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BIOCHEMICAL CHARACTERISTICS OF CARBOHYDRATE AND LIPID METABOLISM DISORDERS IN FATTY LIVER DISEASE

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ABSTRACT. Fatty liver disease, clinically recognized as non-alcoholic or metabolic dysfunction-associated steatotic liver disease, represents a pervasive global health burden characterized by excessive intrahepatic triacylglycerol accumulation in the absence of secondary hepatotoxic causes. At the molecular level, the pathogenesis and progression of hepatic steatosis are governed by a profound, reciprocal disruption of systemic and intrahepatic carbohydrate and lipid metabolism. However, routine clinical evaluations frequently rely on isolated transaminase measurements, overlooking the intricate biochemical interplay between defective insulin signaling, unrestrained hepatic gluconeogenesis, and accelerated de novo lipogenesis. This comprehensive clinical-biochemical study investigates the specific biochemical features and diagnostic interrelations of carbohydrate and lipid metabolism disorders in patients diagnosed with fatty liver disease. A cohort of patients with ultrasonographically and biochemically confirmed hepatic steatosis was systematically evaluated alongside an age- and sex-matched healthy control group. Biochemical profiling encompassed the quantitative assessment of fasting plasma glucose, glycated hemoglobin, immunoreactive insulin, the homeostasis model assessment of insulin resistance index, serum free fatty acids, total cholesterol, triacylglycerols, high-density and low-density lipoprotein cholesterol fractions, and apolipoprotein B, paired with standard hepatobiliary cytolytic enzymes. The findings demonstrate that individuals with fatty liver disease exhibit severe peripheral and hepatic insulin resistance, fasting hyperinsulinemia, and elevated glycated hemoglobin levels, which directly drive a pronounced atherogenic dyslipidemia characterized by hypertriglyceridemia, elevated circulating free fatty acids, increased low-density lipoprotein cholesterol, and depleted high-density lipoprotein cholesterol concentrations. Furthermore, the homeostasis model assessment of insulin resistance index correlated strongly and positively with serum triacylglycerol and free fatty acid concentrations, as well as with alanine aminotransferase activity, while inversely correlating with high-density lipoprotein cholesterol levels. The study concludes that comprehensive, simultaneous profiling of carbohydrate and lipid metabolic indices provides superior insight into the biochemical severity of hepatocellular lipid overload, offering a highly sensitive tool for early cardiometabolic risk stratification and targeted therapeutic monitoring in fatty liver disease.

Keywords: fatty liver disease, hepatic steatosis, carbohydrate metabolism, lipid metabolism, insulin resistance, de novo lipogenesis, atherogenic dyslipidemia, free fatty acids, triacylglycerols, clinical biochemistry.

YOG'LI JIGAR KASALLIGIDA UGLEVOD VA LIPID ALMASHINUVI BUZILISHLARINING BIOKIMYOVIY XUSUSIYATLARI

ANNOTATSIYA. Yog'li jigar kasalligi, klinik amaliyotda noalkogol yoki metabolik disfunksiya bilan bog'liq jigar steatozi sifatida e'tirof etilib, ikkilamchi gepatotoksik omillar bo'lmagan holatda gepatotsitlar ichida triatsilglitserollarning haddan tashqari to'planishi bilan

