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ASSOCIATION BETWEEN CHRONIC HYPERGLYCEMIA AND LIVER FUNCTION TEST ABNORMALITIES IN DIABETIC PATIENTS

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ABSTRACT

Diabetes mellitus is characterized by hyperglycemia and insulin production and activity abnormalities. Some of the liver parameters discussed in this review are Alanine aminotransferase ALT, Alkaline phosphatase (ALP), Aspartate aminotransferase serum (AST), Gamma-glutamyl transpeptidase GGT, Total bilirubin (TBIL). The factors play a significant role in the occurrence of different types of diabetes such as gestational diabetes (GDM), type 1 diabetes (T1DM), and type 2 diabetes (T2DM). The article highlights that high levels of ALT and AST are associated with inflammation or damage of the liver, particularly in the absence of alcoholic fatty liver disease (NAFLD), and low albumin concentrations could indicate inflammation. Raised ALP can have an effect on changes in bone metabolism, biliary malfunction, or liver inflammation. High bilirubin levels are independently related to both a high risk of T2DM and albuminuria in T1DM. The increase of GGT levels is believed to be the evidence of oxidative stress and liver damage in the situation of T2DM..

Keywords: *type 1, type 2, gestational diabetes, liver parameters, etiology, and diabetes mellitus*

INTRODUCTION

Diabetes is a chronic illness that is brought about by excessive glucose level in the blood as a result of inadequate insulin secretion or failure of insulin to be properly used(1). Highly elevated blood glucose levels that are either caused by insufficient insulin or unresponsive cells to its use are therefore the symptom of diabetes. The occurrence of diabetes mellitus (DM) is over 422 million around the world. By 2040, the diabetic population will have reached 642 million, with the majority of them living in the low-income and middle-income countries(2). Diabetes is a national health issue of concern that affects individuals across the globe with the rate of its occurrence in developed and developing nations increasing at a very high rate(3).

Diabetes is one of the most important and challenging health issues encountered by the global population currently, as it is getting more prevalent. The prevalence of diabetes has been on the rise in most regions of the world where the rapid economic growth has led to urbanization and embracement of modern lifestyle practices(4). There are 463 million adults aged 20-79 with diabetes in 2019, constituting 9.3 percent of the total adult population of the world. This is

estimated to increase to 578 million in 2030 or 10.2 per cent of the entire adults in the world, and to 700 million in 2045 or 10.9 per cent of the entire adults worldwide. In 2019, 9.6 percent of men and 9.0 percent of women all over the world had diabetes according to the estimates(5).

Hyperglycemia with the related carbohydrate, fat, and protein metabolic dysfunctions influence various body organs and interfere with their functional activity. The onset of these disruptions is slow and is primarily caused by the harmful impact of hyperglycemia and its associated metabolic anomalies to the normal structure and functioning of micro- and microvasculature that are in the center of the body structure and functions. The dysfunction of organ system vasculature results into micro and macrovascular complications due to the structural and functional impairments of the same(6). These complications are characterized by organ damage, dysfunction, and, finally, organ failure and have an impact on body organs, including eyes, kidneys, heart, and nerves. There are complications surrounding the eyes which lead to retinopathy that advances to blindness. Nephropathy and possible renal failure are the consequences of kidney related complications. Hypertension and coronary heart disease are problems associated with the heart. The renal failure may occur as a result of complications related to the kidneys. The complications associated with the heart are hypertension and coronary heart disease. Nerve complications are associated with neuropathy, which may be either autonomic and/or peripheral(7). Autonomic neuropathy typically presents with cardiovascular, gastrointestinal and genitourinary (including sexual) dysfunctions whereas long-term peripheral neuropathy is frequently linked to foot ulcers necessitating amputations and Charcot joints (osteoarthropathy). The cerebrovascular disease, peripheral arterial disease and coronary heart disease also known as atherosclerotic cardiovascular disease have become quite common in diabetes and form part of the causes of the great majority of morbidity and mortality associated with diabetes(8).

