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Exploring Secreted Frizzled Related Protein-4 (SFRP-4) As an Indicator for Differential Diagnosis of Fatty Liver Diseases

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Abstract: Metabolic-associated fatty liver disease (MAFLD), formerly known as nonalcoholic fatty liver disease (NAFLD), has emerged as a prevalent liver condition globally, closely associated with the rising obesity epidemic. Despite its increasing prevalence, there remains a notable absence of pharmacological treatments tailored specifically for MAFLD. This therapeutic gap can be attributed to the complex nature of MAFLD, characterized by a limited understanding of its underlying mechanisms, insufficiently accurate and affordable imaging techniques, and the lack of non-invasive biomarkers for effective diagnosis and monitoring.

This review examines current diagnostic modalities for MAFLD, with a focus on the growing importance of non-coding RNAs as promising diagnostic biomarkers. The urgent need for non-invasive biomarkers, alongside accurate and cost-effective diagnostic tools, is emphasized, as they play a crucial role in detecting early signs of MAFLD progression. These advancements hold the potential to expedite clinical trials and validate emerging therapeutic approaches, thereby facilitating the development of improved management strategies for MAFLD patients.

Keywords: fatty liver disease, alcohol-associated diseases, fatty hepatosis, non-alcoholic steatohepatitis, visceral obesity, Wnt-antagonist, Secreted Frizzled Related Protein-4, SFRP4.

Introduction:

The liver stands as a sentinel of health, its functional vitality intricately intertwined with the overall well-being of an individual. Profound hepatodysfunction can swiftly jeopardize life itself, underscoring the pivotal role this organ plays in sustaining human health. In contemporary society, the sedentary lifestyle prevalent among many, coupled with dietary imbalances and disruptions in gut microbiota, has fostered the emergence of numerous chronic non-infectious ailments. Chief among these are conditions stemming from perturbations in carbohydrate metabolism, including insulin resistance, prediabetes, metabolic syndrome (MS), and diabetes mellitus (DM). The liver, orchestrating a myriad of metabolic processes, serves as a linchpin in the regulation of carbohydrate metabolism. Its ability to maintain glycemic homeostasis and process nutrients is paramount for sustaining vital physiological functions. However, the modern milieu characterized by sedentary habits and dietary aberrations has imposed unprecedented burdens on the liver's metabolic machinery. The proliferation of processed foods laden with sugars and unhealthy fats, alongside diminished physical activity, has catalyzed a surge in metabolic disorders, placing immense strain on hepatic function. Moreover, the intricate interplay between the gut microbiota and metabolic health has garnered significant attention in recent years. Disruptions in the delicate balance of gut microflora, often precipitated by dietary indiscretions and lifestyle factors, can engender a cascade of metabolic derangements, further exacerbating hepatic dysfunction. The resultant metabolic perturbations not only imperil the liver's integrity but also set the stage for the insidious progression of chronic diseases that exact a heavy toll on global public health

Indeed, within the intricate landscape of metabolic syndrome, the hepatic manifestation assumes a central role, with non-alcoholic fatty liver disease (NAFLD) representing a hallmark pathology. Conversely, alcoholism precipitates a distinct array of hepatic insults, culminating in alcoholic liver disease (ALD). This dichotomy underscores the multifactorial nature of liver pathologies and the diverse etiologic factors driving their progression