kechadigan keng tarqalgan global tibbiy muammo hisoblanadi. Molekulyar darajada jigar steatozining patogenezi va zo'rayishi tizimli hamda jigar ichidagi uglevod va lipid almashinuvining chuqur, o'zaro bog'liq buzilishlari bilan boshqariladi. Biroq, odatiy klinik tekshiruvlar ko'pincha faqat transaminazalar faolligini aniqlash bilan cheklanib, insulin signalizatsiyasining buzilishi, nazoratsiz jigar glyukoneogenezi va tezlashgan de novo lipogenez o'rtasidagi murakkab biokimyoviy bog'liqlikni e'tibordan chetda qoldiradi. Ushbu keng qamrovli klinik-biokimyoviy tadqiqot yog'li jigar kasalligi tashxisi qo'yilgan bemorlarda uglevod va lipid almashinuvi buzilishlarining o'ziga xos biokimyoviy xususiyatlari hamda diagnostik o'zaro bog'liqligini o'rganadi. Ultratovush va biokimyoviy usullar bilan tasdiqlangan jigar steatoziga ega bemorlar guruhi yoshi va jinsi mos keladigan sog'lom nazorat guruhi bilan tizimli ravishda qiyosiy baholandi. Biokimyoviy tahlillar nahorgi plazma glyukozasi, glisirlangan gemoglobin, immunoreaktiv insulin, insulinrezistentlikning gomeostatik model indeksi, qon zardobidagi erkin yog' kislotalari, umumiy xolesterin, triatsilglitserollar, yuqori va past zichlikdagi lipoproteinlar xolesterini fraksiyalari hamda apolipoprotein B miqdorini standart gepatobiliar sitolitik fermentlar bilan birgalikda miqdoriy baholashni o'z ichiga oldi. Natijalar shuni ko'rsatadiki, yog'li jigar kasalligiga chalingan shaxslarda yaqqol periferik va jigar insulinrezistentligi, nahorgi giperinsulinemiya hamda glisirlangan gemoglobin darajasining oshishi kuzatilib, bu holat gipertriglitseridemiya, qondagi erkin yog' kislotalari va past zichlikdagi lipoproteinlar xolesterini oshishi hamda yuqori zichlikdagi lipoproteinlar xolesterini kamayishi bilan tavsiflanadigan aterogen dislipidemiyani bevosita kuchaytiradi. Bundan tashqari, insulinrezistentlikning gomeostatik model indeksi zardobdagi triatsilglitserollar va erkin yog' kislotalari konsentratsiyasi hamda alaninaminotransferaza faolligi bilan kuchli musbat korrelyatsiyani, yuqori zichlikdagi lipoproteinlar xolesterini darajasi bilan esa teskari korrelyatsiyani namoyon etdi. Tadqiqot xulosasiga ko'ra, uglevod va lipid almashinuvi ko'rsatkichlarini kompleks va bir vaqtda tahlil qilish gepatotsellyulyar lipid yuklamasining biokimyoviy og'irlik darajasini chuqurroq tushunish imkonini beradi hamda yog'li jigar kasalligida kardiometabolik xavfni erta tabaqalashtirish va maqsadli davolash samaradorligini monitoring qilish uchun yuqori sezgir vosita bo'lib xizmat qiladi.

Kalit so'zlar: yog'li jigar kasalligi, jigar steatozi, uglevod almashinuvi, lipid almashinuvi, insulinrezistentlik, de novo lipogenez, aterogen dislipidemiya, erkin yog' kislotalari, triatsilglitserollar, klinik biokimyo.

БИОХИМИЧЕСКИЕ ОСОБЕННОСТИ НАРУШЕНИЙ УГЛЕВОДНОГО И ЛИПИДНОГО ОБМЕНА ПРИ ЖИРОВОЙ БОЛЕЗНИ ПЕЧЕНИ

АННОТАЦИЯ. Жировая болезнь печени, клинически определяемая как неалкогольная или ассоциированная с метаболической дисфункцией стеатотическая болезнь печени, представляет собой широко распространенную глобальную проблему здравоохранения, характеризующуюся избыточным внутрипеченочным накоплением триацилглицеролов при отсутствии вторичных гепатотоксических причин. На молекулярном уровне патогенез и прогрессирование печеночного стеатоза определяются глубокими, взаимосвязанными нарушениями системного и внутрипеченочного углеводного и липидного обмена. Однако рутинные клинические обследования часто ограничиваются изолированным определением активности трансаминаз, упуская из виду сложную биохимическую взаимосвязь между дефектной передачей сигналов инсулина, неконтролируемым печеночным глюконеогенезом и ускоренным липогенезом de novo. В данном комплексном клинико-биохимическом исследовании изучаются специфические биохимические особенности и диагностические взаимосвязи нарушений углеводного и липидного обмена у пациентов с диагностированной жировой болезнью печени. Когорта пациентов с ультразвуковым и биохимическим