Diabetes is associated with a range of liver illnesses such as nonalcoholic liver disease, steatohepatitis and liver cirrhosis. The mechanism of pathophysiology between diabetes and liver disease is complicated and not clear-cut. Moreover, diabetes predisposes liver cirrhosis complications and related death. Treatment of such patients involves administration of regular oral diabetes drugs with others proving to have more advantages than others(9).

History Diabetes is a disorder of blood sugar resulting from insufficient insulin production in the body, causing the body's cells to use up glucose that gets absorbed into the body (Nordstrom, 2008).<|human|>Overview of Diabetes Mellitus History Diabetes is a blood sugar disorder that occurs due to lack of enough insulin levels in the body leading to the body cells utilizing the glucose that enters the body (Nordstrom, 2008).

Diabetes mellitus is a serious, chronic, metabolic condition characterized by increased blood sugar concentrations due to lack of enough insulin production by the pancreas or inefficient use of insulin by the body. Type 2 Diabetes Mellitus (T2DM) is associated with around 90 percent of the incidences in adults. The most common type of diabetes is the type-2 diabetes mellitus(T2DM), commonly referred to as the adult-onset diabetes or the age-onset diabetes(10). It is a milder type of diabetes because its onset is gradual (it may develop during decades) and most cases can be controlled by diet and oral drugs. Nevertheless, the outcomes of untreated and uncontrolled type 2 diabetes are no more harmless than type I(11).Nonetheless, it seems that both the environmental and genetic factors are involved. Type 2 diabetes leads to 8595 percent of all cases of diabetes in high-income countries; in low- and middle-income countries the proportion is even greater because of the rapid sociocultural changes, the ageing population, increasing urbanization, declining physical activity, and unhealthy lifestyle and behavioural patterns(12).

The two primary types of diabetes based on the existing categorization are type 1 diabetes (T1DM) and type 2 diabetes (T2DM). Historical factors that have been used to separate the two forms are age of onset, extent of loss of 8 cell functionality,

extent of insulin resistance, presence of autoantibodies associated with diabetes and requirement of insulin to survive(13).

However, none of these characteristics makes a clear distinction between the diseases and does not provide a complete spectrum of diabetes phenotype. There are those individuals with type 1 diabetes who experience a rapid rate of β-cell degradation and those whose rate is slow. Even though it may also occur among adults, the rapid-progressing type of T1DM is normally observed in children. Ketoacidosis can also be a symptom of the first disease in some individuals, particularly children and adolescents. Others might experience mild hyperglycemia, which when exposed to infection, or other stressful events, may easily advance to severe hyperglycemia and/or ketoacidosis. Other individuals, particularly adults may possess sufficient remaining 2 -cell activity to prevent ketoacidosis over several years(14).

When C-peptide levels in blood or urine are low or undetectable, the minimal or absent production of insulin is occurring in the typical clinical course of diabetes type 1. The characteristics of type 2 diabetes are peripheral insulin resistance and pancreatic beta cells insulin deficiency. Insulin resistance leads to reduced uptake of glucose by muscle cells, heightened liver production of glucose and accelerated breakdown of fat, the effects of insulin resistance have been attributed to elevated plasma levels of proinflammatory cytokines and free fatty acids. The role of excess glucagon is impossible to overestimate; in reality, the type 2 diabetes is an islet paracrinopathy in which the reciprocal association between the insulin-secreting beta cell and the glucagon-secreting alpha cell is destroyed leading to hyperglucagonemia and consequent hyperglycemia(11).

Type 2 diabetes mellitus requires both insulin resistance and insulin-deficiency production. As an example, insulin resistance is present in all fat individuals and only the individuals are unable to increase secretion of insulin to the extent of compensating their insulin resistance develop diabetes.

They could possess too low insulin levels that are insufficient to the glycemia(15).

