Review

Gilbert's Syndrome: The Good, the Bad and the Ugly

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Review

Gilbert's Syndrome: The Good, the Bad and the Ugly

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Abstract: Gilbert's syndrome (GS) is a common hereditary condition characterized by mild increases in serum bilirubin levels due to inherited defects in bilirubin metabolism. This review, based on data from peer-reviewed articles and journals spanning from 1977 to January 2024, provides a comprehensive overview of over four decades of research on GS. Early studies primarily focused on defining the clinical and genetic characteristics of the syndrome, laying the foundation for subsequent investigations. More recent research has delved into the genetic mechanisms underlying the reduced expression of bilirubin UDP-glucuronosyltransferase, which has significantly enhanced our understanding of the pathogenesis of GS. Furthermore, recent studies have shed light on the clinical implications of GS, including its association with non-alcoholic fatty liver disease and mortality risk, highlighting the complex interplay between genetic factors, bilirubin metabolism, and clinical outcomes. Despite its generally benign nature, thorough research is essential to fully understand the impact of GS on patients' lives. This review emphasizes the importance of ongoing research to deepen our understanding of GS and its broader implications.

Keywords: Gilbert's syndrome (GS); genetic variations; protective effects of Gilbert's syndrome; cancer risk; drug interactions; pharmacokinetic abnormalities; clinical implications of Gilbert's Syndrome; effect on NASH; liver transplantation; psychology and GS

Introduction

Hereditary hyperbilirubinemia syndromes encompass a spectrum of conditions characterized by mild increases in serum bilirubin levels due to inherited defects in bilirubin metabolism. Among these syndromes, Gilbert's syndrome (GS) stands out as the most prevalent, initially described in 1901 by Gilbert and Lareboullet [1,2]. Epidemiological studies indicate that GS affects approximately 2-13% of the population [3–5] with a higher prevalence observed in individuals without liver disease or hemolysis[6,7]. The hallmark of GS is a notable decrease in hepatic bilirubin UDP-glucuronosyltransferase (UGT) activity, leading to impaired bilirubin conjugation.

Clinically, GS typically presents with fluctuating serum bilirubin levels ranging between 1 and 5 mg/dL,[6,8] with occasional mild jaundice observed in some patients. However, these elevated bilirubin levels rarely lead to clinically significant liver disease,[6,8] as evidenced by normal liver enzyme levels and histological findings in patients with GS. Consequently, individuals with GS and isolated unconjugated hyperbilirubinemia typically require no further work-up beyond confirming the absence of liver disease.

The prevalence of GS appears to be higher in men compared to women, and fasting has been noted to increase serum bilirubin levels in affected individuals[6,8]. Despite the benign nature of GS, it is crucial to recognize and understand this condition to avoid unnecessary investigations and interventions in patients with isolated unconjugated hyperbilirubinemia.

Alongside GS, other hereditary hyperbilirubinemia syndromes, such as Dubin-Johnson syndrome and Rotor syndrome, also contribute to the spectrum of benign bilirubin disorders. These syndromes similarly manifest with mild increases in serum bilirubin levels, occasionally accompanied by jaundice. However, unlike GS, Dubin-Johnson syndrome and Rotor syndrome are

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characterized by distinct pathophysiological mechanisms, including impaired hepatobiliary transport and defective hepatic excretion of bilirubin conjugates, respectively.[9]

Pathophysiology

The pathophysiology of hyperbilirubinemia in Gilbert's syndrome (GS) is multifaceted, [10,22] involving disruptions in bilirubin production, hepatic uptake, and glucuronidation, all influenced by genetic factors. Individuals with GS exhibit increased bilirubin production from both hepatic and erythroid sources, with evidence of elevated hepatic haem production and occasional haemolysis[11]. Moreover, abnormalities in enzymes involved in haem biosynthesis, such as protoporphyrinogen oxidase, have been reported in peripheral blood cells from GS patients, suggesting a dysregulation in haem metabolism contributing to bilirubin elevation.