подтверждением стеатоза печени была систематически обследована в сравнении с контрольной группой здоровых лиц, сопоставимых по возрасту и полу. Биохимическое профилирование включало количественную оценку глюкозы плазмы натощак, гликированного гемоглобина, иммунореактивного инсулина, индекса инсулинорезистентности, свободных жирных кислот сыворотки, общего холестерина, триацилглицеролов, фракций холестерина липопротеинов высокой и низкой плотности и аполипопротеина В в сочетании со стандартными гепатобилиарными цитолитическими ферментами. Результаты показывают, что у лиц с жировой болезнью печени наблюдается выраженная периферическая и печеночная инсулинорезистентность, гиперинсулинемия натощак и повышенный уровень гликированного гемоглобина, которые непосредственно стимулируют развитие выраженной атерогенной дислипидемии, характеризующейся гипертриглицеридемией, повышением уровня циркулирующих свободных жирных кислот и холестерина липопротеинов низкой плотности, а также снижением концентрации холестерина липопротеинов высокой плотности. Кроме того, индекс инсулинорезистентности сильно и положительно коррелировал с концентрацией триацилглицеролов и свободных жирных кислот в сыворотке крови, а также с активностью аланинаминотрансферазы, в то время как с уровнем холестерина липопротеинов высокой плотности наблюдалась обратная корреляция. В заключении исследования делается вывод о том, что комплексное одновременное профилирование показателей углеводного и липидного обмена обеспечивает более глубокое понимание биохимической тяжести гепатоцеллюлярной липидной перегрузки, предлагая высокочувствительный инструмент для ранней стратификации кардиометаболического риска и целенаправленного мониторинга терапии при жировой болезни печени.

Ключевые слова: жировая болезнь печени, стеатоз печени, углеводный обмен, липидный обмен, инсулинорезистентность, липогенез de novo, атерогенная дислипидемия, свободные жирные кислоты, триацилглицеролы, клиническая биохимия.

INTRODUCTION

Fatty liver disease, historically termed non-alcoholic fatty liver disease and more recently reclassified as metabolic dysfunction-associated steatotic liver disease, has emerged as the leading cause of chronic hepatic pathology worldwide, paralleling the global surge in obesity, sedentary behavior, and hypercaloric dietary patterns. Clinically defined by the macrovesicular accumulation of triacylglycerols exceeding five percent of total hepatocyte weight in the absence of significant alcohol consumption or secondary viral and pharmacological etiologies, this condition encompasses a broad pathological spectrum ranging from simple hepatic steatosis to steatohepatitis, progressive fibrosis, cirrhosis, and hepatocellular carcinoma [1]. Epidemiological investigations estimate that fatty liver disease currently affects nearly thirty percent of the global adult population, with prevalence rates exceeding seventy percent among individuals diagnosed with type two diabetes mellitus and visceral obesity. Beyond its direct hepatobiliary consequences, fatty liver disease is increasingly recognized as an independent, potent catalyst for systemic cardiometabolic morbidity, doubling the incidence of atherosclerotic cardiovascular events and accelerating pancreatic beta-cell failure [2].

As the central metabolic hub of the human organism, the liver orchestrates systemic energy homeostasis by tightly coordinating the synthesis, storage, oxidation, and export of both carbohydrates and lipids. Under physiological postprandial conditions, pancreatic insulin binds to hepatic transmembrane receptors to suppress endogenous glucose production via gluconeogenesis and glycogenolysis, while simultaneously stimulating glycogenesis and moderate lipogenesis to

store excess nutritional energy [3]. However, in the pathophysiological setting of fatty liver disease, hepatocytes exhibit a paradoxical state known as selective hepatic insulin resistance. In this deranged biochemical state, the insulin signaling pathway mediated by insulin receptor substrate-two and forkhead box protein O1 becomes profoundly blunted, failing to suppress hepatic gluconeogenesis and resulting in persistent fasting and postprandial hyperglycemia. Conversely, the parallel lipogenic signaling arm mediated by sterol regulatory element-binding protein-1c remains exquisitely sensitive to the compensatory hyperinsulinemia present in the portal circulation, driving unrestrained hepatic fatty acid synthesis even in the presence of severe intracellular lipid overload [4].

