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Sexually Dimorphic Differences in the Regulation of Pancreatic Hormones and Growth Factors on Liver Metabolism in Patients with Cirrhosis

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Abstract

Hepatocyte growth factor (HGF) exerts potent mitogenic effects in multiple tissues, whereas epidermal growth factor (EGF) functions as a molecular integration point for diverse signaling stimuli. The HGF–Met system plays an active role in hepatic metabolism. In this observational study, we aimed to identify correlations among serum levels of HGF and EGF, insulin, glucagon, and major serum lipids in patients with cirrhosis, with particular attention to sex-related differences. Serum concentrations of HGF, EGF, insulin, glucagon, major lipids, and nitrogen-related metabolites were measured through analytical methods to assess the relationships among these parameters in patients with cirrhosis and healthy controls. We observed clear differences in glucose, insulin, and glucagon regulation between healthy men and women, along with opposing associations with growth factors, potentially reflecting the distinct modulatory effects of sex hormones. At the onset of liver fibrosis/cirrhosis, most of the correlations observed in healthy individuals were lost, and sex-related differences became markedly attenuated. In addition, metabolites such as glucose, albumin, direct bilirubin, nitrites, and ammonia appeared to influence circulating growth factor and hormone levels. In conclusion, our findings support a role for HGF and EGF in the regulation of serum glucose, lipid and nitrogen metabolism, as well as in the modulation of insulin and glucagon levels, in a sex-dependent manner. These relationships were particularly evident in patients with liver fibrosis/cirrhosis, in whom impaired cellular growth or repair mechanisms are associated with metabolic dysregulation. Collectively, these observations suggest that growth factors may contribute to the physiopathology of chronic liver disease.

1. Introduction

Chronic liver injury resulting from diverse etiologies is characterized by the excessive accumulation of extracellular matrix components in response to sustained hepatic damage [1]. Liver fibrosis, particularly in its advanced stage as cirrhosis, represents a major cause of morbidity and mortality in patients with chronic liver disease. The progression of these pathological conditions is closely linked to the activation of hepatic stellate cells (HSCs), which constitute the principal fibrogenic cell population following their transdifferentiation into an activated, myofibroblast-like phenotype [2, 3]. Upon activation, HSCs secrete a broad spectrum of growth factors and signaling molecules, including transforming growth factor-β (TGF-β), epidermal growth factor (EGF), hepatocyte growth factor (HGF), and interleukin-6 (IL-6), as well as macrophage chemoattractant, autocrine mediators, and HSC-specific profibrogenic signals [4, 5].

HGF plays a pivotal role in tissue repair and regeneration in several organs, including the liver and lungs, as well as in other epithelial and non-epithelial tissues, exerting protective effects through the suppression of apoptosis and inflammation [6, 7]. Although quiescent hepatic stellate cells can produce HGF, its expression is markedly downregulated during liver injury because of TGF-β–mediated inhibition [8].

Plasma HGF levels fluctuate during the repair process and remain elevated throughout the regenerative phase until tissue restoration is complete [9]. In humans, the role of HGF in liver regeneration induced by

clinical interventions has been investigated predominantly in the context of living donor liver transplantation rather than hepatic resection [10, 11]. The interaction between HGF and its receptor c-Met activates multiple downstream signaling cascades, including the JAK/STAT3, PI3K/Akt/NF-κB, and Ras/Raf pathways [9].

In non-alcoholic fatty liver disease (NAFLD), excessive triglyceride accumulation within hepatocytes contributes to alterations in liver volumetry, reflecting impaired regenerative capacity [12]. The consequent reduction in hepatocyte proliferation or the onset of replicative senescence observed in NAFLD-related cirrhosis may result from increased cytokine production [13], dysfunction of the epidermal growth factor receptor (EGFR) signaling pathway [14], and oxidative stress [15]. The EGFR pathway plays a pivotal role in regulating cell growth, proliferation, migration, and differentiation under both physiological and pathological conditions [16]. Accordingly, epidermal growth factor (EGF) has been implicated in multiple hepatic pathological processes, including inflammation, fibrosis, and tumor metastasis [17, 18]. Indeed, HGF interacts with insulin to regulate glucose metabolism in hepatocytes contributing to glucose homeostasis. EGF may also influence glucagon secretion by counteracting its suppression by plasma glucose [19].

Moreover, obesity—encompassing both generalized adiposities, as reflected by an elevated body mass index (BMI) and visceral fat accumulation—represents a major risk factor for the development of NAFLD. Epidemiological studies indicate that NAFLD affects a substantial proportion of individuals with obesity and up to 69% of patients with type 2 diabetes mellitus [20]. Progression to fibrosis disrupts hepatic blood flow and tissue oxygenation, thereby impairing the functional and regenerative capacities of the liver to an extent that becomes detectable through routine laboratory parameters [21].

In previous work, we highlighted the regulatory roles of insulin and glucagon in modulating serum glucose and lipid homeostasis, as well as sex-related differences in circulating HGF and EGF concentrations. These associations were particularly evident in diabetes mellitus, a condition in which defective cellular proliferation or impaired repair mechanisms contribute to metabolic deregulation [22]. Building on these observations, the present study aimed to investigate potential correlations between serum levels of HGF, EGF, insulin, and glucagon and glucose levels, lipid profiles, and key liver-related metabolites in patients with established cirrhosis.

2. Material and Methods

2.1 Study Population.

A cohort of patients with liver fibrosis/cirrhosis at different stages of disease was recruited from outpatient clinics primarily affiliated with the Ministry of Public Health (SSA, Mexico), particularly the “Xoco” General Hospital. The study population comprised 45 women (Child–Pugh classification: 35 class A and 9 class B) and 55 men (Child–Pugh classification: 48 class A and 7 class B) with a

confirmed diagnosis of cirrhosis. Inclusion criteria included the absence of recent alcohol consumption, non-smoking status, and receipt of palliative treatment for cirrhosis.

A control group consisting of 50 women and 50 men, all non-smokers, non–alcohol consumers, and healthy, was also included. After an overnight fast of 10 h, venous blood samples were collected from all participants. Patients were instructed to refrain from taking their morning medications prior to sample collection.

The study was conducted in accordance with the Declaration of Helsinki (2000) of the World Medical Association and was approved by the Ethics Committee of the “Xoco” General Hospital (Ministry of Public Health, Mexico). Written informed consent was obtained from all participants. The study was registered under project number 207.010.30.18.

2.2 Serum Collection and Clinical Tests.

Serum was obtained by centrifugation of whole blood samples. Serum concentrations of glucose, cholesterol, and triacylglycerols (TG), as well as the activities of γ-glutamyl transferase (γ-GT) and alkaline phosphatase (ALP), were determined using standardized protocols and commercially available kits from SPINREACT (Spain).

2.3 Insulin, Glucagon, HGF, and EGF Measurements.

Serum insulin and glucagon levels were quantified using a commercially available enzyme-linked immunosorbent assay (ELISA) kit from RayBiotech. HGF and EGF concentrations were measured using ELISA kits from BioSys-Kovalent, according to the manufacturers’ instructions (Table 1).