Diabetes mellitus (DM) is becoming increasingly prevalent in individuals across all ages globally, becoming a major burden to the health care systems of the population. Insulin is the most important hormone in energy metabolism, glucose, fat, and protein metabolism and in the maintenance of homeostasis, being a peptide hormone composed of 51 amino acids. Reduced insulin secretion and action is one of the leading causes of the pathophysiology of diabetes mellitus. Hyperglycemia and diabetes mellitus necessitate reduced pancreatic 8-cell activity and progressive hyperglycemia is also associated with progressive degradation of 8-cell activity(16).

The current definition of insulin resistance is reduced responsiveness (maximal effect of insulin) or sensitivity (insulin concentration that causes a half-maximal response) to the metabolic actions of insulin including insulin-mediated glucose disposal of muscle and adipose tissue and liver gluconeogenesis inhibition, that was initially proposed to account for the high dose of insulin required by patients with diabetes. Obesity and related dyslipidemia and hypertension are associated with insulin resistance and increase the chances of cardiovascular disease, a state referred to as metabolic syndrome. When working with patients in the clinical setting, it is important to assess insulin resistance and 8 cell functions of the pancreas to determine the type of diabetes mellitus and the formulate the most effective care and prevention plan(17). Also, it can be applied in science such as the development of new antidiabetic drugs and other experimental and clinical studies on diabetes mellitus and metabolic diseases. There have been several methods and indices that have been established to measure insulin resistance/sensitivity and the 8-cell functioning basing on the results of both static and dynamic tests. The latter are still challenging, albeit, due to the complexity of the 3-cell response to various stimuli, feedback, insulin signaling, and organ metabolism. The development of a new index is an ongoing research to help in solving the theoretical and practical issues. In order to choose the optimal method and index to be used in the proposed work and clinical case, it is also essential

to understand the theoretical foundation, advantages, and limitations of each strategy(18).

Insulin is secreted by the pancreatic 2-cell in reaction to the plasma concentration of glucose and nutrition (free fatty acids, amino acids), and also is regulated by other signals, including hormones, neurotransmitters, and metabolic factors. Glucose is the major regulator of the survival and performance of the β-cells. The arrival of glucose at 20 cells via glucose transporter is immediately phosphorylated by glucokinase to glucose-6-phosphate which is oxidized in mitochondria to form adenosine triphosphate (ATP). An increase in the ATP/adenosine diphosphate ratio of the β-cell leads to the closure of the KATP channel, leading to cell membrane depolarization, and opening of L-type voltage-dependent calcium channels to release insulin/proinsulin into the intracellular granules(18). The elimination of insulin occurs primarily through insulinase activity in the liver, kidneys and a few other organs and the pharmacologic half-life of insulin is estimated to be between five and eight minutes. The induction of insulin secretion (GSIS) by glucose occurs in a biphasic manner; the initial phase is a fast, initial peak and the later phase is a slow, gradually increasing peak. First phase insulin secretion is rapidly triggered by increased cytosolic Ca2+, and is primarily the effect of exocytosis of insulin granules that were already primed (ready-to-release). The second phase of insulin secretion is slow and is triggered by the formation of cytosolic Ca2+, ATP, and cyclic adenosine monophosphate and the release of fresh insulin granules(19).

Insulin promotes the integrative response of nutritional availability anabiosis by binding to the plasma membrane-bound receptor on the target cell. The insulin receptor is composed of the α and 2 chains, which are known as the insulin receptor (IR), is a tyrosine kinase activated by insulin and insulin-like growth factors I and II. A and B represent the two IR isoforms; although B is more insulin-specific and is the predominant isoform. Adipose tissue and the liver express B isoform as well as muscle, and thus it is thought that most of the metabolic effects of insulin are mediated by it. The binding of these endogenous ligands to the alpha chain of IR causes structural changes in the 2 nd chain by causing auto- phosphorylation of the tyrosine residues. These changes are important to further activities such as the binding of IR substrates by adaptorproteins(20).