Against this backdrop, epidemiological studies offer valuable insights into the prevalence and burden of NAFLD within diverse demographic cohorts. The findings from the open national multicenter prospective study DIREG 2 provide compelling evidence of the pervasive nature of NAFLD within the Russian population, with a staggering 37.3% of outpatients exhibiting varying degrees of hepatic steatosis. This high prevalence underscores the urgent need for heightened awareness, early detection, and comprehensive management strategies to curb the escalating tide of NAFLD-related morbidity and mortality. Despite disparate etiologic triggers, NAFLD and ALD share strikingly similar pathogenic mechanisms, underscoring the concept of a "hepatic continuum" wherein a common sequence of events precipitates liver injury and dysfunction. Central to this paradigm is the dysregulation of lipid metabolism, oxidative stress, and inflammation, culminating in hepatic steatosis, fibrosis, and ultimately, cirrhosis. The convergence of these pathogenic pathways underscores the potential for shared therapeutic targets and intervention strategies aimed at ameliorating liver damage across a spectrum of metabolic and alcoholic liver diseases. The pathogenetic similarities between non-alcoholic fatty liver disease (NAFLD) and alcoholic liver disease (ALD) pose significant challenges in the realm of differential diagnosis. Despite distinct etiologic triggers, the absence of pathognomonic clinical manifestations and the convergence of key laboratory and instrumental findings complicate the diagnostic process. Consequently, clinicians are often confronted with a diagnostic dilemma, unable to definitively ascertain the underlying etiology of hepatic pathology based on conventional diagnostic modalities alone. Numerous studies have sought to elucidate the nuanced differences between NAFLD and ALD, offering insights into potential diagnostic markers and algorithms. However, the quest for a definitive diagnostic method that meets the stringent criteria for widespread clinical adoption remains elusive. The lack of a universally accepted diagnostic paradigm underscores the complexity of the differential diagnosis and the need for continued research to identify novel biomarkers and diagnostic tools. In the absence of a gold standard diagnostic test, clinicians must rely on a multifaceted approach that integrates clinical history, physical examination, laboratory investigations, and imaging studies to differentiate between NAFLD and ALD. Nevertheless, the inherent limitations of existing diagnostic modalities underscore the imperative for ongoing research aimed at refining diagnostic algorithms and identifying robust biomarkers that afford greater diagnostic accuracy and reliability

Objectively assessing the presence of visceral obesity in an individual researcher presents a multifaceted challenge, with various parameters offering insights into adiposity and its associated metabolic implications. Waist volume, waist/hip ratio, waist/height ratio, neck/hip ratio, and body mass index (BMI) are commonly employed anthropometric measures that provide valuable clues regarding visceral adiposity. However, it's essential to acknowledge their inherent limitations, as these parameters can be influenced by individual characteristics such as body composition, ethnicity, and genetic predisposition. Anthropometric indices serve as valuable screening tools, but their interpretation must be contextualized within the broader clinical framework, considering factors such as age, sex, and overall health status. While these measures offer valuable insights into adiposity-related health risks, they are not infallible and may yield discordant results in certain populations or clinical contexts. In addition to anthropometric measures, laboratory hematologic tests offer a complementary approach to assessing metabolic health and distinguishing between non-alcoholic fatty liver disease (NAFLD) and alcoholic liver disease (ALD). These tests leverage biochemical markers and biomarkers associated with hepatic dysfunction and metabolic dysregulation, providing valuable diagnostic insights.

Key hematologic parameters implicated in the differentiation of NAFLD from ALD include:

1. De Ritis coefficient (AST/ALT ratio): Elevated levels may suggest alcoholic liver injury, whereas a lower ratio may indicate NAFLD.
2. γ-Glutamyl transpeptidase (GGT): Elevated levels are often associated with alcohol consumption and ALD.
3. Uric acid: Elevated levels may correlate with NAFLD and metabolic syndrome.
4. Immunoglobulin class A (IgA): Increased levels may be indicative of alcoholic liver injury.

5. Phosphatase and tensin homolog (PTEN): Dysregulation may contribute to metabolic dysfunction and NAFLD pathogenesis.
6. Phosphatidylethanol (PEth): Biomarker of alcohol consumption, useful in distinguishing ALD.
7. M30 fragment of cytokeratin-18 (CK-18-M30): Elevated levels indicate hepatocyte apoptosis, observed in both NAFLD and ALD but may be more pronounced in NAFLD.
8. Fibroblast growth factor-21 (FGF-21): Elevated levels may correlate with NAFLD severity.
9. Interleukin-1 receptor antagonist (IL-1Ra), pigment epithelial growth factor (PEDF), and osteoprotegerin (OPG): Potential markers of inflammation and metabolic dysfunction associated with NAFLD.

The electrical and viscoelastic characteristics of red blood cells are established through a process called erythrocyte dielectrophoresis [6]. Despite its high sensitivity (88.5%) and specificity (92.9%), this method necessitates specific equipment, software, and specialized training for laboratory personnel and physicians. In distinguishing between non-alcoholic fatty liver disease (NAFLD) and alcoholic liver damage, the aspartate aminotransferase (AST) level is often more than double that of alanine aminotransferase (ALT). However, the increased de Ritis coefficient doesn't align with the severity of the condition and isn't linked to the extent of steatosis or liver fibrosis [7].

