and L-aspartic acid, with or without insulin administration (Stein et al. 1976). Overall, these studies shed light on the relationship between hyperammonemia, diabetes mellitus, and encephalopathy, emphasizing the need for further investigation and understanding of these connections.

Bilirubin

Bilirubin belonging to tetrapyrrolic superfamily, is a highly conserved group of molecules found in both plants and organisms. Tetrapyrroles play various roles in chronobiology, energy production, transportation, and oxygen homeostasis through hemoglobins and myoglobin (Vitek 2012). Heme proteins are broken down by heme oxygenase into bilirubin, which is further converted to biliverdin and then bilirubin by biliverdin reductase. Hepatocytes process bilirubin, converting it into a water-soluble form for excretion through the enzyme uridine diphosphate-glucuronosyl transferase. In healthy individuals, the total bilirubin level, a combination of conjugated and unconjugated bilirubin, typically ranges from 0.3 to 1.2 mg/dL (Hull and Agarwal 2014). Despite previous concerns about its toxicity, recent research has demonstrated that bilirubin can have beneficial effects on the human body, such as scavenging reactive oxygen species, anti-inflammatory effects, and direct effects on cell signaling (Vitek 2012).

Low serum bilirubin levels in patients with T2DM may indicate the need for improved management, and monitoring serum bilirubin alongside HbA1c testing can be helpful in the follow-up of diabetic individuals (Erkus et al. 2018). Low levels of total bilirubin in the blood have been associated with a higher incidence of T2DM in individuals with impaired fasting glycemia or impaired glucose tolerance (Yang et al. 2019). However, Wang et al. (2017) have found contradictory results, suggesting that direct bilirubin levels were associated with an increased risk of developing T2DM in middle-aged and elderly individuals. Another study has revealed a linear relationship between the occurrence of diabetes in older individuals and quartiles of serum total bilirubin, with a decrease in diabetes prevalence as serum total bilirubin levels increased within the physiological range. Serum total bilirubin within the physiological range has been identified as an independent risk factor for diabetes in older patients (Zhong et al. 2019).

Recent studies have identified a correlation between albuminuria and total bilirubin levels in individuals with T2DM. Li et al. (2017) have focused on Chinese patients with T1DM and examined the relationship between bilirubin levels and the prevalence of diabetic nephropathy. The study has found that high bilirubin concentrations were independently and adversely associated with albuminuria and the prevalence of diabetic nephropathy in individuals with T1DM. In another study, Wei et al. (2021) have investigated whether obesity could modify the cross-sectional association between serum total bilirubin and the risk of T2DM in the general population. The findings have revealed that higher serum total bilirubin levels were associated with an increased incidence of T2DM, and it was observed for the first time that body mass index might attenuate the relationship between bilirubin and T2DM. Furthermore, Zhu et al. (2017) have discovered a connection between bilirubin levels and a higher risk of developing diabetic retinopathy, diabetic nephropathy, and diabetic neuropathy. The results of their meta-analysis suggested that bilirubin might serve as a preventive measure against the development of diabetes complications.

The retrospective study was performed to examine the relationship between neonatal hyperbilirubinemia and hypoglycemia in Chinese pregnant women

with diabetes, as well as the factors that influence this correlation. The study findings have revealed that among neonatal outcomes, congenital heart disease was identified as a risk factor for both neonatal hypoglycemia and hyperbilirubinemia. Notably, there was a significant correlation between neonatal hyperbilirubinemia and hypoglycemia in women with diabetes in pregnancy. Furthermore, the offspring of diabetes in pregnancy with multiple risk factors were found to have a significantly higher likelihood of experiencing neonatal hyperbilirubinemia (He et al. 2022). In another study, it has been investigated how bilirubin levels change in newborns of women with gestational diabetes during the first 48 hours after birth. It is indicated that future research focusing on the risk of high bilirubin levels in these newborns should take into account the bilirubin trajectory beyond the initial 48 hours. Additionally, it is important to consider a comprehensive range of pre-pregnancy and gestational factors that can affect the prognosis (Zanardo et al. 2023). In addition, it has been found that an inverse relationship between elevated levels of direct bilirubin was present in the second trimester of pregnancy and a reduced likelihood of developing GDM (Liu et al. 2017).