Insulin also affects the skeletal muscle, the liver, and white adipocytes in a direct manner which shows the role of insulin in glucose homeostasis. These tissues require tissue specific insulin signaling pathways. Insulin enhances the movement of glucose and net glycogen synthesis in skeletal muscle, which is a common insulin-acting tissue to aid in glucose uptake and storage. Insulin inhibits gluconeogenesis through down-regulation of gluconeogenic genes, up-regulation of adipogenic genes, and initiation of liver glycogen. Insulin enhances glucose uptake and adipogenesis with inhibition of lipolysis in the white adipocyte tissue(21).

The first stage insulin secretion GSIS is known to be critical in the processes by which fasting is replaced by feeding by inhibiting hepatic glucose production (HGP), inhibiting lipolysis, and preparing target cells to act on insulin across the endothelial barrier. Similar to the initial phase albeit to lesser extent, the second phase insulin secretion of GSIS reduces HGP [15]. More importantly, it enhances the peripheral tissue glucose utilization. Therefore, the second phase level of insulin secretion is important in saving glucose homeostasis despite the fact that its importance is relatively underestimated when compared to the first phase.(22).

Liver Function Tests: An Overview

The analysis of several proteins and enzymes, such as albumin (ALB), total protein (TP), total bilirubin (TBIL), alkaline phosphatase (ALP), ALT, and AST, is a typical LFT. Usually asked with an LFT are prothrombin time (PT) and gamma-glutamyl transpeptidase (GGT) levels. LFTs are not a direct measurement of the liver function and hence the name liver function test is not an accurate name. Rather, they indicate cholestasis (obstruction or damage of biliary system) or hepatocyte injury. ALB and PT though nonspecific, assess the synthetic liver activity. Protein-losing enteropathies, nephropathies,

nutritional status may alter ALB levels, and warfarin, vitamin K deficiency, or consumptive coagulopathy may alter. PT(23).

Table no 1: Test results: what's normal, what suggests liver damage

Parameter	Description	Normal Range	Range indicating liver damage
Alanine aminotransferase ALT	highly concentrated in the liver	3 to 30 U/L	>3 times upper limit of normal
Alkaline phosphatase (ALP)	highly concentrated in the liver, bile ducts, placenta, and bone normal	35 to 150 U/L	>2 times upper limit of normal
Aspartate aminotransferase serum (AST)	Enzymes are highly concentrated in heart muscle, liver cells, skeletal muscle cells, and (to a lesser enzyme level degree) other tissues	11 to 32 U/L	Used to evaluate elevations in other serum enzyme level
Gamma-glutamyl transpeptidase GGT	Enzymes are highly concentrated in the liver, bile ducts, and kidneys	5 to 40 U/L	Used to evaluate elevations in other serum enzyme level
Total bilirubin (TBIL)	Yellow bile pigment produced when liver processes waste products	0.3 to 1.1 mg/dL	>2 times upper limit of normal if associated with elevation in ALT or ALP

Aspartate aminotransferase serum (AST)

These tissues that contain the enzyme ALP include the liver, bile ducts, bones and the intestines.

High concentration of ALP can be an indication of certain types of cancer, bone defects or liver or bile duct problems. Higher ALP levels have been observed in individuals with diabetes particularly individuals having advanced liver disease or complications although the direct relationship between ALP and diabetes is less obvious. The levels of ALP can be influenced by such issues as a dysfunction of the biliary, or inflammation in the liver, and alterations in the bone metabolism, which are connected to diabetes-related issues. Cases of NAFLD have been associated with increased prevalence of chronic renal disease in people with T1DM(24). The association between NAFLD predictors such as ALP in the patients with T1DM has been examined. The individuals with highest percentile rank of albumin leakage in the urine excretion rate possessed large amounts of ALP when compared to the ones with the lowest percentile rank. Moreover, hyperfiltration individuals had higher levels of ALP in comparison with people with normal or mildly impaired estimated glomerular filtration rate (eGFR). It has been established that renal function is associated with markers of NAFLD especially ALP in T1DM patients without albuminuria. Persons with type 1 diabetes have been observed to have intestinal inflammation. The level of fecal intestinal ALP was lower in patients with diabetes compared to the control group. Supplementation of oral intestinal alkaline phosphatase (IAP) increased intestinal IgA hugely in the mice model(25).