The convergence of peripheral and hepatic carbohydrate intolerance directly amplifies intrahepatic lipid accumulation through multiple interconnected biochemical pathways. First, insulin resistance within visceral and subcutaneous adipose tissue fails to inhibit hormone-sensitive lipase and adipose triglyceride lipase, unleashing an unrelenting lipolytic flux of non-esterified free fatty acids directly into the portal vein [5]. Second, chronic hyperglycemia and elevated dietary fructose intake activate the carbohydrate-responsive element-binding protein within hepatocytes, acting synergistically with sterol regulatory element-binding protein-1c to upregulate key glycolytic and lipogenic enzymes, including glucokinase, liver-type pyruvate kinase, acetyl-CoA carboxylase, and fatty acid synthase. Consequently, excess carbohydrate substrates are rapidly shunted into the de novo lipogenesis pathway, generating elevated intracellular pools of malonyl-CoA. Because malonyl-CoA serves as a potent allosteric inhibitor of carnitine palmitoyltransferase-one, the transport of long-chain fatty acyl-CoA molecules into the mitochondrial matrix for beta-oxidation is severely curtailed, trapping fatty acids within the cytosol and forcing their esterification into inert triacylglycerol droplets and hepatotoxic lipid intermediates such as diacylglycerols and ceramides [6, 7].

To alleviate this overwhelming intracellular lipid burden, steatotic hepatocytes markedly accelerate the assembly and secretion of apolipoprotein B-100-containing very-low-density lipoprotein particles into the systemic circulation. This compensatory hepatic export initiates a cascade of intravascular lipoprotein remodelingthat defines the classic atherogenic dyslipidemia of fatty liver disease [8]. Elevated circulating concentrations of triglyceride-rich very-low-density lipoproteins stimulate the activity of cholesteryl ester transfer protein, which catalyzes the equimolar exchange of triacylglycerols from very-low-density lipoproteins for cholesteryl esters residing within high-density and low-density lipoprotein particles. Subsequent hydrolysis of these triglyceride-enriched lipoproteins by hepatic lipase yields small, dense, highly oxidizable low-density lipoprotein particles that readily penetrate the arterial endothelium, alongside unstable, lipid-poor apolipoprotein A-I particles that are rapidly cleared by the renal glomeruli, culminating in a profound depletion of cardioprotective high-density lipoprotein cholesterol [9]. Despite this intricate biochemical interdependence, routine clinical protocols for evaluating suspected fatty liver disease frequently rely on conventional ultrasonography and isolated measurements of serum alanine and aspartate aminotransferases, which remain within normal reference intervals in up to half of all patients with histologically confirmed steatosis [10].

The primary objective of this comprehensive clinical-biochemical investigation is to systematically characterize and quantify the specific alterations in carbohydrate and lipid metabolism in patients diagnosed with fatty liver disease compared to healthy controls. This study specifically aims to establish the precise mathematical correlations between indices of insulin resistance and glycemic control—namely fasting plasma glucose, glycated hemoglobin, immunoreactive insulin, and the homeostasis model assessment of insulin resistance—and the

spectrum of circulating lipid fractions, including non-esterified free fatty acids, triacylglycerols, lipoprotein cholesterol subfractions, and apolipoprotein B, alongside hepatobiliary enzyme activities. By elucidating the quantitative biochemical architecture linking disturbed glucose homeostasis to hepatocellular lipid accumulation and atherogenic dyslipidemia, this research seeks to refine diagnostic algorithms for early metabolic risk stratification and targeted therapeutic intervention.

MATERIALS AND METHODS

To fulfill the stated research objectives, a prospective, observational, case-control clinical and biochemical investigation was conducted at the multidisciplinary clinical hospital and the central biochemical research laboratory of Andijan State Medical Institute over a twenty-two-month period. The study protocol was thoroughly reviewed and approved by the institutional medical ethics committee, and all investigative procedures involving human subjects were performed in strict compliance with the ethical principles outlined in the Declaration of Helsinki. Prior to clinical examination and blood collection, written informed consent was obtained from each participant following a detailed explanation of the study design and laboratory methodologies.

The study population encompassed a total of two hundred and ten adult individuals aged between thirty and sixty-five years, systematically stratified into two distinct cohorts. The primary clinical group comprised one hundred and forty patients definitively diagnosed with fatty liver disease based on standardized abdominal ultrasonography, transient elastography with controlled attenuation parameter assessment, and comprehensive clinical evaluation. Hepatic steatosis on high-resolution B-mode ultrasonography was diagnosed by experienced hepatobiliary radiologists based on the presence of diffuse hyperechoic hepatic parenchyma relative to the right renal cortex, deep ultrasound beam attenuation, and poor visualization of intrahepatic portal venous walls and the diaphragm. To examine metabolic trends across disease severity, the patient cohort was further categorized into mild, moderate, and severe ultrasonographic steatosis subgroups. The control group consisted of seventy clinically healthy, non-obese volunteers matched for age and sex who demonstrated normal hepatic echogenicity, normal glucose tolerance, an unremarkable lipid profile, and no history of hepatobiliary, endocrine, or cardiovascular disorders.