Increased levels of bilirubin in the blood due to higher carbohydrate intake during the early stages of pregnancy are associated with a decreased incidence of GDM in overweight and obese pregnant women (He et al. 2021). However, physiological importance of total bilirubin in GDM was elucidated. There has been a correlation found between decreased levels of total bilirubin in the bloodstream and a higher occurrence of GDM in pregnant women from Japan. The study findings have suggested that reduced levels of bilirubin may play a role in the development of GDM (Nishimura et al. 2018).

Bilirubin has the potential to be a biomarker and treatment target for diabetic nephropathy. Future studies should focus on evaluating the accuracy of bilirubin in predicting the rate of diabetic nephropathy progression for effective treatment planning. Investigating animal models of hyperbilirubinemia, such as the Gunn rat, in the context of diabetic kidney disease, may be an important area of research. It is recommended that future studies should clearly define the usefulness of bilirubin as a clinical tool for diagnosis and treatment of diabetic nephropathy by determining whether it serves a prognostic or therapeutic role, identifying specific disease states associated with bilirubin causality, and elucidating the underlying mechanisms (Hull and Agarwal 2014).

Bile acid

Hepatocytes are responsible for producing primary bile acids, which are then converted into secondary bile acids by gut bacteria in the intestine. Bile acids play a crucial role in controlling lipid, glucose, and energy balance by activating the Takeda G protein-coupled receptor 5 on cell membranes and the farnesoid X receptor in the nucleus. They also help maintain the integrity of the intestinal barrier and regulate the population and growth of gut bacteria. The composition and amount of circulating bile acids are influenced by the gut microbiome. Dysbiosis and disruptions in bile acid homeostasis are associated with conditions like diabetes, obesity, and NAFLD, and targeting bile acid signaling and the gut microbiome holds therapeutic potential in these conditions (Ferrell and Chiang 2019).

The bile cholesterol saturation and bile acid composition were examined in 12 non-obese male individuals with insulin-dependent diabetes and 28 control subjects. In the diabetic group, the total concentration of bile lipids in the bile-rich duodenal aspirate was found to be lower. The higher glycine-taurine ratio of the conjugated bile acids and the increased levels of secondary bile acids observed in these insulin-dependent diabetics could be attributed to either increased bacterial infiltration in the small intestine or reduced absorption of bile acids in the terminal ileum (Meinders et al. 1981). Moreover, the impact of taurine conjugated bile acid, tauroursodeoxycholic (TUDCA) on the regulation of blood sugar levels in the initial phases of T1DM has not been thoroughly investigated. Hence, a study was conducted to evaluate the effects of TUDCA on glycemic control in mice with early-stage T1DM. The study findings indicate that TUDCA positively influenced glucose metabolism in these mice, suggesting that it could be a promising treatment option for managing blood sugar levels during the early stages of T1DM (Bronczek et al. 2019).

In addition to their primary role in fat absorption, bile acids have various other functions. Derived from cholesterol, they contribute to maintaining healthy cholesterol levels. Bile acids also participate in carbohydrate and fat metabolism by promoting the synthesis of glucagon-like peptide 1 in the distal small bowel and colon. They enhance insulin sensitivity, thereby impacting T2DM and insulin resistance. Bile acid metabolism is influenced by obesity and diabetes. Dietary restrictions and weight loss, such as those induced by bariatric surgery, affect the utilization of lipids, carbohydrates, and

bile acids in the body. Recent studies suggest that the forkhead transcription factor plays a pivotal role in regulating bile, lipid, and glucose metabolism, although findings have been contradictory (Tomkin and Owens 2016).