2.4 Statistical Analysis.

A total of 52 determinations were carried out, with each data set comprising 50 values categorized by metabolite, blood compartment, group, and sex. A pooling strategy was used, in which blood samples were collected from each patient and control group member, and determinations were performed on clusters of samples. Therefore, it is important to note that the results and conclusions are based on cluster-level data rather than individual patient data. The complete data sets are available in the Data Sets section of the Open Science Framework project (https://osf.io/a6cd3/?view_only=90dfd426c06648f5bbb96470c689d106). The statistical analysis we applied in our research belongs to the non-parametric inference. This approach focuses on the hierarchy of data and therefore is not affected by extreme values or asymmetrical distributions. We proceed as follows: First, we make an explorative data analysis and then non-parametric hypothesis testing to identify the best-fit distribution that more closely describes the data.

The best-fit analysis is the Kolmogorov-Smirnov (KS) test. Finally, for statistical differences between subgroups, we apply the non-parametric Mann-Whitney test for medians when required. This non-parametric approach, therefore, has its advantages because it does not assume ex ante any distribution of the data.

This approach makes strong assumptions regarding the underlying distribution of the data. These assumptions set the distribution of the data as symmetrical with small variance. Comparably, another approach also found in clinical research is Bayesian statistics. This approach presents an alternative for clinical analysis [22, 23] and has the advantage that provides a flexible and intuitive approach with some limitations.

3. Results

3.1 Clinical Parameters and Serum Levels of HGF, EGF, Insulin, and Glucagon in Healthy Subjects. Statistical analysis of the clinical parameters revealed distinct probability distributions and fitted adjustment curves across variables. Most parameters exhibited skewed distributions (Supplementary, Fig. 1); therefore, median values were used as the primary measure for comparisons across datasets (Supplementary Figs. 1 and 2). In health control subjects, the median values of all clinical parameters fell within established normal reference ranges [22].

Comparative analyses of distributional patterns identified sex-related differences in glucose, HOMA-IR, and TG levels within the control group (Supplementary Fig. 2). Spearman's rank correlation analysis revealed a weak inverse association between HOMA-IR and TG ($\rho = -0.236$). Glucose levels showed a moderate negative correlation with these parameters ($\rho = -0.528$), whereas glucagon exhibited similar sex-specific distribution patterns (power-law behavior) but no significant correlation (Table 1; Supplementary Figs. 2–4). Collectively, these findings suggest sex-dependent differences in glucose homeostasis and related metabolic pathways in healthy individuals.

Sex-based differences were also observed in the distribution of liver function–related parameters, including cholesterol, albumin, total bilirubin, and direct bilirubin, among healthy subjects (Supplementary Fig. 1; Table 1). Spearman correlation analyses further supported these observations (Supplementary Fig. 3). Total bilirubin demonstrated a weak inverse correlation ($\rho = -0.347$), suggesting sex-specific regulation of bilirubin metabolism in healthy individuals (Table 1; Supplementary Fig. 3).

Within the control group, median serum hepatocyte growth factor (HGF) levels were comparable between women and men, whereas epidermal growth factor (EGF) levels were modestly higher in men (approximately 18%; Table 1). The distribution of HGF showed no significant sex-related differences (beta distribution; $p = 0.550$ and $p = 0.999$, respectively; Supplementary Fig. 1), and no meaningful correlation with sex was detected (Supplementary Fig. 4). In contrast, EGF exhibited a weak positive correlation with sex ($\rho = 0.250$) (Supplementary Figs. 2 and 4).

3.2 Clinical Parameters and Serum Levels of HGF, EGF, Insulin, and Glucagon in Patients with Cirrhosis. Comparison of clinical parameters between patients with cirrhosis and healthy controls revealed increased median values for glycemia-related variables, including glucose, HOMA-IR, and insulin, although these values remained within established reference ranges. Notably, these parameters displayed sex-specific distribution patterns (Supplementary Figs. 1 and 2). Spearman's rank correlation

analysis showed weak inverse associations between men and women with cirrhosis for glucose and insulin levels, whereas no significant correlation was observed for HOMA-IR (Supplementary Fig. 4).

In patients with cirrhosis, median TG and cholesterol levels were reduced. As expected in this condition, median concentrations of total and direct bilirubin were elevated, while albumin levels were decreased compared with healthy individuals. In addition, median serum levels of HGF and EGF were increased, with higher EGF concentrations observed in men than in women (Table 1; Supplementary Fig. 1). Distribution fitting analyses revealed distinct probability distributions for TG, albumin, total bilirubin, and HGF (Supplementary Fig. 2). Again, total bilirubin exhibited an inverse correlation between men and women with fibrosis/cirrhosis ($\rho = -0.357$; Supplementary Fig. 4).

For cholesterol, direct bilirubin, and EGF, maximum likelihood estimation indicated similar distribution patterns between sexes, whereas the Mann–Whitney U test revealed statistically significant differences ($p < 0.05$). In contrast, for HGF, maximum likelihood estimation suggested distinct distributions by sex, while the Mann–Whitney U test indicated no statistically significant differences (Supplementary Figs. 2 and 3). Notably, glucagon exhibited identical distribution patterns between sexes across statistical approaches, following a power-law distribution (Supplementary Figs. 2–4).

3.3 Serum Levels of Nitrogen-Related Metabolites (Nitrites and Ammonia) in Patients with Cirrhosis. Serum nitrite levels were comparable between healthy men and women, whereas nitrate levels were increased in patients with fibrotic/cirrhotic liver disease, particularly among women (Table 1; Supplementary Fig. 1). Notably, the median values observed in female patients with fibrosis/cirrhosis exhibited a distribution pattern like that of healthy controls (Supplementary Fig. 2). Spearman correlation analysis revealed a weak sex-based association for this nitrogen-related metabolite in both healthy individuals and patients with fibrosis/cirrhosis (Supplementary Fig. 4).

In contrast, serum ammonia levels were markedly elevated in patients with fibrosis/cirrhosis (Table 1; Supplementary Fig. 1). Under these conditions, Spearman's rank correlation coefficient indicated a weak sex-based association. However, ammonia levels exhibited a moderate correlation with sex ($\rho = 0.667$; Supplementary Fig. 4).

3.4 Correlations between Growth Factors, Indicators of Glucose Metabolism, Major Lipids, and Pancreatic Hormones in Serum from Healthy Subjects and Patients with Cirrhosis. The relationships between HGF, EGF, and metabolic parameters were systematically analyzed. Overall, weak to moderate correlations were identified ($\rho > 0.250$, $p < 0.05$). In healthy women, serum HGF showed inverse correlations with EGF ($\rho = -0.286$) and with the major circulating lipids, cholesterol and TG ($\rho = -0.267$ and -0.365, respectively). In addition to its inverse association with HGF, EGF also exhibited a significant negative correlation with glucagon ($r = -0.391$; Fig. 1A).

In healthy men, HGF likewise correlated inversely with EGF ($r = -0.303$; Fig. 1B) and additionally showed negative correlations with insulin, HOMA-IR ($\rho = -0.328$ and -0.263, respectively), and the insulin-to-glucagon ratio ($\rho = -0.346$). In contrast to women, positive correlations were observed in men between

HGF and both cholesterol and TG, (ρ = 0.262 and 0.313, respectively; Fig. 1B). In healthy women, HOMA-IR correlated inversely with glucagon (ρ = −0.279), which in turn correlated inversely with the insulin-to-glucagon ratio (ρ = −0.327). Furthermore, serum TG levels showed a strong positive correlation with cholesterol (ρ = 0.612; Fig. 1A).