The relationship between hyperglycemia and bone deterioration in diabetic patients has been discussed and hence looked into the potential mechanisms that could be contributing to bone

abnormalities in the diabetic patients with varying serum glucose levels. A comparable relationship between the extent of diabetic bone damage and the extent of diabetes was found in which investigated a cohort of diabetics with greater levels of ALP and found a significant relationship with greater mean levels of fasting serum glucose.

ALP is proven to predict death and heart attacks, including insulin resistance and vascular calcification. However, the relationship between ALP and insulin resistance is not evident. investigated the correlation between ALP (total and bone-specific) and insulin resistance characteristics. They found that, but not total ALP levels, the serum levels of bone-specific ALP were closely and independently related with the characteristics of insulin resistance.

Although the correlation between insulin resistance and hepatic inflammation was expected, this novel correlation between insulin resistance and bone-specific ALP demonstrates the connection of insulin resistance with vascular calcification on a molecular level. According to some theories(26), ALP inhibitors can be used to decrease the calification of the arteries of individuals with type 2 diabetes.

The relationship between survival in patients with myocardial infarction and T2DM and plasma ALP has been studied. High levels of ALP were predictors of bad survival in diabetic people with acute myocardial infarction and particularly in cases where renal dysfunction remained low. This observation was specific to the male patients indicating that phosphatase activity might have a unique role in cardiovascular disease among T2DM patients of both male and female gender.

The potential effect modifiers and the potential association of serum ALP and the risk of developing new-onset type 2 diabetes in hypertensive individuals were explored. They found that among this hypertensive non-diabetic group, elevated blood ALP had a significant positive relationship with the risk of new-onset diabetes, especially when considered in people with a lower total homocysteine or higher fasting glucose levels(27).

Also, previous studies have established that IAP, an anti-inflammatory enzyme released by enterocytes, plays the protective role in type 2 diabetes. (28) has studied the long-term impact of IAP deficiency on the pathophysiology of T2DM. They found that IAP deficiency increased the chances of T2DM and that the risk of a patient having T2DM can be ascertained through routine stool alkaline phosphatase (STAP) tests. T2DM can be prevented using oral IAP supplements. The other study established that absence of IAP in animals results in type 2 diabetes. High IAP levels appeared to be protective of diabetes regardless of weight and temporal profiling of IAP can be a useful way of predicting the development of metabolic syndrome, even at an early stage of diabetes development(29).

The severe elevation of ALP was observed in a child with neonatal alloimmune thrombocytopenia and a fetus with GDM issues. The elevation of levels during the early pregnancy was associated with the elevated risk of GDM even when the levels of ALP were in the upper limit of the normal range in the mother. Greater fasting and postprandial blood glucose level was also associated with increased early maternal ALP level. A pregnant woman of 25 years having GDM was observed to have significantly high placental ALP of the isozymes. An abdominal ultrasound scan showed no signs of hepatobiliary disease. The ALP level decreased following delivery; once again not reaching the reference range(30).

Alanine aminotransferase (ALT)

Though AST is an enzyme that is located in liver cells, there are other tissues like kidneys, muscles, and heart where AST can also be located. ALT is primarily concentrated in liver cells(30). The raised ALT in the blood may be attributed to hepatitis or liver cirrhosis or liver cancer. High AST is not as liver-specific as ALT, but in any case, it can be a symptom of liver disease. AST and ALT measures are often measured simultaneously. In the case of diabetes, NAFLD has been associated with insulin resistance and type 2 diabetes. NAFLD patients often experience high ALT and AST levels that can be signs of liver inflammation or liver damage and aggravate the glucose metabolism and insulin insensitivity.