A key feature of GS is a minimum 50% decrease in hepatic bilirubin UDP-glucuronosyltransferase (UGT) activity,[12] leading to impaired bilirubin conjugation.[12] Immunohistochemical studies have demonstrated reduced expression of UGT throughout the hepatic lobule in individuals with GS compared to normal controls. The underlying genetic basis for this reduction involves mutations or polymorphisms in the UGT1A1 gene, with homozygosity for the (TA)7TAA variant in the promoter region being particularly prevalent in white populations[13]. Conversely, Asian populations exhibit mutations such as the Gly71Arg mutation (UGT1A1*6) in exon 1 of the UGT1A1 gene, highlighting ethnic variations in UGT1A1 gene polymorphisms.

These genetic variations underscore the complex interplay of genetic factors in bilirubin metabolism, with different populations exhibiting distinct patterns of UGT1A1 gene mutations and polymorphisms. Ethnic differences in the prevalence of specific variants, such as varying TA repeat numbers and allele frequencies, contribute to the heterogeneous presentation of GS across different ethnic groups.[13]

Furthermore, abnormalities in hepatic uptake of bilirubin and potential defects in hepatocellular transport may further contribute to the pathogenesis of hyperbilirubinemia in GS [11,12]. Compromised hepatic uptake and impaired bilirubin glucuronidation, combined with genetic predispositions, collectively contribute to the characteristic elevation of serum bilirubin levels observed in individuals with GS.

Genetic Background

Gilbert's syndrome (GS) is a common hereditary disorder characterized by mild unconjugated hyperbilirubinemia, and comprehending its genetic underpinnings is essential for precise diagnosis and effective management. Mutations in the UDP-glucuronosyltransferase 1A1 (UGT1A1) gene on chromosome 2 (2q37) are central to the pathogenesis of GS. The UGT1A1 enzyme is crucial for bilirubin conjugation and elimination, as well as for processing various drugs, foreign substances, and natural compounds through glucuronidation.[2]

Several genetic mutations and variations have been identified in UGT genes, with a common defect in the TATA box promoter of the UGT1A1 gene linked to GS, resulting in elevated bilirubin levels[14]. Notable variants include UGT1A128, UGT1A160, and UGT1A193, with UGT1A128 being prevalent in Caucasians. The presence of an additional TA repeat in the TATAA element of the UGT1A1 gene promoter is associated with reduced enzyme expression and higher serum bilirubin levels in GS patients[6].

GS exhibits genetic heterogeneity, with over 100 mutations identified, and various mutations display distinct prevalence across different ethnic groups[2,14,15]. African individuals, despite having less efficient UGT1A1 promoters, often exhibit lower bilirubin levels compared to Caucasians, possibly due to genetic differences beyond UGT1A1 variations, such as lower hemoglobin levels and a smaller red cell mass[3]. In contrast, limited data suggest higher bilirubin levels among Asian infants, possibly attributable to a shorter red cell lifespan[2,7,13].

Among Caucasians, the most common genotype associated with GS is the homozygous polymorphism A(TA)7TAA, also known as UGT1A128, featuring two extra TA repeats in the UGT1A1 gene promoter, which decreases gene expression. In East Asians, GS commonly arises from

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the Gly71Arg mutation (G71R; UGT1A16) in exon 1 of the UGT1A1 gene, leading to impaired bilirubin conjugation. The allelic frequency of these mutations varies across ethnic populations[2].

Understanding the genetic basis of GS not only aids in diagnosis but also provides insights into ethnic differences in bilirubin metabolism and susceptibility to the syndrome. Further research into the molecular mechanisms underlying UGT1A1 gene regulation and bilirubin metabolism may uncover novel therapeutic targets for GS management.

Clinical Presentation

The clinical presentation of Gilbert's syndrome (GS) is variable, typically characterized by mild unconjugated hyperbilirubinemia without evidence of liver disease or hemolysis. Individuals with GS may experience intermittent jaundice, particularly during periods of fasting, stress, illness, or physical exertion[16–18]. This jaundice is often mild and asymptomatic, although some patients may report occasional upper abdominal pain, fat intolerance, and fatigue. Despite the variability in symptoms, GS is generally considered a benign condition, with nonspecific symptoms such as malaise, abdominal discomfort, or fatigue being reported in some patients[17].

Diagnosing GS relies primarily on clinical evaluation and laboratory findings. Elevated levels of unconjugated bilirubin on repeated testing are indicative of the condition. Importantly, liver function tests are typically normal, and markers of hemolysis are absent in individuals with GS. The diagnosis of GS is thus established through a combination of clinical history, physical examination, and laboratory testing.