In healthy men, glucagon correlated positively with the insulin-to-glucagon ratio (ρ = 0.418) and, unexpectedly, inversely with serum cholesterol (ρ = −0.346). Nevertheless, TG levels were positively correlated with cholesterol in both sexes (ρ = 0.593 in men; Fig. 1B). Compared with healthy women, female patients with cirrhosis exhibited a distinct correlation profile, characterized by significant positive associations between HGF and EGF (ρ = 0.250), as well as between HGF and HOMA-IR (ρ = 0.470), glucagon (ρ = 0.298), and serum TG (ρ = 0.440). In addition, serum EGF levels correlated positively with glucose (ρ = 0.269) and TG (ρ = 0.357; Fig. 2A).

In men with cirrhosis, the pattern of HGF correlations also differed markedly from that observed in healthy men (Fig. 2B). In this group, HGF correlated inversely with glucose (ρ = −0.324) and positively with insulin (ρ = 0.342), glucagon (ρ = 0.468), the insulin-to-glucagon ratio (ρ = 0.250), and TG (ρ = 0.410). Notably, EGF did not correlate with HGF in these patients but instead showed stronger positive correlations with glucose (ρ = 0.336), HOMA-IR (ρ = 0.256), and glucagon (ρ = 0.250; Fig. 2B).

Collectively, these findings indicate that the relationships between growth factors and markers of glucose homeostasis and circulating lipids differ markedly by sex in healthy individuals. In contrast, in both women and men with liver disease, these associations appear more heterogeneous and less clearly defined (Figs. 2A and 2B).

In women with cirrhosis, glucose levels showed a strong inverse correlation with cholesterol (ρ = −0.495), whereas insulin exhibited an unexpected positive correlation with both glucagon (ρ = 0.293) and cholesterol (ρ = 0.326). Unlike healthy women, female patients with cirrhosis displayed positive correlations between HOMA-IR and both glucagon (ρ = 0.335) and TG (ρ = 0.418), along with a negative correlation with cholesterol (ρ = −0.397; Fig. 2A). In this group, glucagon also correlated positively with both TG and cholesterol (ρ = 0.303 and ρ = 0.492, respectively; Fig. 2A) and showed a stronger inverse correlation with the insulin-to-glucagon ratio (ρ = −0.449; Fig. 2A).

Accordingly, in cirrhotic women, cholesterol was inversely correlated with glucose (ρ = −0.495) and, consequently, with HOMA-IR (ρ = −0.397), while showing positive correlations with both insulin and glucagon (ρ = 0.326 and ρ = 0.492, respectively; Fig. 2A). This correlation pattern was not observed in healthy women.

In men with cirrhosis, glucose showed a positive correlation with cholesterol (ρ = 0.326), and insulin correlated positively with both HOMA-IR (ρ = 0.256) and TG (ρ = 0.341). HOMA-IR also correlated with cholesterol (ρ = −0.292). Compared with the other study groups, men with cirrhosis exhibited a strong inverse correlation between glucagon and both the insulin-to-glucagon ratio (ρ = −0.637) and cholesterol

(ρ = −0.346). Finally, this group also showed a strong positive correlation between cholesterol and TG (ρ = 0.379).

Collectively, these multiple and sex-specific correlations among serum parameters suggest regulatory patterns that vary not only according to liver pathology but also according to sex (Figs. 1 and 2).

3.5 Correlations of Growth Factors, Glucose, Insulin, and Glucagon with Albumin, Bilirubin, and Nitrogen-Related Metabolites in Serum from Healthy Subjects and Patients with Cirrhosis. Spearman correlation analyses performed separately by sex in healthy control subjects revealed distinct association patterns. In healthy women, HGF was inversely correlated with total bilirubin (ρ = −0.337), ammonia (ρ = −0.267), and nitrites (ρ = −0.343), whereas EGF showed positive correlations with uric acid (ρ = 0.395) and nitrites (ρ = 0.275; Fig. 3A)

In contrast, in healthy men, HGF correlated positively with albumin (ρ = 0.353) and nitrites (ρ = 0.275; Fig. 3B), displaying a pattern opposite to that observed in women. In this group, HGF was directly associated only with albumin and nitrites, whereas EGF exhibited several inverse correlations, including direct and total bilirubin (ρ = −0.272 and − 0.282, respectively; Fig. 3B). Moreover, in healthy men, EGF showed a stronger positive correlation with uric acid than that observed in healthy women (Figs. 3A and 3B). In the group of female patients with cirrhosis, HGF correlated positively only with albumin (ρ = 0.353), whereas EGF did not show significant associations with any of the analyzed parameters (Fig. 4A). In men with cirrhosis, HGF correlated positively with both direct and total bilirubin (ρ = 0.251) and inversely with albumin (ρ = −0.356), urea (ρ = −0.272), and nitrites (ρ = −0.337; Fig. 4B). Notably, EGF did not exhibit significant correlations with any of the evaluated parameters in this group (Fig. 4B).

Taken together, these findings indicate that the regulatory relationships between EGF and albumin, bilirubin, and nitrogen-containing metabolites observed in healthy individuals of both sexes are largely disrupted in the context of cirrhosis (Figs. 3 and 4).

In healthy women, glucose levels correlated inversely with uric acid (ρ = −0.314) and nitrites (ρ = −0.268), whereas insulin showed a positive correlation with direct bilirubin (ρ = 0.289) and inverse correlations with uric acid (ρ = −0.289) and ammonia (ρ = −0.342; Fig. 3A). Although glucose and insulin did not show significant associations with albumin, total bilirubin, urea, or nitrites, HOMA-IR displayed positive correlations with albumin (ρ = 0.370), total bilirubin (ρ = 0.278), and nitrites (ρ = 0.416), as well as a strong inverse correlation with urea (ρ = −0.471; Fig. 3A).

In this group, glucagon exhibited multiple associations: it correlated positively with direct bilirubin (ρ = 0.281) but inversely with urea (ρ = −0.393), uric acid (ρ = −0.409), and nitrites (ρ = −0.317; Fig. 3A). TG showed strong positive correlations with albumin (ρ = 0.565) and total bilirubin (ρ = 0.442), along with a moderate positive correlation with nitrites (ρ = 0.360). By contrast, cholesterol also correlated positively with albumin but exhibited an inverse association with nitrites (ρ = −0.440; Fig. 3A).

In healthy men, glucose exhibited significant positive correlations with urea (ρ = 0.426) and uric acid (ρ = 0.383), whereas insulin was inversely correlated with direct bilirubin (ρ = −0.312) and positively correlated with nitrites (ρ = 0.421). Control men also showed multiple associations involving HOMA-IR, including a negative correlation with total bilirubin (ρ = −0.395) and positive correlations with urea (ρ = 0.392), uric acid (ρ = 0.359), ammonia (ρ = 0.357), and nitrites (ρ = 0.291). In addition, glucagon was inversely correlated exclusively with nitrites (ρ = −0.396), while the insulin/glucagon ratio displayed a strong positive correlation with nitrites (ρ = 0.474; Fig. 3B). This association profile contrasted markedly with that observed in control women (Fig. 3A).