The prevalence of high ALT levels was assessed in a big sample of patients with T1DM and the clinical relationships and potential causes were investigated. Based on the results of the study, individuals with T1DM often experience an elevated level of ALT, which is also associated with NAFLD risk factors. As stated in the article, patients with T1DM and a high level of ALT will have to be investigated further to determine any significant abnormalities that can be addressed through treatments. Moreover, glycogenic hepatopathy is a rare side effect of poor T1DM therapy. Its hallmarks are hepatomegaly (enlarged liver), raised liver enzymes ALT and AST and glycogen accumulation in the liver(23).

Diabetes mellitus (DM) is a non-communicable metabolic disorder, which may be caused by the lack of insulin, or resistance. Some of the liver enzymes which are commonly used as indicators of liver health include ALT and AST. The liver cell damage is manifested by the high level of liver enzymes that are associated with insulin resistance and type 2 diabetes. In spite of the fact that amino acid based hepatic gluconeogenesis significantly contributes to the case of hyperglycemia in diabetes, very little is known regarding the exact biochemical mechanisms involved. The alanine transaminases (ALT1 and ALT2) assist in converting alanine to pyruvate, which is necessary in the process of gluconeogenesis of alanine. ALT2 significantly influences amino acid hepatic gluconeogenesis in diabetes(24).

High liver enzyme levels and in particular ALT levels have been associated with a doubling of risk of type 2 diabetes, without regard to usual risk factors. It means that, especially in Asian societies, ALT can become a useful indicator of identifying individuals who are at high risk of contracting type 2 diabetes. Transaminase levels of blood are an indicator of liver related mortality, which has demonstrated that diabetes is a risk factor in relation to chronic liver disease.

The higher the levels of ALT were three to four times higher in T1DM or T2DM patients compared to those of the general population(25). Suggestions on effective early interventions can be made by further research into the cause and mechanisms of this rise.

have confirmed that the presence of high levels of ALT was a risk of type 2 diabetes, meaning that the liver might be involved in the development of the illness. Rafsanjani cohort study has recently assessed the relationship between diabetes and ALT, AST, GGT, and ALP. These liver enzymes have been identified to be increased in level with increased risks of developing diabetes. These findings suggest that the elevated liver enzymes can serve as indicators of threat of the onset of diabetes(30).

Their measurements of the serum ALT levels of these people showed that the level of serum ALT in first-degree relatives of diabetics who had normal levels of blood sugar was higher, and it might be indicative of an impending illness. The liver enzyme activity was more active in patients with type 2 diabetes compared to healthy people and liver parameters showed significant correlation with diabetes. This is an indication that early intervention based on abnormal liver parameters can reduce mortality and liver complications among diabetics. On the one hand, earlier studies have strongly associated high concentration of ALT, AST, GGT, and ALP with predisposing to diabetes.

ALT, AST, GGT, and ALP were found to be predictive variables of incident diabetes among men and women independently. Whereas T2DM has been associated with abnormal levels of ALT, there is a question of whether higher levels of ALT in the normal range can be used to predict the threat. Even at normal levels, higher ALT levels are reliable indicators of type 2 diabetes irrespective of body mass index levels as, who found that ALT showed a dose-response relationship, found a significant relationship between ALT and AST in a different study, a fact that might reflect transaminase abnormalities in the livers of individuals with type 2 diabetes. The most widespread chronic liver disease is NAFLD that is tightly connected with type 2 diabetes(31).

Approximately three-quarters of patients with type 2 diabetes have fatty livers, and since NAFLD turns into non-alcoholic steatohepatitis, the chances of cirrhosis and hepatocellular cancer grow exponentially. A research conducted by evaluated the hepatic enzyme patterns of

individuals with T2DM and NAFLD. The researchers found the level of ALT to rise in patients with diabetes, but the serum levels of AST, GGT and ALP did not significantly elevate in NAFLD cases.