GS can also impact neonatal jaundice development, particularly in breast-fed neonates. The condition may accelerate the onset of jaundice, and interactions with other factors such as glucose-6-phosphate dehydrogenase (G-6-PD) deficiency and ABO incompatibility can prolong hyperbilirubinemia in affected infants[16] Also highlights the importance of recognizing and managing GS-related jaundice in neonates, especially in the context of breastfeeding and potential comorbidities.

Diagnosis

Diagnosing Gilbert's syndrome (GS) involves a comprehensive assessment of clinical presentation, laboratory findings, and genetic testing. Typically, GS is diagnosed by observing mild, fluctuating unconjugated hyperbilirubinemia alongside normal liver function tests and the absence of hemolysis[13]. An associated family history, though not always present, can further support the diagnosis[19]. Additionally, GS manifests with normal liver function tests and histology, with delayed bilirubin clearance leading to mild jaundice that varies in intensity, often exacerbated by factors such as fasting, surgery, infection, physical exertion, and alcohol intake. Standard liver enzyme tests usually remain normal, and urine bilirubin and urobilinogen levels are typically within normal or subnormal ranges[20]. Liver biopsy is not indicated and is usually normal, although ultrasound may be used to detect structural liver abnormalities[2,21]. If initial examinations yield normal results, re-evaluation after 6 to 12 months can confirm the diagnosis if no new abnormalities arise.[21]

While there are no specific diagnostic laboratory tests for GS[19] genetic testing for UGT1A1 TA repeat and Gly71Arg mutation aids in diagnosing prolonged neonatal jaundice, though it's not widely available[13]. This genetic analysis can confirm the presence of specific mutations associated with GS but its applicability may vary across different populations due to the variability of mutations. Nonetheless, screening for GS through real-time PCR detection for the UGT1A1*28 mutation is crucial, especially considering potential drug susceptibilities associated with GS[2]. However, the precise cause of its high prevalence in Caucasians remains unclear.

Differential diagnosis from other unconjugated hyperbilirubinemic states, such as Crigler-Najjar syndrome types I and II, is important for proper management. Acquired unconjugated hyperbilirubinemias, like Lucey-Driscoll syndrome and breast milk jaundice, should also be considered[22].

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Studies have shown that individuals with GS undergo various diagnostic tests to confirm the diagnosis, such as the fasting test, which involves a 24-hour calorie restriction followed by blood sample collection, revealing a significant increase in total and unconjugated bilirubin levels.Similarly, the rifampin provocative test, administered with rifampicin, demonstrates a notable elevation in unconjugated bilirubin levels, aiding in the diagnosis of GS[7].

Furthermore, additional diagnostic approaches include measuring bilirubin-UDP-glucuronosyltransferase activity in the liver, which is typically low in GS patients but may[23] not always correlate with serum bilirubin levels due to various factors[7]. Fractionation of total serum bilirubin using alkaline methanolysis and thin-layer chromatography helps diagnose GS by precisely measuring conjugated and unconjugated bilirubin levels[13]. However, the presence of hemolysis can complicate diagnosis, leading to the use of additional tests for confirmation, such as nicotinic acid infusion or rifampin administration.

Management and Prognosis of Gilbert's Syndrome

Management of Gilbert's syndrome (GS) primarily involves reassurance, as no specific treatment or dietary restrictions are necessary due to its benign nature[16].

Once diagnosed, individuals should be informed that GS does not require medical intervention or lifestyle changes. Instead, emphasis should be placed on providing education and addressing any concerns to alleviate unnecessary patient anxiety[20,22]. The clinical significance of GS lies in the potential for mild hyperbilirubinemia to be mistaken for a sign of liver disease[24], highlighting the importance of accurate diagnosis and patient education.

Despite the presence of elevated bilirubin levels, the prognosis for individuals with GS is excellent, with no long-term sequelae reported[24]. This underscores the benign nature of the condition and provides further reassurance to affected individuals and their families. Overall, the management approach for GS focuses on patient education, reassurance, and accurate diagnosis to ensure optimal patient outcomes and quality of life.

Individuals with Gilbert's syndrome exhibit mortality rates nearly half those of individuals without evidence of the syndrome, suggesting a potential protective effect against all-cause mortality in the general population[25–27].