Unlike healthy women, control men exhibited an inverse correlation between TG and urea (ρ = −0.261), together with a positive correlation between TG and ammonia (ρ = 0.276). Moreover, cholesterol was positively correlated with albumin (ρ = 0.304) and nitrites (ρ = 0.493) and inversely correlated with uric acid (ρ = −0.256).

In women with cirrhosis, neither glucose nor insulin showed significant correlations with the analyzed parameters (Fig. 4A). However, HOMA-IR exhibited significant positive correlations with albumin (ρ = 0.352), total bilirubin (ρ = 0.355), and nitrites (ρ = 0.363), as well as a negative correlation with urea (ρ = −0.452; Fig. 4A), closely resembling the pattern observed in healthy women. In this group, glucagon was inversely correlated with albumin (ρ = −0.288) and positively correlated with uric acid (ρ = 0.322), representing a pattern opposite to that found in healthy women (Fig. 4A). Additionally, women with cirrhosis showed a positive correlation between TG and direct bilirubin (ρ = 0.290). In contrast, cholesterol was inversely correlated with albumin (ρ = −0.272) and nitrites (ρ = −0.272) and positively correlated with urea (ρ = 0.312; Fig. 4A).

In men with cirrhosis, glucose showed a positive correlation with urea (ρ = 0.392), whereas insulin did not exhibit significant associations with the parameters analyzed (Fig. 4B). By contrast, HOMA-IR was inversely correlated with both direct and total bilirubin (ρ = −0.360 and − 0.367, respectively) and positively correlated with urea (ρ = 0.390) and nitrites (ρ = 0.255), displaying a pattern similar to that observed in control men. In this group, glucagon was inversely correlated exclusively with nitrites (ρ = −0.419), while the insulin/glucagon ratio also showed a positive correlation with nitrites (ρ = 0.383; Fig. 4B). This pattern differed from that observed in control women (Fig. 4A).

Unlike women with cirrhosis, male patients with liver disease exhibited an inverse correlation between TG and urea (ρ = −0.271), along with positive correlations between cholesterol and albumin (ρ = 0.433), ammonia (ρ = 0.285), and nitrites (ρ = 0.361). Overall, the correlations among serum parameters shown in Figs. 3 and 4 suggest regulatory patterns that are less profoundly altered by the onset of cirrhosis than those described in Figs. 1 and 2, thereby preserving distinct sex-based differences.

3.6 Correlations among albumin, bilirubin, and nitrogen-related metabolites in serum from healthy subjects and patients with cirrhosis. Spearman correlation analysis stratified by sex in control subjects revealed distinct association patterns. In healthy women, albumin was positively correlated with total bilirubin (ρ = 0.319), whereas direct bilirubin was inversely correlated with uric acid (ρ = −0.267; Fig. 5A).

As expected, urea was inversely correlated with ammonia (ρ = −0.226), which in turn showed a positive correlation with serum nitrite levels (ρ = 0.278; Fig. 5A).

In healthy men, albumin was positively correlated with uric acid (ρ = 0.275) and nitrites (ρ = 0.286; Fig. 5B). Total bilirubin exhibited an inverse correlation with uric acid (ρ = −0.374), while urea was negatively correlated with ammonia (ρ = −0.327), thus reproducing the pattern observed in healthy women (Figs. 5A and 5B).

In women with cirrhosis, albumin remained positively correlated with total bilirubin (ρ = 0.364). However, in contrast to healthy women, direct bilirubin showed strong positive correlations with both total bilirubin (ρ = 0.562) and uric acid (ρ = 0.306; Fig. 6A). In addition, urea was strongly positively correlated with uric acid (ρ = 0.442), which in turn correlated positively with serum ammonia levels (ρ = 0.265; Fig. 6A). Notably, nitrites did not show significant associations with any of the other parameters evaluated in this group.

In men with cirrhosis, albumin did not exhibit significant correlations with the analyzed variables, whereas the association between direct and total bilirubin represented the strongest relationship identified (ρ = 0.986; Fig. 6B). In this group, urea, uric acid, and nitrites did not show significant correlations among themselves or with albumin or bilirubin. However, ammonia displayed a positive correlation with nitrates (ρ = 0.278; Fig. 6B).

4. Discussion

In a recent publication [22], we demonstrated the critical roles of insulin and glucagon in regulating serum glucose and lipid homeostasis in patients with type 2 diabetes mellitus (T2DM). These endocrine alterations were strongly associated with changes in two key growth factors, hepatocyte growth factor (HGF) and epidermal growth factor (EGF). In the present study, we extend these findings to patients with cirrhosis by examining pancreatic hormones and growth factors in relation to serum albumin, bilirubin, and nitrogen-containing metabolites, parameters that are characteristically dysregulated in chronic liver disease.

Despite the limited number of available studies, most of the published evidence suggests that premenopausal women are relatively protected against the development of severe fibrosis across multiple organs [24]. Sex-related differences in the onset and progression of chronic diseases, as well as in responses to therapy, have become increasingly relevant in the context of an aging population [24].

In healthy control subjects of both sexes, an inverse correlation between circulating HGF and EGF levels was observed in the present study. In contrast, women with cirrhosis exhibited a positive correlation between these growth factors, whereas no significant association was detected in men with cirrhosis (Fig. 7). These sex-specific changes may be related to hepatic regenerative processes, in which cytokines such as interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and HGF play pivotal roles [25]. Through activation of its receptor, c-Met, HGF also exerts anti-inflammatory effects and promotes tissue

repair and regenerative processes [26]. Furthermore, quiescent hepatic stellate cells (HSCs) contribute to physiological hepatocyte turnover through the secretion of growth factors, including HGF [21].

Conversely, EGF and transforming growth factor-α (TGF-α) are potent epithelial mitogens secreted by HSCs that stimulate hepatocyte proliferation and play critical roles in paracrine signaling during liver regeneration [27]. In addition, EGF and fibroblast growth factor-2 (FGF-2) can act synergistically to revert activated HSCs toward a transitional phenotype [28], suggesting a role for EGF that contrasts with that of HGF. Under pathological conditions, growth factors and cytokines—including EGF, transforming growth factor-β (TGF-β), platelet-derived growth factor (PDGF), and leptin—secreted by activated HSCs may further perpetuate fibrogenesis through both paracrine and autocrine mechanisms within the injured liver [29]. Notably, the reciprocal relationship between HGF and EGF observed under physiological conditions was disrupted in patients with cirrhosis (**Fig. 7**). This loss of coordinated regulation may reflect an altered regenerative response to hepatic injury that attempts to promote tissue repair while simultaneously limiting further fibrotic progression.

In control subjects, EGF levels were inversely correlated with circulating glucagon, whereas HGF levels were inversely correlated with insulin (**Fig. 7**). In contrast, in women with cirrhosis, both HGF and insulin were positively correlated with serum glucagon levels. In men with cirrhosis, HGF was positively correlated with both pancreatic hormones, whereas EGF was positively associated with glucagon (**Fig. 7**). Collectively, these findings suggest that cirrhosis profoundly alters the physiological interactions between growth factors and pancreatic hormones (**Fig. 7**). In this context, the activation of HSCs, which has also been associated with increased insulin sensitivity, may represent a double-edged process [30].