The Chinese pregnant women who had high liver enzymes (ALT and AST) and a hepatic steatosis index in the early pregnancy period were identified to be at higher risks of GDM regardless of whether or not their levels were within the normal range. There were changes in lipid metabolism that greatly influenced the correlation between HSI and GDM and this showed a possible relationship between the altered lipid processing and the occurrence of GDM among this group of people. It has connected high and inexplicable levels of ALT in the initial pregnancy stages to a heightened tendency of GDM and preeclampsia in the later stages of pregnancy. A study conducted on the correlation between the ALT/AST ratio and the GDM frequency showed that the GDM population bore higher ALT/AST ratio than the normal glucose population. However, it was determined that there was an inverse relationship between the risk of GDM and the early proportion of the AST/ALT levels in the pregnant women. The use of AST/ALT in a nomogram at the early stages of pregnancy demonstrated a good predictive potential in determining the occurrence of GDM.(28).

Gamma-glutamyl transferase (GGT)

Glutathione is an essential element of antioxidant defenses within cells which is carried into the cell by GGT, located on the cell surface of many cells, such as the liver and the biliary system. In most cases, GGT is associated with other liver enzymes when assessing liver performance. High amount of GGT has been determined to be an indicator of alcohol consumption or liver issues. The increased GGT has also been related to insulin resistance and increased risk of developing diabetes type 2. GGT levels have been recommended as an indicator of liver dysfunction and oxidative stress that is associated with the pathophysiology of diabetes. Toxic oxidative stress on GGT expression, which is secretable as a response to cellular stress(32). Recently serum GGT levels have also been associated with several risk factors of cardiovascular disease and also with components of insulin resistance syndrome. It has been shown that an increase in the concentration of GGT in the normal range can serve as an early and sensitive predictor of the onset of diabetes.

Observational studies have identified high levels of serum GGT to be associated with high probability of prediabetes and type 2 diabetes. What remains unclear however, is whether this association is caused by some residual confounding, reverse causality, or both. Mendelian randomization studies have not revealed an association between GGT and the risk of prediabetes or diabetes. This means that a correlation is most likely to be attributed to confounding bias or reverse causality in observational studies(33).

GGT is a sensitive diagnostic marker of the early detection and prediction of metabolic syndrome and diminished glucose tolerance. It is a simple, cheap, very sensitive, and precise lab examination, which can be used as a convenient indicator of metabolic syndrome and poor glucose tolerance. As the research shows, GGT levels allow foreseeing the probability of developing prediabetes and have a positive correlation with the probability of having impaired fasting glucose. Moreover, uric acid and GGT have also been observed to be new risk factors of diabetes(28). The combination of GGT and uric acid could possibly serve as a predictor of the development of diabetes in particular in Korean women. The possible causes of GDM are the elevated levels of GGT during the early and mid-pregnancy, although they are retained at the normal range, slow rise in GGT levels during the early and mid-pregnancy. This shows that GGT levels could be used to screen or take prophylactic measures to prevent GDM early in the pregnancy. On the same note, the findings indicate that pregnant women who are in the early and middle pregnancies with higher GGT tendencies are more likely to have GDM(33). A GGT over 26.9 U/L might be indicative of increased risk of GDM-associated development in the future and will need to be followed up. The pregravid GGT level has been found out as a predictor of future risk of GDM.

GGT levels are predictors of liver fat storage which can be located many years before pregnancy and could be used to identify the women that are likely to develop GDM(25).

Bilirubin

Tetrapyrrolic superfamily including bilirubin is a very conserved group of chemicals found in vegetation and in living organisms. Tetrapyrroles play numerous roles in chronobiology, energy production, transport and homeostasis of oxygen through hemoglobins and myoglobins. Heme oxygenase decomposes heme proteins to bilirubin which is further converted to biliverdin and bilirubin using biliverdin reductase. The enzyme uridine diphosphate-glucuronosyl transferase is used by hepatocytes to degrade bilirubin into a state that is water soluble to excrete it. In healthy individuals, the total bilirubin (the conjugated plus unconjugated bilirubin) is expected to range between 0.3 and 1.2 mg/dL(34).