As important signaling molecules, bile acids affect glucose homeostasis by activating receptors on the nucleus and cell surface. Changes in bile acid metabolism are observed in T2DM, but it is not yet clear if these changes have pathogenic effects. Elevations in bile acid signaling in T2DM patients with normal weight and overweight may represent compensatory increases to maintain glucose balance. Further research is needed to understand the weight-dependent effects of bile acid signaling on the development of T2DM, as these alterations appear to be diminished by obesity (Taylor et al. 2014). Legry et al. (2017) have evaluated the changes in bile acids associated with non-alcoholic steatohepatitis were examined independently of insulin resistance or body mass index. Although liver necroinflammation does not occur in obese patients, changes in bile acid metabolism are linked to the metabolic profile of non-alcoholic steatohepatitis, particularly insulin resistance (Legry et al. 2017).

The metabolism of bile acids is a significant factor in overall metabolism, but it remains unclear whether the presence of bile acid metabolites during early pregnancy is linked to the risk of GDM. The potential correlation between total bile acid (TBA) levels during the first trimester of pregnancy and the occurrence of GDM was examined. The study findings have indicated that women in the highest category of TBA levels had a significant increase in the risk of developing GDM compared to those in the first category. It has been found that elevated TBA levels during the first trimester, even within the normal range, may serve as an indicator of an increased risk for GDM (Hou et al. 2016). The nested case-control study was conducted to find the association between bile acid metabolites during early pregnancy and the risk of gestational diabetes in Chinese women. Bile acids have shown an inverse association with the risk of GDM (Li et al. 2018). The relationships between plasma bile acid metabolites, particularly during early pregnancy and the risk of GDM in pregnant women were examined. The study findings indicate that the levels of circulating bile acids in early pregnancy were linked to the risk of GDM, regardless of other risk factors for GDM. The bile acids most strongly associated with GDM were primary conjugated bile acids and secondary unconjugated bile acids (Wu and Xu 2022).

Gamma-glutamyl transferase (GGT)

GGT is found on the outer surface of many cells including liver and biliary system, facilitates the transport of glutathione, a vital element of cellular antioxidant defenses, into the cell. GGT is often used in conjunction with other liver enzymes to assess liver function. Elevated levels of GGT have been recognized as an indicator of alcohol consumption or liver disorders. In addition, elevated levels of GGT have been linked to insulin resistance and an increased risk of developing T2DM. GGT levels have been proposed as a marker for oxidative stress and liver dysfunction, which are both associated with the pathogenesis of diabetes. GGT expression is influenced by oxidative stress and can be released in response to cellular stress. In recent years, serum GGT values have been linked to various cardiovascular disease risk factors and components of insulin resistance syndrome. Research suggests that an increase in GGT concentration within its normal range could serve as a sensitive and early biomarker for the onset of diabetes (Lee et al. 2003).

Observational studies have shown that high levels of serum GGT are associated with an increased risk of prediabetes and T2DM. However, it remains unclear whether this relationship is due to reverse causality, residual confounding, or both. Mendelian randomization studies have not provided evidence for a causal relationship between GGT and the risk of diabetes or prediabetes. Therefore, the association observed in observational studies is likely attributed to confounding bias or reverse causation. It is unlikely that interventions targeting GGT reduction would effectively prevent diabetes (Nano et al. 2017). Considering that GGT activity may reflect various processes relevant to diabetes pathogenesis, measuring GGT levels in first-degree relatives of T2DM patients can help identify individuals at high risk for developing diabetes (Haghighi et al. 2011).

GGT is a sensitive diagnostic marker for the early detection and prediction of impaired glucose tolerance and metabolic syndrome. It is a low-cost, highly sensitive, accurate, and widely used laboratory test that can serve as a helpful marker for both impaired glucose tolerance and metabolic syndrome (Yousefzadeh et al. 2012). Studies have shown that GGT levels have a positive correlation with the risk of impaired fasting glucose and can be used to predict the likelihood of progression to prediabetes (Wang et al. 2021). Additionally, GGT and uric acid have been identified as new risk factors for developing diabetes. The combined levels of GGT and uric acid may have

predictive value for the onset of diabetes, particularly in Korean women (Lee et al. 2017b).