Rigorous exclusion criteria were enforced across both cohorts to eliminate secondary causes of hepatic steatosis and confounding metabolic variables. Individuals were excluded if they reported significant alcohol consumption exceeding twenty grams of pure ethanol per day for women or thirty grams per day for men. Furthermore, patients testing positive for hepatitis B surface antigen or hepatitis C virus antibodies, as well as those presenting with autoimmune hepatitis, primary biliary cholangitis, Wilson's disease, hereditary hemochromatosis, alpha-1 antitrypsin deficiency, or decompensated hepatic cirrhosis were strictly excluded. Additional exclusion criteria included pre-existing type one diabetes mellitus, decompensated type two diabetes mellitus treated with exogenous insulin or thiazolidinediones, chronic kidney disease with an estimated glomerular filtration rate below sixty milliliters per minute, active malignancy, pregnancy, and the recent administration of hepatotoxic or steatogenic medications such as systemic corticosteroids, amiodarone, methotrexate, tamoxifen, or lipid-lowering fibrates and statins within six weeks prior to enrollment.

All participants underwent a standardized clinical and anthropometric evaluation. Body weight and standing height were recorded to calculate the body mass index as weight in kilograms divided by the square of height in meters. Waist circumference was measured at the midpoint between the inferior margin of the lowest rib and the superior border of the iliac crest at the end of a normal expiration. Venous blood samples were drawn from the antecubital vein between eight

and nine o'clock in the morning following a mandatory twelve-hour overnight fast. Blood was collected into three specialized vacutainer tubes: one containing tripotassium ethylenediaminetetraacetic acid for whole blood glycated hemoglobin quantification, one containing sodium fluoride and potassium oxalate to inhibit erythrocyte glycolysis for accurate plasma glucose measurement, and a plain serum separator tube for lipid, hormone, and enzymatic assays. Serum and plasma aliquots were isolated within thirty minutes of venipuncture by centrifugation at three thousand revolutions per minute for fifteen minutes at four degrees Celsius.

Biochemical analysis of carbohydrate metabolism was performed using high-precision automated analytical platforms. Fasting plasma glucose concentrations were quantified via the enzymatic reference hexokinase method, utilizing glucose-6-phosphate dehydrogenase and measuring the nicotinamide adenine dinucleotide phosphate absorbance shift at three hundred and forty nanometers. Whole blood glycated hemoglobin fractions were determined using turbidimetric inhibition immunoassay standardized according to the National Glycohemoglobin Standardization Program and expressed as a percentage of total hemoglobin. Fasting serum immunoreactive insulin levels were measured via solid-phase sandwich enzyme-linked immunosorbent assay using monoclonal antibodies directed against distinct antigenic determinants on the insulin molecule, expressed in micro-international units per milliliter. Systemic and hepatic insulin sensitivity was mathematically quantified using the homeostasis model assessment of insulin resistance index, calculated by multiplying fasting plasma glucose in millimoles per liter by fasting serum insulin in micro-international units per milliliter and dividing the resulting product by the constant twenty-two point five.

Comprehensive profiling of lipid metabolism and hepatobiliary integrity was conducted on an automated clinical chemistry analyzer. Serum total cholesterol and triacylglycerol concentrations were determined using standardized enzymatic colorimetric methods involving cholesterol esterase, cholesterol oxidase, and glycerol-3-phosphate oxidase, respectively. High-density lipoprotein cholesterol and low-density lipoprotein cholesterol concentrations were measured directly using homogenous enzymatic colorimetric assays with selective detergent solubilization. Very-low-density lipoprotein cholesterol was estimated by dividing serum triacylglycerol levels in millimoles per liter by two point two, and the atherogenic coefficient was calculated as the ratio of non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol. Serum non-esterified free fatty acid concentrations were quantified via an enzymatic colorimetric acyl-CoA synthetase and acyl-CoA oxidase assay, expressed in millimoles per liter. Serum apolipoprotein B levels were measured by immunoturbidimetry and expressed in milligrams per deciliter. Hepatocellular cytolysis and cholestasis were evaluated by measuring the catalytic activities of alanine aminotransferase, aspartate aminotransferase, and gamma-glutamyltransferase using standardized kinetic spectrophotometric methods formulated by the International Federation of Clinical Chemistry.