Gamma-glutamyl transferase (GGT) serves as a reliable indicator of liver damage. Research indicates that serum GGT levels rise in both non-alcoholic fatty liver disease (NAFLD) and alcoholic liver disease, facilitating a qualitative differentiation between the two conditions through gel filtration [8]. Moreover, elevated GGT levels are observed in various conditions, including nonspecific ulcerative colitis, hepatobiliary diseases such as toxic hepatitis unrelated to alcohol, infectious liver diseases like acute and chronic viral hepatitis, Epstein-Barr virus infection, and liver cirrhosis. Increased GGT is also associated with early diagnostic signs of conditions like atherosclerosis, ischemic heart disease, heart failure, systemic connective tissue diseases, metabolic syndrome, type 2 diabetes mellitus, gestational diabetes, osteoporosis, certain cancers, and other ailments.

Serum immunoglobulin A (IgA) levels show a significant increase in hepatic fibrosis associated with non-alcoholic fatty liver disease (NAFLD) and alcoholic liver disease (ALD). However, it's important to note that IgA elevation isn't specific to the progression of either condition [9].

Carbohydrate-deficient transferrin (CDT) serves as a reliable marker for alcohol abuse within the preceding two weeks, corresponding to the half-life of transferrin [10]. However, it loses its effectiveness in individuals with a history of alcohol abuse who have been abstinent for more than two weeks or have undergone withdrawal for 14 days or longer.

Markers such as PTEN and Peth, though expensive and relatively underexplored, exhibit comparable informativeness to CDT. Currently, they hold significance primarily in individual studies for scientific research purposes [11]. Other potential markers include CK-18-M30, FGF-21, IL-1Ra, PEDF, 17β-HSD13, OPG, ethyl glucuronide, and acetaldehyde-modified hemoglobin.

A novel marker of metabolic changes is Secreted Frizzled Related Protein-4 (SFRP4), a soluble serum protein identified in 2008 by Swedish scientist Anders Rosengren, who conducted research at Lund University. Further investigations revealed that SFRP4 acts as one of the antagonists of the Wnt signaling pathway, which plays a role in glucose-lipid metabolism by interacting with Wnt ligands [12]. It's widely acknowledged that serum SFRP4 levels increase even in the early stages of type 2 diabetes [12]. This prompts the question of whether this marker can indicate the development of components of metabolic syndrome, particularly hepatic arterial buffer response dysfunction (HABRD). Regarding modern diagnostic instrumental methods for non-alcoholic fatty liver disease (NAFLD) and alcoholic liver disease (ALD), several notable techniques include ultrasound examination (USI) of abdominal cavity organs (ACO), transient elastography, shear wave elastography (SWE) with elastometry, computed tomography (including contrast-enhanced), magnetic resonance tomography, magnetic resonance spectroscopy, and magnetic resonance elastography. Each of these

methods possesses numerous favorable attributes, with high sensitivity and specificity (varying depending on the method). However, only magnetic resonance spectroscopy (MRS) is capable of suggesting the etiology of the underlying pathology. Currently, MRS devices are limited and costly in Russia, but there's potential for wider adoption of the method in the future

Liver biopsy is considered the "gold standard" for diagnosing non-alcoholic fatty liver disease (NAFLD) and alcoholic liver disease (ALD). However, distinguishing between these two pathologies under the microscope in a clinical setting can be challenging. In both diseases, microscopic findings typically include features such as steatosis, fibrosis, inflammatory changes, balloon and/or necrotic degeneration, and hepatocyte apoptosis [13]. Only a skilled pathologist, upon detailed examination of alcohol-associated liver damage, may observe that Mallory's bodies, neutrophilic infiltration, and large-drop fatty dystrophy are more prevalent compared to NAFLD cases. Additionally, necroinflammatory activity tends to be higher, and Perls staining may reveal increased iron deposition in "alcoholic" livers [14]. Fatty liver disease associated with metabolic syndrome (MS) often presents with severe steatosis, glycogenated nuclei, and the presence of lipogranules. When conducting a biopsy, it's important to consider that the procedure can be subjectively unpleasant, requires specialized conditions, carries a significant risk of complications during and after the manipulation, and only samples about 0.2% of the liver parenchyma. Additionally, it doesn't provide information about whether infiltrates are distributed homogeneously or heterogeneously [15]. Furthermore, assessing the histologic structure of the organ is time-consuming and isn't considered an "urgent" diagnostic procedure.

The goal is to identify markers for the differential diagnosis of non-alcoholic and alcoholic fatty liver disease that are most suitable for use in primary care to prevent disease progression.