Higher levels of GGT during the initial and middle stages of pregnancy, even if they fall within the typical normal range and the gradual rise from early to mid-pregnancy might play a role in the development of GDM. This emphasizes the possibility of utilizing GGT levels for early screening or preventive measures to reduce the risk of GDM (Zhu et al. 2018). In the same line, the findings indicate that pregnant women who have elevated GGT levels in the early to middle stages of pregnancy are at a greater likelihood of developing GDM. Having a GGT level above 26.9 U/L may serve as an indicator of heightened risk for future GDM development and should be given additional attention (Kong et al. 2018). The level of pregravid GGT has been found to be a predictor of the future risk of GDM. Indicators of liver fat accumulation, such as GGT levels, can be detected years before pregnancy and may aid in the identification of women who are at higher risk of developing GDM (Sridhar et al. 2014).

Immunoglobulins

Patients with DM are more susceptible to specific infections and experience more severe consequences associated with common diseases. Quantifying immunoglobulin levels can improve our understanding of immune dysfunction in T1DM. The occurrence of low immunoglobulin levels in these patients was found to be statistically significant when compared to the general population. In T1DM patients, a higher prevalence of deficiencies in IgG, IgA, IgM, or a combination of these immunoglobulins was observed. Impaired humoral immune response due to hypoglycemia may increase the vulnerability to infections. Further research on immunoglobulin levels and antibody production in T1DM can provide insights into the underlying reasons for poor immunity (Mazer et al. 2011). The link between T1DM and immunoglobulin A deficiency (IgA-D) has long been recognized in various populations. The prevalence of IgA-D was determined among individuals with T1DM from a specific geographical area and explore the clinical characteristics of these individuals. This study reveals that the prevalence of IgA-D among Sicilian patients with T1DM is 5.3%, which is significantly higher than what has been reported in other studies conducted in Italy. Furthermore, our findings indicate a higher occurrence of IgA-D in males and highlight thyroiditis as the most common autoimmune disorder found in these patients. Lastly, this case report demonstrates that the diagnosis of IgA-D consistently followed routine IgA measurements when screening for celiac disease, with no history of recurrent infections observed in each patient (Greco and Maggio 2015). In another study, the variations in serum concentrations of IgA, IgG, and IgM were investigated in relation to sex and HLA-B phenotype. Among the T1DM patients, two individuals whom diabetes developed before the age of 15 were found to have complete IgA deficiency, and an additional patient had complete IgG deficiency. However, the IgG levels in diabetic patients were significantly lower than those in control subjects. We observed a potential association between lower IgA concentrations and the presence of HLA-B8 in the subgroup of 53 patients. No significant relationship was found between HLA phenotypes and IgM or IgG levels (Hoddinott et al. 1982).

Poor glycemic management may be associated with elevated levels of IgA and IgG serum antibodies in T2DM patients. Increased antibody levels could contribute to the promotion of periodontal disease (infections and inflammation of the gums and bone) in poorly managed in T2DM patients (Awartani 2010). The levels of circulating immunoglobulins were assessed and identify additional metabolic factors that affect the humoral immune response in Ghanaian individuals with T2DM. The study showed that median levels of IgA and IgG were found to be higher in the T2DM patients. These study findings indicate that the humoral immune response is modified in individuals with T2DM and serum immunoglobulin levels could potentially serve as valuable biomarkers in the investigation and treatment of DM (Asare-Anane et al. 2018). In another study, new connections were established between the IgG N-glycome (glycan profile) and T2DM within an Australian population, highlighting the potential involvement of proinflammatory mechanisms. Additionally, the changes observed in IgG N-glycomic patterns hold promise as potential biomarkers of inflammation for diagnosing T2DM and monitoring its progression towards cardiovascular disease or renal failure (Li et al. 2019b). The relationship between IgG N-glycans and the risk factors for T2DM has been established. However, it is still uncertain whether these associations signify causal effects. Among individuals of East Asian descent, there is a notable correlation between genetically determined IgG N-glycans and an increased susceptibility to T2DM. Additionally, the connection between IgG N-glycans and inflammation is not fully comprehended. This study findings present innovative genetic evidence suggesting a

causal association between IgG N-glycans and T2DM (Wang et al. 2022).