The liver is a major target organ for several endocrine hormones, including insulin, glucagon, thyroid hormones, and cortisol. Induction of hepatocyte DNA synthesis by EGF has been shown to require insulin [31], whereas glucagon has been reported to exert additive or synergistic effects on EGF-mediated DNA synthesis [32]. HGF interacts with the glucoregulatory hormones insulin and glucagon and modulates their actions during liver regeneration, including inhibition of insulin signaling [33]. The HGF–c-Met signaling axis may also indirectly contribute to glucose homeostasis by promoting pancreatic β-cell proliferation and function [34]. Furthermore, the combined action of HGF and EGF has been shown to induce β-cell differentiation during pancreatic progenitor development [34]. Accordingly, HGF has been proposed as an important regulator of glucose homeostasis through activation of its receptor, c-Met [35].

Observed sex-related disparities in disease prevalence strongly support a physiological role for estrogens and other ovarian hormones, both in conferring protection during the reproductive years and in influencing disease progression after menopause [36]. In healthy women, circulating HGF levels were inversely correlated with total bilirubin, triglycerides (TG), and cholesterol (**Fig. 7**). Intriguingly, the opposite pattern was observed in healthy men, in whom HGF levels were positively correlated with albumin, TG, and cholesterol (**Fig. 7**). HGF has been implicated in the regulation of hepatic bile acid synthesis, which may partially account for its association with bilirubin levels. In addition, liver growth

factor (LGF), bilirubin, and albumin have been reported to protect endothelial nitric oxide (NO) from degradation by superoxide anions [37].

Accumulation of TG within hepatocytes during nonalcoholic fatty liver disease (NAFLD) has been associated with impaired liver volumetry and reduced regenerative capacity [38]. Moreover, free cholesterol is a potent activator of hepatic stellate cells (HSCs), and dietary cholesterol supplementation promotes cholesterol accumulation in HSCs, thereby accelerating experimental liver fibrosis [21, 39]. From this perspective, the inverse associations between HGF and both TG and cholesterol observed in healthy women (**Fig. 7**) may be consistent with a protective or metabolically favorable effect. Notably, women with cirrhosis exhibited correlation patterns that more closely resembled those observed in healthy men, rather than maintaining a distinct sex-specific profile (**Fig. 7**).

In healthy women, circulating HGF levels were inversely correlated with nitrogen-containing metabolites, including ammonia and nitrites, the latter representing stable products of nitric oxide (NO) metabolism. In contrast, the opposite pattern was observed in healthy men (Fig. 7). Among patients with cirrhosis, men exhibited an inverse correlation between urea and nitrites (Fig. 7), suggesting alterations in regulatory pathways involved in nitrogen metabolism. In the liver, ammonia accumulation promotes HSC activation and fibrogenesis. Although hyperammonemia exerts systemic deleterious effects, it may also contribute to sarcopenia, immune dysfunction, and an increased risk of hepatocellular carcinoma [40]. Kupffer cells are a major source of NO in the liver, and NO can counteract reactive oxygen species (ROS) by inhibiting HSC proliferation and type I collagen synthesis. However, NO-derived peroxynitrite may exert potent profibrogenic effects on HSCs [41]. To date, no direct effects of HGF or EGF on ammonia detoxification or NO metabolism have been reported.

In healthy women, EGF levels were positively correlated with uric acid and nitrites but showed no significant associations with major circulating lipids, in contrast to the correlation profile observed for HGF in this group (**Fig. 7**). In healthy men, circulating EGF levels were positively correlated with bilirubin and uric acid and inversely correlated with glucose (**Fig. 7**). Collectively, these findings suggest that the relationships between EGF and both TG and glucose are altered in cirrhosis compared with healthy conditions, with the direction of these associations changing irrespective of sex.

Deficient hepatic expression of the epidermal growth factor receptor (EGFR), together with reduced expression of the kinases Wee1 and Myt1, has been associated with increased oxidative stress and impaired hepatocyte macroautophagy [42]. In adipocytes, EGF, similar to insulin, has been shown to promote lipid accumulation and stimulate glucose metabolism through oxidative pathways and incorporation into lipids, while concurrently inhibiting catecholamine-stimulated lipolysis [43]. profile (**Fig. 7**).

In women with cirrhosis, elevated serum insulin levels were accompanied by increased circulating glucagon concentrations. Glucagon levels were positively correlated with cholesterol, TG, and uric acid and inversely correlated with albumin (**Fig. 7**). In contrast, in men with cirrhosis, variations in insulin levels were not accompanied by parallel changes in glucagon. Nevertheless, in this group, both

pancreatic hormones appeared to exhibit stronger associations with growth factors and showed significant correlations with major lipids and nitrites, although the direction of these associations was opposite to that observed in women (**Fig. 7**).

Insulin resistance, as observed in nonalcoholic steatohepatitis (NASH), promotes the accumulation of free fatty acids and other lipotoxic metabolites, leading to increased oxidative stress, mitochondrial dysfunction, and hepatocyte lipoapoptosis, while also triggering inflammatory responses [44]. Moreover, the accumulation of saturated free fatty acid metabolites secondary to insulin resistance contributes to lipotoxicity, which damages hepatocytes and further exacerbates oxidative stress [45]. Glucagon is the most potent physiological up-regulator of the urea cycle through induction of urea cycle gene expression [45]. Under physiological conditions, suppression of glucagon by glucose, together with insulin-mediated signaling, contributes to reduced urea synthesis and nitrogen production following carbohydrate intake; however, this regulatory mechanism is disrupted in cirrhosis [46] (**Fig. 7**).

An adequate functional liver mass is essential for normal urea production; consequently, the capacity for urea synthesis is markedly reduced in patients with cirrhosis [47]. Accordingly, the present study provides evidence of complex relationships and potential interactions among growth factors, insulin, glucagon, and selected metabolites at the hepatic level, consistent with observations previously reported in experimental animal models and human studies. In this context, metabolic dysfunction-associated steatotic liver disease (MASLD) is now widely recognized as a sexually dimorphic condition closely associated with metabolic comorbidities and requiring a multidisciplinary therapeutic approach to address patient heterogeneity and differences in responses to pharmacological interventions [48].

From a mechanistic perspective, sex hormones may contribute to the patterns observed in the present study by modulating fibrogenesis through both direct and indirect pathways, although their precise contributions remain incompletely defined [24]. Experimental studies in animal models have demonstrated that estradiol administration reduces serum levels of AST, ALT, hyaluronic acid, and type IV collagen, while also decreasing hepatic collagen content and smooth muscle actin expression in hepatic stellate cells [49]. In this context, progesterone receptor membrane component 1 (PGRMC1), a non-canonical progesterone receptor, has been implicated in hepatic metabolism. Recent evidence further suggests that PGRMC1 plays an important role in the progression of liver fibrosis through regulation of the TGF-β receptor (TGF-βR) pathway, highlighting its potential as a therapeutic target [50].

Our study has several limitations. Despite the robustness of the findings and the statistical methods employed, the sample size remains relatively limited. Furthermore, this was a cross-sectional study; therefore, longitudinal follow-up is needed to determine whether the observed sex-related differences become more pronounced with disease progression or whether some of the identified alterations may be reversible over time. In this context, a comprehensive analysis of the treatments received by the patients is also warranted to determine whether specific therapeutic interventions contribute to the emergence, persistence, or resolution of the changes observed in the variables assessed in the present study.