Statistical processing of the clinical and biochemical dataset was executed using specialized biostatistical software. The normality of distribution for all continuous variables was assessed via the Shapiro-Wilk test. Normally distributed parametric data were presented as arithmetic means and standard deviations, and intergroup comparisons between the fatty liver disease cohort and the healthy control group were evaluated using the unpaired two-tailed Student's t-test. One-way analysis of variance followed by Tukey's post-hoc multiple comparison test was employed to analyze biochemical variations across mild, moderate, and severe hepatic steatosis subgroups. Bivariate linear associations between carbohydrate and lipid metabolic parameters were quantified using Pearson's correlation coefficient. Furthermore, receiver operating characteristic

curve analysis was conducted to evaluate the diagnostic accuracy of the combined triglyceride-glucose index—calculated as the natural logarithm of the product of fasting triacylglycerols and fasting glucose divided by two—in identifying moderate-to-severe hepatic steatosis. A probability value of less than zero point zero five was considered statistically significant across all analyses.

RESULTS

Baseline anthropometric and hepatobiliary enzymatic evaluations demonstrated pronounced visceral adiposity and subclinical hepatocellular injury in patients diagnosed with fatty liver disease compared to healthy controls. The mean body mass index in the fatty liver disease cohort reached thirty-two point 六 (thirty-two point six) kilograms per square meter, accompanied by a mean waist circumference of one hundred and six point four centimeters, both of which were statistically significantly elevated compared to the control group averages of twenty-three point four kilograms per square meter and seventy-eight point five centimeters, respectively. Assessment of hepatobiliary enzymes revealed a mean serum alanine aminotransferase activity of fifty-eight point four units per liter and an aspartate aminotransferase activity of forty-two point one units per liter in the patient cohort, compared to nineteen point six units per liter and eighteen point two units per liter in healthy volunteers. Similarly, serum gamma-glutamyltransferase activity was more than twofold higher in the fatty liver disease group, averaging sixty-four point eight units per liter versus twenty-four point three units per liter in controls, reflecting oxidative stress and intrahepatic biliary strain associated with hepatocellular lipid accumulation.

Detailed biochemical profiling of carbohydrate metabolism uncovered profound dysregulation of glucose homeostasis and severe insulin resistance in the fatty liver disease cohort. Fasting plasma glucose concentrations averaged six point three millimoles per liter among patients with hepatic steatosis, which was significantly higher than the four point seven millimoles per liter recorded in the control group. Chronic glycemic exposure, reflected by whole blood glycated hemoglobin, averaged six point two percent in the patient group compared to four point nine percent in healthy controls. The most striking abnormality within the carbohydrate profile was observed in fasting serum immunoreactive insulin concentrations, which surged to a mean of twenty-one point four micro-international units per milliliter in patients with fatty liver disease, representing a more than threefold elevation over the control group average ofsix point four micro-international units per milliliter. Consequently, the calculated homeostasis model assessment of insulin resistance index reached a mean value of six point zero in the fatty liver disease cohort compared to one point three in healthy subjects, confirming marked peripheral and hepatic insulin insensitivity. Stratification by ultrasonographic steatosis severity revealed a progressive escalation of the insulin resistance index, rising from four point two in patients with mild steatosis tofive point eight in moderate steatosis, and reaching seven point nine in individuals with severe hepatic steatosis.

Parallel evaluation of the lipid spectrum demonstrated a comprehensive, statistically significant shift toward pro-atherogenic dyslipidemia and heightened lipolytic flux in patients with fatty liver disease. Serum non-esterified free fatty acid concentrations averaged zero point eighty-eight millimoles per liter in the steatotic cohort, more than double the control group mean of zero point thirty-nine millimoles per liter, providing direct biochemical evidence of unrestrained adipose tissue lipolysis. Serum triacylglycerol concentrations were markedly elevated in the patient group, averaging two point eighty-four millimoles per liter compared to one point zero five millimoles per liter in healthy controls, accompanied by a parallel surge in calculated very-low-density lipoprotein cholesterol from zero point forty-eight millimoles per liter in controls to one point twenty-nine millimoles per liter in patients. Furthermore, total serum cholesterol and low-density lipoprotein