The influence of GDM on the concentrations of lactoferrin, secretory immunoglobulin A (SIgA), IgG, and IgM in early colostrum, colostrum, and transitional milk samples was investigated. The results have indicated that early colostral IgG and colostral lactoferrin levels were higher in mothers treated with insulin compared to diet-control diabetic mothers. However, the presence of GDM in mothers did not significantly affect the immunological quality of early milk. It should be noted that GDM is associated with an elevated risk of having a high-care newborn and can impact maternal well-being (Lis-Kuberka et al. 2021). The progression from early to late pregnancy showed a correlation between alterations in the coating of bacteria by SIgA and the occurrence of GDM. In GDM cases, there was a depletion of SIgA-coated beneficial gut bacteria. These findings have suggested that probiotics consisting of these beneficial bacteria, which are lacking in GDM, have the potential to be as a preventive measure against the development of GDM. In individuals with GDM, markers associated with a "leaky gut" condition, such as zonulin and lipopolysaccharide (LPS), exhibited a significant increase compared to the non-diabetic control group. The diversity of SIgA-coated microbiota, as measured by the Shannon index, was higher in late pregnancy compared to early pregnancy and reached the highest levels in the GDM group. These findings have suggested that GDM may be linked to intestinal mucosal damage and inflammation-induced dysbiosis of SIgA-coated microbiota. Furthermore, laboratory experiments demonstrated that SIgA-coated *L. reuteri* can effectively lower the level of LPS in GDM cases (Zhang et al. 2021).

The specific immune response was assessed and compared in pregnant women who have chronic *Toxoplasma gondii* infection, both with and without GDM, as well as the humoral response in their newborns. The findings have revealed a correlation between elevated blood glucose levels and reduced levels of anti-*T. gondii* antibodies, accompanied by decreased IgG avidity in patients who developed GDM. Additionally, the group with GDM displayed weakened immune responses in Th1, Th2, and Th17 profiles, indicating a potential link between GDM and the negative modulation of both humoral and cellular immune responses against *Toxoplasma gondii* (Oliveira-Scussel et al. 2022). However, various aspects of glucose homeostasis and lipid metabolism during pregnancy demonstrate strong connections with different N-glycosylation characteristics. However, the N-glycans present in plasma proteins, IgG, and IgA were unable to distinguish between pregnant women with and without GDM. This lack of differentiation may be attributed to the numerous physiological changes that occur during pregnancy, which can complicate the influence of GDM on protein glycosylation (Stambuk et al. 2023).

Lactate dehydrogenase (LDH)

LDH is an enzyme involved in energy metabolism, and alterations in LDH levels have been observed in individuals with diabetes. Increased LDH activity may reflect metabolic disturbances, including impaired glucose utilization and altered lactate production, which can contribute to diabetic complications. DM is characterized by a deficiency in insulin secretion and/or action, leading to hyperglycemia, which can result in damage to various organs, including the salivary glands. Malicka et al. (2016) have compared the levels of salivary LDH, AST, and ALT in individuals with diabetes. The study has found higher concentrations of salivary LDH, AST, and ALT in T1DM compared to T2DM or the control group, supporting the hypothesis that autoimmune damage to the salivary glands is related to the pathogenesis of diabetes. In some types of T2DM, overexpression of LDH activity disrupts the normal glucose metabolism and insulin secretion of beta cells, potentially leading to insulin secretory abnormalities (Ainscow et al. 2000). Diabetes is often associated with inflammatory diseases, and LDH is an inflammatory marker that can be useful for monitoring disease progression. Dmour et al. (2020) have suggested that measuring LDH levels can help assess the prevalence of diabetes. LDH isoenzyme profiles in patients with T1DM and T2DM and vascular complications have been evaluated using an advanced micro-method. Although analyzing LDH isoenzyme patterns can aid in identifying diabetic vascular complications, a broader classification is preferred since non-diabetic patients with vascular complications also showed a similarly high LDH-3/LDH-4 ratio (Nair et al. 1985).