Protective Effects of Gilbert's Syndrome

Research suggests that individuals with Gilbert's syndrome (GS), characterized by mildly elevated bilirubin levels, may benefit from a lower risk of cardiovascular disease (CVD) compared to the general population, indicating a potential protective role of bilirubin against heart disease[22,28–30]. Each 1-mmol/L increase in serum bilirubin level correlates with a 6.5% decrease in CVD risk[23], highlighting the significance of bilirubin in cardiovascular health. Significant reductions in infarct size and lipid and protein oxidation indicate a mechanism related to protection from oxidative damage and indicate the potential utility of this molecule as a post-MI treatment[31].

Also found that markers of arrhythmia risk, such as P-wave dispersion and QT dispersion, are reduced in patients with Gilbert's syndrome compared to healthy subjects, finding significantly lower values in the Gilbert's syndrome group, suggesting a potential protective role of elevated bilirubin levels against cardiac arrhythmias[32].

Additionally, elevated serum bilirubin levels, particularly in GS patients, have been associated with a reduced risk of diabetes, metabolic syndrome, and obesity, along with autoimmune and neurodegenerative diseases, attributed to its antioxidant and anti-inflammatory properties[23,27,33]. The antioxidant properties of bilirubin play a pivotal role in mitigating oxidative stress and inflammation, contributing to its protective effects against various diseases[28].

Indeed, patients with Gilbert's syndrome demonstrate significantly reduced levels of many proatherogenic risk markers in lipid metabolism, including low-density lipoprotein (LDL), triacylglycerol (TAG), and total cholesterol, further underscoring the potential cardioprotective benefits of elevated bilirubin levels[9].

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However, the relationship between GS and cancer risk is complex. While some studies suggest a reduced risk of colorectal cancer, Hodgkin's lymphoma, and endometrial cancer in GS patients[16], associations with breast cancer risk are conflicting and require further investigation to elucidate[23].

Moreover, individuals with Gilbert's syndrome exhibit higher hemoglobin levels and lower markers of immune system activation, such as white blood cells and platelets, factors that could contribute to better tolerance of strenuous exercise and potentially confer additional health benefits[21]. Observational studies indicate that mild hyperbilirubinemia, as observed in Gilbert syndrome, may confer genetic advantages due to bilirubin's antioxidant properties, suggesting potential strategies to mimic this condition or boost bilirubin levels as a preventive measure against oxidative stress-related diseases[27,30]. Overall, the protective effects of Gilbert's syndrome extend beyond cardiovascular health, encompassing various aspects of metabolic, autoimmune, and oncologic diseases, highlighting the multifaceted role of bilirubin in maintaining overall health and well-being.

Drug Interactions in Gilbert's Syndrome

Individuals with Gilbert's syndrome (GS) may experience altered hepatic handling of various drugs metabolized by glucuronidation, posing challenges in pharmacotherapy management. Despite being metabolized by UDP-glucuronosyltransferase 1A1 (UGT1A1), there's no clear correlation between Gilbert's syndrome mutation and susceptibility to ethinylestradiol or endogenous estrogens, which are linked to breast cancer risk.[2]

Similarly, studies on acetaminophen metabolism in GS patients have conflicting results, with recent findings suggesting a possible co-occurrence of UGT1A6 polymorphism and Gilbert's syndrome mutation affecting acetaminophen metabolism.[2,34]Also safe acetaminophen tolerance despite the mutation, suggesting the potential of mutation analysis combined with acetaminophen loading tests for managing adverse effects in GS patients. [35]However, caution is warranted in the administration of certain drugs metabolized by UGT1A1 in GS patients. For instance, GS patients, especially those homozygous for the UGT1A1*28 mutation, are at increased risk of adverse effects of irinotecan, which is metabolized by UGT1A1. [2,7,36,37] Administration of irinotecan to GS patients has resulted in severe toxicity, including severe diarrhea and myelosuppression with severe neutropenia. [23] Similarly, GS patients, particularly those with the UGT1A1*28 allele, may be more susceptible to indinavir-induced hyperbilirubinemia due to competitive inhibition of UGT1A1 activity and increased hemolysis caused by indinavir.