5. Conclusion

In summary, the present study highlights the central roles of the growth factors HGF and EGF, as well as their interactions with the pancreatic hormones insulin and glucagon, in the regulation of serum glucose and lipid homeostasis and in the alterations of metabolites indicative of hepatic function, including albumin, bilirubin, ammonia, and nitric oxide-related products. These interactions appear to be particularly pronounced in patients with cirrhosis, in whom metabolic dysregulation and impaired regenerative capacity coexist.

Declarations

Declaration of Competing Interests

The authors declare that there are no competing interests associated with the manuscript.

Data Availability

Other database sets generated during this study, besides those in the supplemental material are available from the corresponding authors on reasonable request.

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Ethical Approval The study was conducted in accordance with the Declaration of Helsinki (2000) of the World Medical Association and was approved by the Ethics Committee of the “Xoco” General Hospital (Ministry of Public Health, Mexico). Written informed consent was obtained from all participants. The study was registered under project number 207.010.30.18.

Authorship Contribution Statement:

Martha L. Contreras-Zentella: Conceptualization, Methodology, Investigation, Visualization, Funding acquisition, Writing – Original Draft,Writing – Review & Editing. **Martha G. Alatriste-Contreras:** Methodology, Investigation, Visualization, Writing – Original Draft,Writing – Review & Editing. **Juan A. Suárez-Cuenca:** Methodology, Investigation, Visualization, Writing – Review & Editing. **Rolando Hernández-Muñoz:** Conceptualization, Methodology, Investigation, Visualization, Funding acquisition, Project administration, Writing – Original Draft,Writing – Review & Editing.

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Table 1

Table 1 is available in the Supplementary Files section.