High lactate production is a common biological characteristic of both cancer and diabetes, and aberrant lactate metabolism has been associated with both diseases. Elevated lactate levels promote the onset and progression of diabetes and cancer by increasing insulin resistance and the malignant phenotype of cancer cells (Wu et al. 2016). LDH, a diagnostic marker for the metabolic syndrome, can be used to investigate metabolic abnormalities related to breast cancer and diabetic complications.

Elevated LDH is associated with poor outcomes in breast cancer and affects the prognosis of breast cancer metastases. Kashtl et al. (2023) have suggested that LDH may serve as a predictor for breast cancer. Additionally, DM is increasingly recognized as a significant cause of death in cancer patients and a risk factor for cancer.

Total protein

Insulin resistance is a characteristic feature of T2DM, a metabolic disorder affecting protein metabolism. There is significant interest in proteomic analysis of plasma and serum to identify and characterize protein biomarkers for various diseases. Analyzing biomarker levels can aid in the early diagnosis and treatment of T2DM (Zaidi et al. 2019). Protein glycation, particularly of hemoglobin and albumin, has been associated with T2DM. A study by Nazki et al. (2017) have investigated the relationship between variations in albumin and total protein levels and glycated hemoglobin. The findings have suggested a potential inverse correlation between HbA1c readings and albumin levels, which may provide insights into the interaction between proteins and glucose, contributing to our understanding of hyperglycemia (Nazki et al. 2017). Another study by Gul and Rahman (2006) have compared blood protein levels in diabetic patients with and without retinopathy. Diabetic patients with and without complications exhibited higher levels of various parameters, such as fasting plasma glucose, glycosylated hemoglobin, and glycosylated plasma proteins. Non-diabetic patients with retinopathy; however, had these parameters within normal ranges, although their gamma globulin levels may have decreased due to retinopathy. The consumption of total protein and animal protein from red meat showed a positive correlation with T2DM. Conversely, there was an inverse relationship between animal protein intake and the consumption of refined grains. The associations between protein intake and T2DM may vary based on dietary patterns. Protein intake recommendations for preventing diabetes may consider the individual's dietary pattern (Ke et al. 2018). For many patients with T2DM, the target is to consume 20–30% of total calories as protein, with exceptions for individuals with compromised renal function. This level of protein intake can assist in glycemic management, promote satiety, maintain lean body mass during weight loss in individuals with diabetes and prediabetes, and meet the higher protein requirements of older adults (Campbell and Rains 2015).

Conclusions

This article concludes that liver parameters including albumin, ALT and AST, ALP, AFP, AAT, ammonia, bilirubin, bile acid, GGT, immunoglobulin, LDH, and total protein, play significant role in the pathogenesis of different types of DM (T1DM, T2DM, and GDM) as explained in Figures 2 and 3. The role of AFP and total protein in T1DM, as well as ammonia, LDH and total protein in GDM, is not as well-documented due to limited available data. In summary, liver parameters are important in diabetes because they provide insights into liver health, help assess the impact of diabetes on liver function, detect liver-related complications, and ensure the safe use of diabetes medications. Regular monitoring of liver parameters is essential for managing diabetes effectively and preventing potential complications. In addition, it is recommended that therapeutic approaches are essential to manage these liver parameters in DM so that, the prevalence of DM could be reduced.

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