The materials and methods section details the study's design and participant selection process. Thirty apparently healthy individuals with no pathological findings in general and biochemical blood tests, normal abdominal ultrasound results, and no history of liver or other organ diseases were randomly chosen to form the control group (referred to as group N). These individuals volunteered for the study.

The experimental group comprised two equal subgroups:

1. Group O1: Consisted of 30 patients diagnosed with non-alcoholic fatty liver disease (NAFLD) confirmed by biopsy.
2. Group O2: Included 30 patients diagnosed with alcohol dependence based on medical history, previous completion of questionnaires (such as CAGE and AUDIT), and laboratory tests indicating alcohol consumption. These patients had abstained from alcohol for over a month and were currently undergoing treatment in the rehabilitation department.

All participants provided voluntary consent for the use of their clinical data for research purposes.

The study included an equal number of male and female participants, ranging in age from 18 to 60 years, with a mean age of 43.4 ± 1.67 years. Their body mass index (BMI) fell within the range of 18 to 30 kg/m².

Various parameters were analyzed, including waist volume, waist/hip ratio, waist/height ratio, neck/hip ratio, BMI, as well as results from general and biochemical blood tests, lipid profile, coagulation profile, carbohydrate-deficient transferrin (CDT) levels, and serum Secreted Frizzled Related Protein-4 (SFRP4) levels. Additionally, ultrasound examination of the liver (OBP) and transient elastography (ESV) with elastometry were conducted.

BMI was calculated using the Ketle method: BMI = weight (kg) / height (m)². Serum SFRP4 levels were measured using an ELISA Kit for SFRP4, with the results interpreted based on a controlled international study. Serum SFRP4 levels ranging from 5.8 to 11.8 ng/ml were considered acceptable for relatively healthy individuals [12]. The data obtained were statistically processed using the Statistica 6.0 computer program. The parameters in the samples were designated as follows: Me for median, Q1 for upper quartile, Q3 for lower quartile, n for the volume of the analyzed subgroup, and p

for the value of statistical significance of differences. A critical significance level of 5% ($p \leq 0.05$) was applied.

The results and their discussion revealed statistically significant differences in several parameters: waist volume (11.1%), waist/hip ratio (35.54%), serum Secreted Frizzled Related Protein-4 (SFRP4) level (48.54%), and liver transient elastography (ESV) values (27.46%).

Waist circumference, waist/hip ratio, and serum SFRP4 level are markers of visceral obesity. The observed differences in these indicators in the differential diagnosis of non-alcoholic fatty liver disease (NAFLD) and alcoholic liver disease (ALD) can be attributed to the close correlation between NAFLD and visceral obesity. Additionally, the significant role of the direct damaging effect of ethyl alcohol in the formation of ALD should be considered.

In patients with alcoholic liver disease (ABP) undergoing prolonged withdrawal, liver transient elastography (ESV) indices were notably better compared to those in patients with non-alcoholic fatty liver disease (NAFLD). This observation could be attributed to the liver's high regenerative capacity, which underscores the importance of continued monitoring over a period of 3, 6, and 12 months following withdrawal.

Both experimental groups exhibited significantly higher de Ritis coefficients, as well as elevated levels of gamma-glutamyl transferase (GGT) and uric acid in serum, compared to the control group. These findings suggest hepatotoxicity occurs in both NAFLD and ABP. Therefore, nonspecific markers such as the de Ritis coefficient, GGT, and serum uric acid levels provide results significantly higher than those in the control group in both cases.

Furthermore, upon analyzing indicators from general blood tests, lipid profiles, coagulation profiles, and serum carbohydrate-deficient transferrin (CDT) levels, no significant differences were found among the groups. Additionally, ultrasound examination of the liver (OPD) revealed increased liver echogenicity in both cases.

In conclusion, markers of visceral obesity, including waist circumference, waist/hip ratio, and serum Secreted Frizzled Related Protein-4 (SFRP4) levels, demonstrate reliable differences in differentiating between non-alcoholic fatty liver disease (NAFLD) and alcoholic liver disease (ABP). Serum SFRP4 level stands out as a potentially valuable tool for the differential diagnosis of non-alcoholic steatohepatitis (NASH) and ABP in routine clinical practice. Its utilization could aid in timely diagnosis, differential diagnosis, and the selection of specific treatment strategies, thereby contributing to the prevention of disease progression and severity.

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