cholesterol averaged six point twelve millimoles per liter and three point ninety-five millimoles per liter in the fatty liver disease cohort, compared to four point fifty-six millimoles per liter and two point fifty-eight millimoles per liter in healthy volunteers, respectively. Conversely, cardioprotective high-density lipoprotein cholesterol concentrations were significantly depleted in the patient group, dropping to an average of zero point eighty-eight millimoles per liter versus one point fifty millimoles per liter in controls. Serum apolipoprotein B concentrations were also substantially elevated in patients with fatty liver disease, averaging one hundred and thirty-four point six milligrams per deciliter compared to eighty-two point three milligrams per deciliter in the control cohort, while the calculated atherogenic coefficient rose sharply from two point zero four in controls tofive point ninety-five in patients with hepatic steatosis.

To elucidate the pathogenic coupling between disturbed carbohydrate metabolism, dyslipidemia, and hepatocellular damage, bivariate Pearson correlation analysis was conducted within the fatty liver disease cohort. The homeostasis model assessment of insulin resistance index exhibited a powerful, statistically significant positive linear correlation with serum triacylglycerol concentrations, yielding a correlation coefficient of zero point seventy-six, and an equally robust positive correlation with circulating non-esterified free fatty acid levels at zero point seventy-two. Furthermore, fasting serum insulin levels correlated positively with serum apolipoprotein B concentrations at zero point sixty-eight, underscoring the direct stimulatory effect of hyperinsulinemia on hepatic very-low-density lipoprotein secretion. Conversely, the insulin resistance index demonstrated a pronounced inverse correlation with high-density lipoprotein cholesterol concentrations, yielding a correlation coefficient of minus zero point sixty-one. Markers of hepatobiliary cytolysis also tracked closely with metabolic derangement; serum alanine aminotransferase activity correlated positively with both the insulin resistance index at zero point sixty-four and serum free fatty acid concentrations at zero point sixty-seven. Receiver operating characteristic curve analysis revealed that the integrated triglyceride-glucose index surpassed isolated transaminase or fasting glucose measurements in diagnostic performance, predicting moderate-to-severe ultrasonographic hepatic steatosis at a cutoff value of nine point twelve with a diagnostic sensitivity of ninety-one point two percent, a specificity of eighty-seven point five percent, and an area under the curve of zero point ninety-four.

DISCUSSION

The empirical results generated by this clinical-biochemical investigation demonstrate that fatty liver disease is fundamentally anchored in a bidirectional, self-reinforcing disruption of systemic carbohydrate and lipid metabolism. The more than twofold elevation in circulating non-esterified free fatty acids alongside a threefold surge in fasting immunoreactive insulin observed in our patient cohort provides clear clinical confirmation of the dual-hit metabolic model governing hepatic steatosis [11]. In states of visceral adiposity, hypertrophic adipocytes become resistant to the antilipolytic action of insulin, resulting in persistent activation of intracellular lipases and a massive efflux of free fatty acids into the portal circulation. Isotope tracer studies established in the literature indicate that nearly sixty percent of the triacylglycerol accumulated within steatotic hepatocytes originates directly from this circulating pool of non-esterified fatty acids, while approximately twenty-five percent is derived from carbohydrate-driven de novo lipogenesis and fifteen percent from dietary chylomicron remnants [12]. The robust positive correlation of zero point seventy-two between the homeostasis model assessment of insulin resistance index and serum free fatty acids documented in our study directly reflects this pathological adipose-hepatic axis.

Crucially, our findings illuminate how intrahepatic lipid overload reciprocally worsens carbohydrate intolerance, creating a metabolic vicious cycle. When the influx of free fatty acids and

the rate of de novo lipogenesis exceed the capacities of mitochondrial beta-oxidation and very-low-density lipoprotein export, bioactive lipid intermediates—most notably sn-1,2-diacylglycerols and ceramides—accumulate within the hepatocyte cytosol and endoplasmic reticulum [13]. Elevated intracellular diacylglycerol concentrations directly bind to and activate protein kinase C-epsilon, which translocates to the hepatocellular plasma membrane and phosphorylates an inhibitory threonine residue on the intracellular kinase domain of the insulin receptor. This molecular blockade impairs insulin receptor substrate-two tyrosine phosphorylation, preventing the inactivation of forkhead box protein O1 and permitting the constitutive transcription of rate-limiting gluconeogenic enzymes, specifically phosphoenolpyruvate carboxykinase and glucose-6-phosphatase. Consequently, the steatotic liver continues to pour glucose into the systemic circulation despite existing fasting hyperglycemia, stimulating pancreatic beta-cells to secrete ever-increasing quantities of insulin and explaining the progressive rise in the insulin resistance index across mild, moderate, and severe steatosis subgroups in our cohort.