(35) found some contradicting results, which stated that the direct bilirubin level of middle-aged and older people was associated with the increased risk of contracting type 2 diabetes. In another study, the relationship between quartiles of serum total bilirubin and the prevalence of diabetes among old age is linear. The less the serum total bilirubin levels are within the physiological range, the lower is the level of diabetes prevalence. The presence of serum total bilirubin into the physiological range in elderly patients has been discovered to be an independent risk factor of diabetes with conflicting results, which suggest that the serum bilirubin levels of middle-aged and elderly patients directly correlated with their developing type 2 diabetes. A different study claims that, serum total bilirubin quartiles have a linear relationship between the prevalence of diabetes among the older individuals(36). The higher the serum total bilirubin level in the physiological range, the less is the incidence of diabetes. The level of serum total bilirubin in physiological range has been observed to be an in the elderly patients.

Recent studies indicate a relationship between albuminuria and total bilirubin in individuals with type 2 diabetes. examined how levels of bilirubin and the occurrence of diabetic nephropathy relate in Chinese patients with type 1 diabetes.

The levels of high bilirubin concentration were observed to be negatively and independently correlated with albuminuria and cases of diabetic nephropathy in individuals with type 1 diabetes.examined whether obesity would modify cross-sectional association between blood total bilirubin and the risk of type 2 diabetes in the general population. Increased blood total bilirubin level was associated with increased risk of diabetes type 2, and it was found that body mass index could counteract the relationship between bilirubin and T2DM, the first time. The retrospective study was aimed at determining the relationship between hypoglycemia and newborn hyperbilirubinemia in Chinese pregnant women(37).

with diabetes, and those variables that influence this relationship. The study results revealed that congenital heart disease was a risk factor of both neonatal hypoglycemia and hyperbilirubinemia. It is important to note that in the case of pregnant women who have diabetes, the relationship between hypoglycemia and hyperbilirubinemia in newborns was significant.

Also, the probability of the occurrence of hyperbilirubinemia in the babies at birth was far more evident among the infants of pregnant diabetic women with high-risk factors. In another study, they compared the bilirubin levels before and after delivery in infants born to females with gestational diabetes in the first 48 hours of delivery. Further research on the risk posed by high levels of bilirubin in such infants should put in mind the bilirubin pattern after the initial 48 hours. In addition, it is also necessary to consider a great variety of pre-pregnancy and gestational factors that can affect the prognosis.

Reduced GDM occurrence among overweight and obese pregnant women is associated with a higher level of blood bilirubin caused by the high amount of carbohydrate consumed during the early pregnancy. However, the physiological role of total bilirubin in GDM was identified. Lower concentration of total bilirubin in the blood has

been associated with the high-risk of GDM among Japanese pregnant women(38).

Bilirubin is a potential biomarker and therapeutic target to diabetic nephropathy. To plan the treatment effectively, the future research needs to focus on the evaluation of the accuracy of bilirubin in relation to the predicting pace of diabetic nephropathy progression. Analysis of the Gunn rats and other animal models of hyperbilirubinemia relative to diabetic kidney disease may be a remarkable prospect. The recommendation of future studies is to clear up the utility of bilirubin as a clinical aid to the diagnosis and management of diabetic nephropathy by determining whether it is a therapeutic or a prognostic factor, the disease states which are associated with the causality of bilirubin, and the mechanisms involved(39).

Conclusion

This paper concludes that liver tests such as Alanine aminotransferase ALT, Alkaline phosphatase (ALP), Aspartate aminotransferase serum (AST), Gamma-glutamyl transpeptidase GGT, Total bilirubin (TBIL) are useful in the pathogenesis of various forms of DM (T1DM, T2DM and GDM). The liver parameters play a very important role in diabetes as they provide the information concerning the liver health, help revealing how diabetes impacts liver functioning, define the problems related to the liver, and ensure the safety of the diabetes medications. Liver parameters should be checked on a regular basis to be able to control diabetes and prevent any complications.

Besides, it is recommended that these liver traits in DM should be contained through therapeutic means to reduce the rates of the disease..

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