Figures

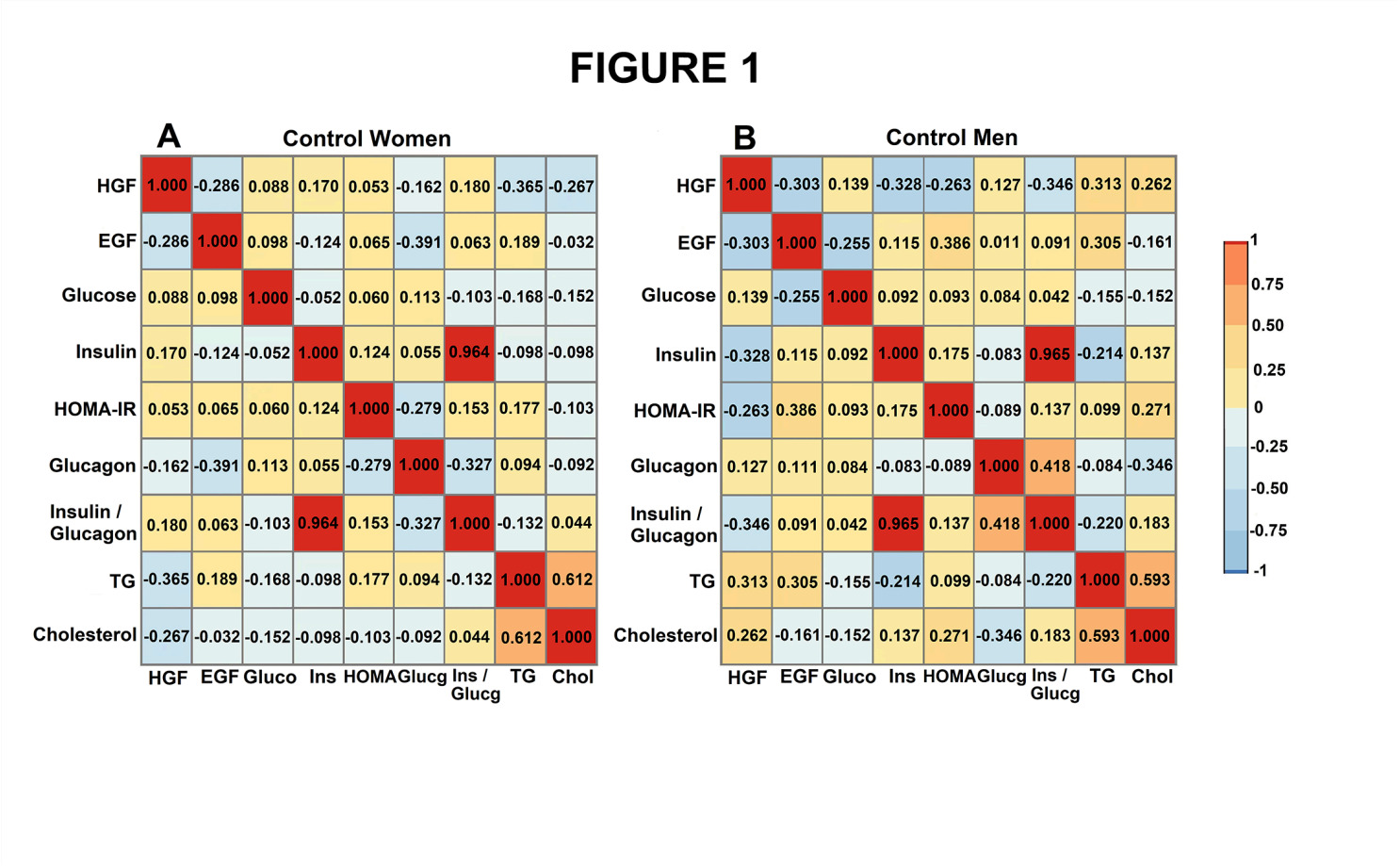


Figure 1

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FIGURE 2

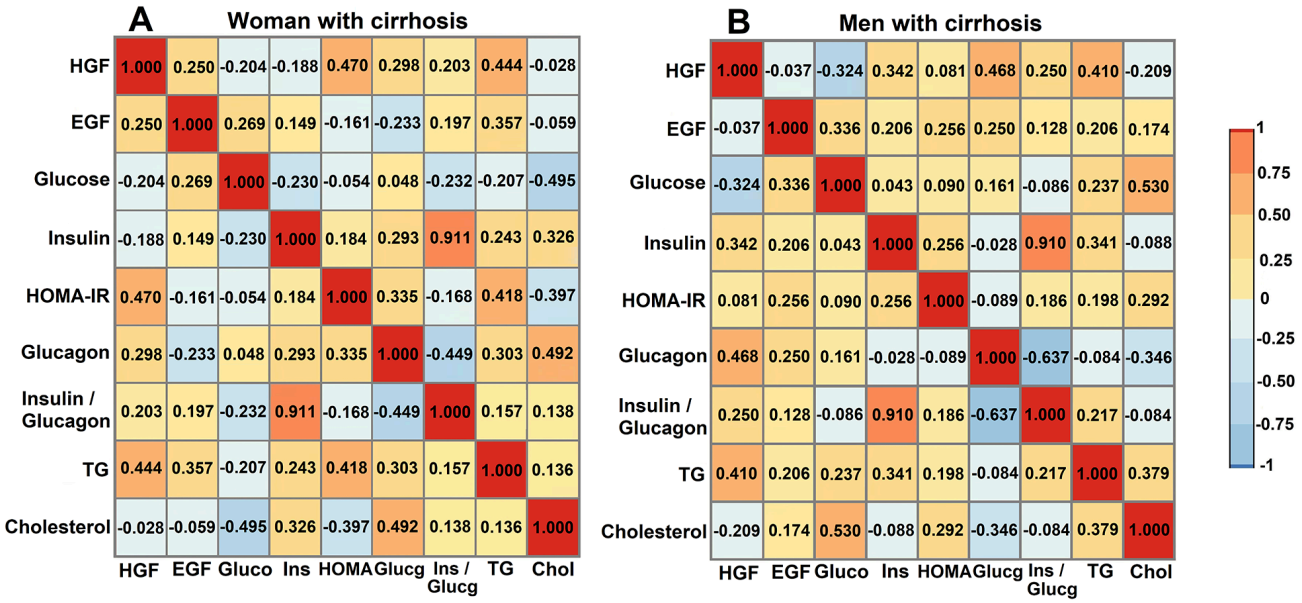


Figure 2

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FIGURE 3

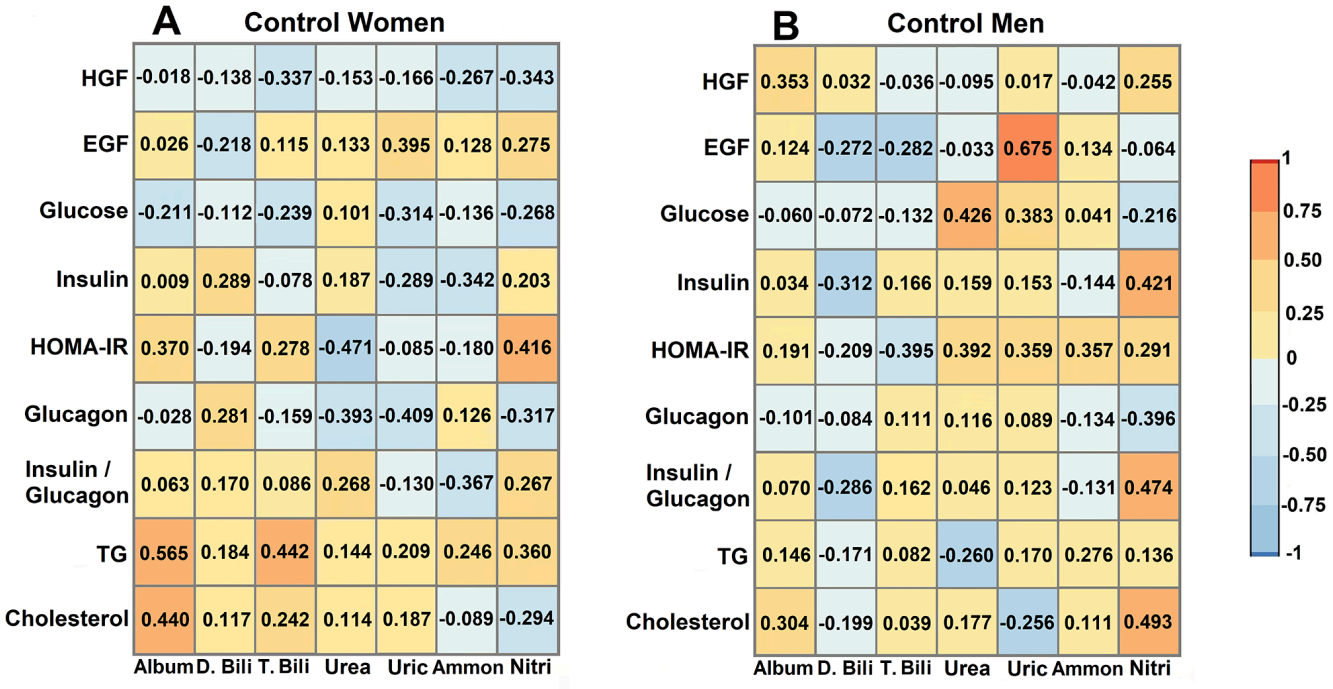


Figure 3

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FIGURE 4

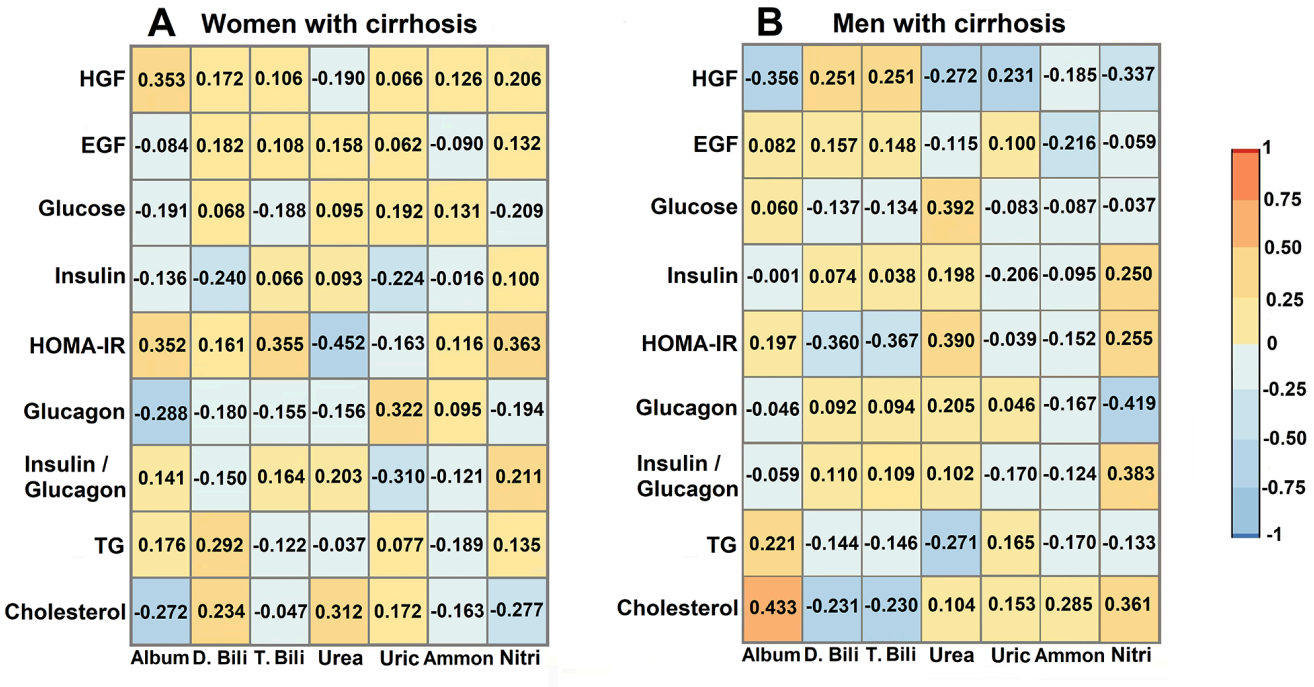