Simultaneously, the powerful positive correlations established between the insulin resistance index, serum triacylglycerols, and apolipoprotein B concentrations highlight the central role of the steatotic liver in driving systemic atherogenesis. Because hyperinsulinemia continues to activate sterol regulatory element-binding protein-1c while elevated plasma glucose activates carbohydrate-responsive element-binding protein, hepatocytes synthesize copious quantities of palmitate and oleate that are esterified into triacylglycerols and packaged onto apolipoprotein B-100 backbones via microsomal triglyceride transfer protein [14]. The resulting oversecretion of large, triglyceride-rich very-low-density lipoprotein particles overwhelms peripheral lipoprotein lipase activity and accelerates cholesteryl ester transfer protein-mediated lipid exchange. This intravascular remodeling explains the profound depletion of high-density lipoprotein cholesterol and the nearly threefold elevation in the atherogenic coefficient observed in our patients. Moreover, the strong correlation between serum free fatty acids, insulin resistance, and alanine aminotransferase activity confirms the phenomenon of hepatic lipotoxicity, wherein excess saturated fatty acids induce endoplasmic reticulum stress, mitochondrial reactive oxygen species generation, and hepatocyte membrane permeability.

From a translational clinical perspective, the superior diagnostic performance of the combined triglyceride-glucose index demonstrated by our receiver operating characteristic curve analysis carries substantial practical value for routine medical practice. Standard hepatobiliary screening relying solely on serum transaminases frequently fails to detect early or even moderate hepatic steatosis, as cytolytic enzyme release can remain intermittent or minimal despite severe intracellular metabolic derangement. Conversely, integrating simultaneous measurements of fasting plasma glucose, immunoreactive insulin, triacylglycerols, non-esterified free fatty acids, and apolipoprotein B into the standard diagnostic panel provides clinicians with a sensitive, quantitative window into the underlying biochemical drivers of fatty liver disease. While certain methodological limitations of this investigation should be acknowledged—including its cross-sectional case-control framework and the reliance on ultrasonographic and elastographic grading rather than invasive percutaneous liver biopsy—the biochemical assays evaluated are highly standardized, cost-effective, and universally accessible across clinical laboratories. Early identification of selective hepatic insulin resistance and lipogenic overactivity enables timely implementation of targeted nutritional interventions, structured physical activity, and pharmacological agents such as glucagon-like peptide-1 receptor agonists, sodium-glucose cotransporter-2 inhibitors, and selective peroxisome proliferator-activated receptor modulators to halt disease progression before irreversible hepatic fibrosis or cardiovascular events occur.

CONCLUSION

The comprehensive clinical-biochemical evaluation of patients with fatty liver disease demonstrates that hepatocellular steatosis is inextricably linked to profound, mutually reinforcing disturbances in systemic and intrahepatic carbohydrate and lipid metabolism. This investigation conclusively establishes that individuals with fatty liver disease exhibit marked peripheral and hepatic insulin resistance, fasting hyperinsulinemia, and impaired glycemic regulation, which directly fuel unrestrained adipose tissue lipolysis and hepatic de novo lipogenesis. Biochemically, these alterations manifest as a significant elevation in circulating non-esterified free fatty acids, triacylglycerols, very-low-density and low-density lipoprotein cholesterol, and apolipoprotein B, accompanied by a severe depletion of cardioprotective high-density lipoprotein cholesterol. Crucially, the severity of insulin resistance correlates directly with circulating triacylglycerol and free fatty acid concentrations, hepatobiliary cytolytic enzyme activity, and the ultrasonographic grade of hepatic steatosis. Incorporating combined metabolic indices—specifically the homeostasis model assessment of insulin resistance and the triglyceride-glucose index—alongside extended lipid profiling into routine clinical algorithms provides a highly sensitive, pathogenetically grounded tool for early diagnosis, cardiometabolic risk stratification, and the precise monitoring of therapeutic efficacy in fatty liver disease.

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