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FIGURE 5

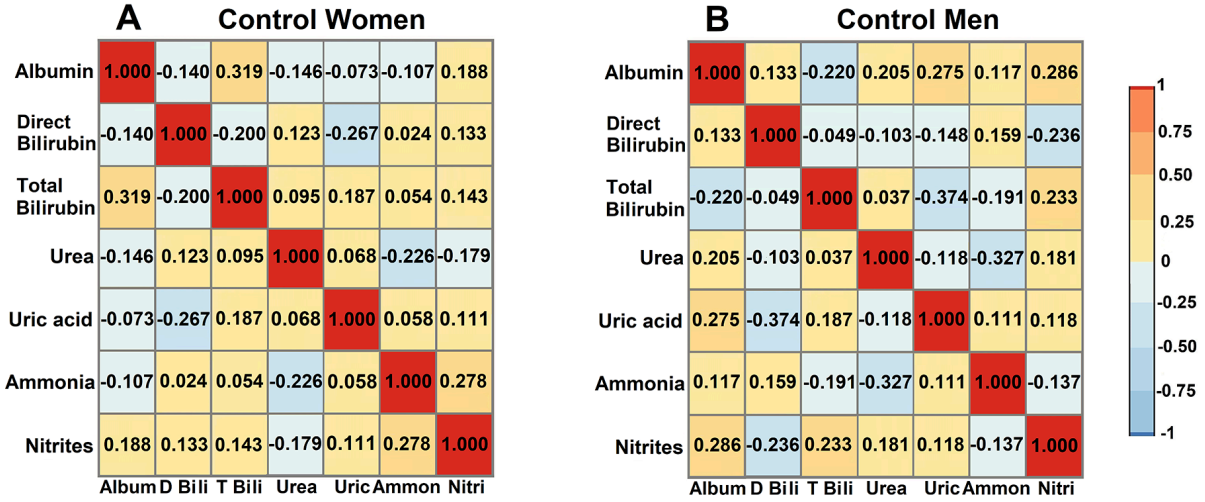


Figure 5

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FIGURE 6

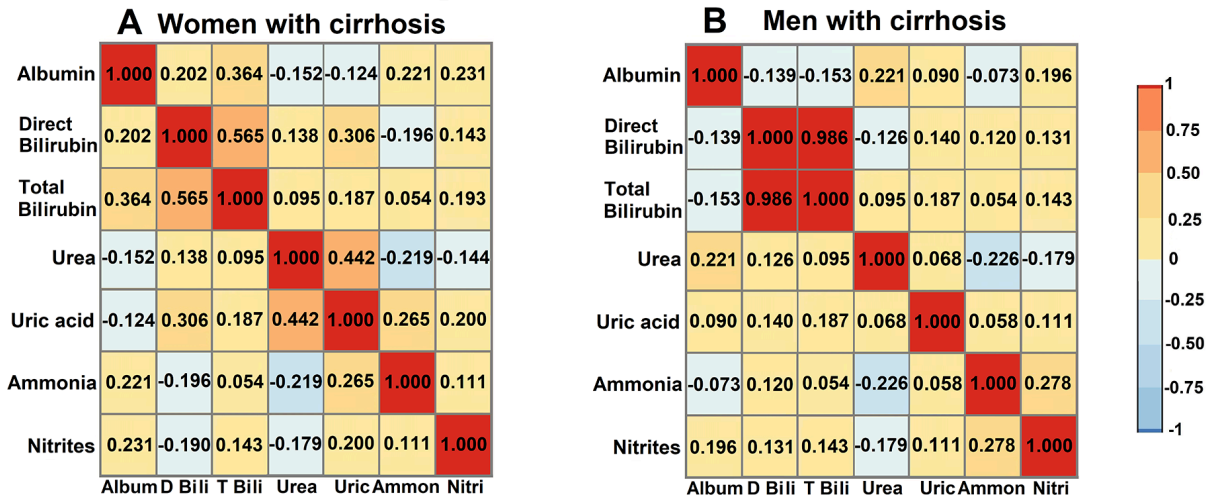


Figure 6

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FIGURE 7

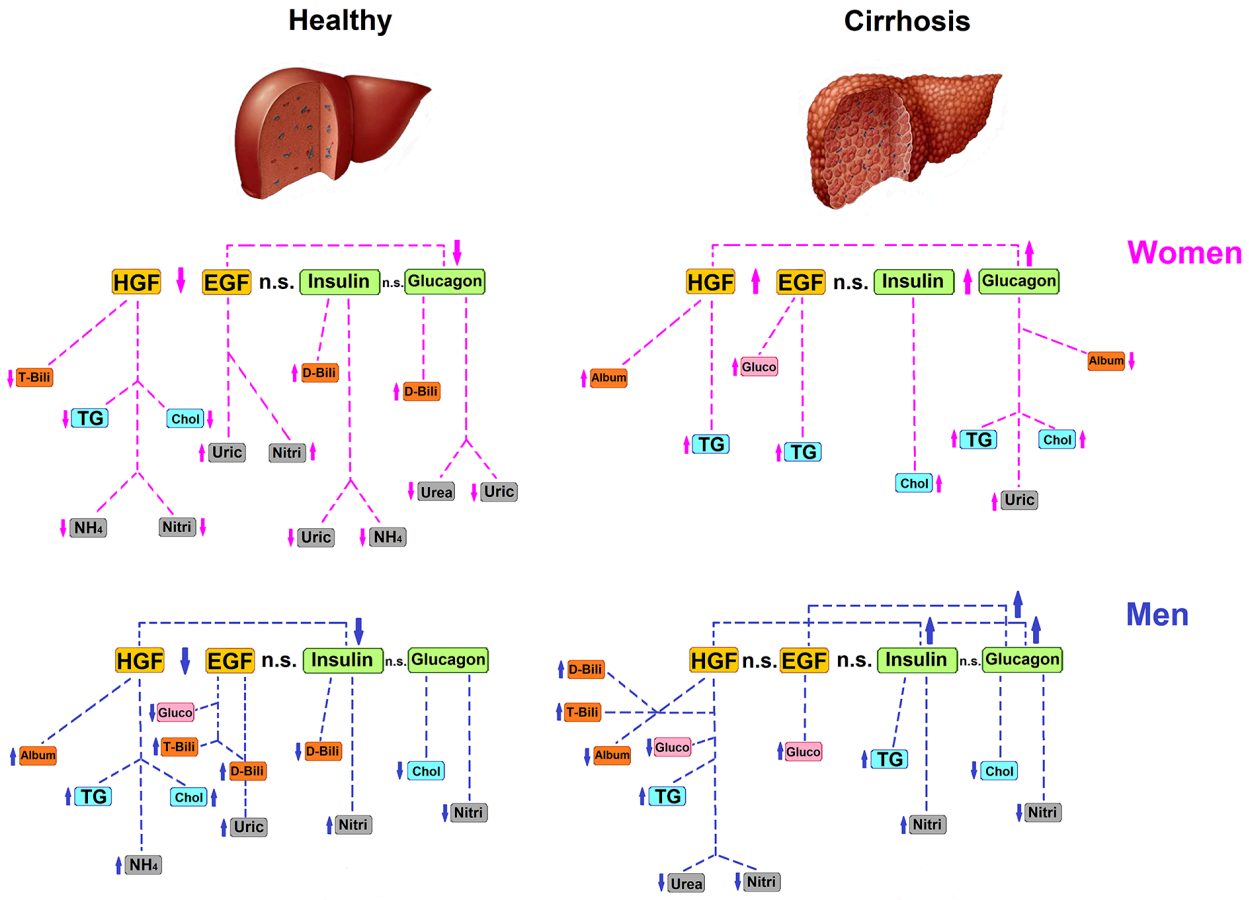


Figure 7

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