Moreover, GS patients may experience pharmacokinetic abnormalities with various drugs metabolized by glucuronidation, including menthol, estradiol benzoate, lamotrigine, tolbutamide, rifamycin SV, acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), statins, gemfibrozil, and HIV protease inhibitors.[23] While these abnormalities rarely lead to significant toxicity, individuals with compound UGT1A127 and UGT1A128 genotypes may face an increased risk of antitubercular drug toxicity.[23] Various drugs are substrates of UGT isoforms, including paracetamol, morphine, oxazepam, temazepam, amitriptyline, ritodrine, diflunisal, zidovudine, ibuprofen, and probenecid, and may undergo glucuronidation affected in individuals with GS.[22]

Clinicians should also be aware of potential drug-induced liver injury in GS patients. Severe hepatitis following standard doses of mebendazole in a patient with Gilbert's syndrome suggests a potential link between reduced hepatic glucuronidation activity and the development of liver injury[38]. Therefore, careful monitoring and dose adjustments may be necessary when prescribing medications metabolized by UGT enzymes in individuals with Gilbert's syndrome, emphasizing the importance of personalized medicine and pharmacovigilance in this population.

Clinical Implications of Gilbert's Syndrome

Gilbert's Syndrome (GS) poses various clinical implications, ranging from altered drug metabolism to potential complications during pregnancy and neonatal care. A study indicated that GS does not impair the formation and excretion of ethanol glucuronidation products, EtG and EtS, suggesting that EtG could still be a suitable marker in individuals with GS[4]. However, there is

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variability in marker concentrations and detectability, highlighting the need for careful monitoring and interpretation.

Moreover, women with Gilbert's syndrome may experience increased frequency and duration of jaundice episodes, particularly associated with menstruation abnormalities, oral contraceptive pill use, and cesarean delivery[7]. Exacerbated unconjugated hyperbilirubinemia during pregnancy can sometimes necessitate cesarean section and result in neonatal hyperbilirubinemia, requiring close monitoring and management during pregnancy and childbirth.

Additionally, the association between UGT1A1 variants and gallstones warrants careful consideration[23], especially when co-inherited with conditions like hereditary spherocytosis, thalassemia, or sickle cell disease[16]. The presence of Gilbert's syndrome can unmask individuals during chemotherapy treatment with agents such as cytarabine, necessitating adjustments in treatment regimens to prevent adverse effects[10].

GS also contributes to hyperbilirubinemia in patients with heterozygous β-thalassemia, glucose-6-phosphate dehydrogenase (G-6-PD) deficiency, or α-thalassemia trait, as well as during acute hemolysis in G-6-PD deficient subjects[16]. This highlights the importance of recognizing and managing GS in individuals with these comorbidities to prevent complications associated with hyperbilirubinemia.

In neonates, GS in combination with other factors may potentiate severe hyperbilirubinemia, potentially leading to complications like bilirubin encephalopathy[20]. Therefore, close monitoring and appropriate management are essential to prevent adverse outcomes in neonates with GS.

Furthermore, the association between celiac disease and GS suggests that children with GS who have failure to thrive should be screened for celiac disease[39]. This underscores the importance of considering potential comorbidities and addressing them promptly to optimize the health and well-being of individuals with GS.

Effect on MASLD

Recent studies have suggested a potential inverse relationship between unconjugated hyperbilirubinemia and Metabolic dysfunction associated steatotic Liver disease (MASLD), particularly in the context of Gilbert's syndrome[40,41]. Unconjugated hyperbilirubinemia, often seen in individuals with Gilbert's syndrome, has been associated with a lower risk of developing MASLD. This phenomenon has sparked interest in understanding the protective effects of unconjugated hyperbilirubinemia against MASLD development.

Bilirubin, the end product of heme catabolism, is known for its antioxidant, anti-inflammatory, and anti-fibrogenic properties, which are believed to play a role in its potential protective effects against MASLD. These properties enable bilirubin to neutralize reactive oxygen species, reduce inflammation, and inhibit the progression of fibrosis, all of which are key factors in the pathogenesis of MASLD [42–44]. Studies have highlighted the importance of these mechanisms in protecting against liver damage and inflammation, which are central features of MASH.

The concept of inducing an "iatrogenic Gilbert's syndrome" has been proposed as a potential therapeutic strategy for individuals at high risk for MASLD [44,45]. This approach involves using therapies that decrease hepatic glucuronidation activity, leading to higher levels of unconjugated bilirubin in the bloodstream. By mimicking the biochemical profile of Gilbert's syndrome, these therapies could potentially confer a protective effect against MASLD development.

However, it is essential to note that while the association between unconjugated hyperbilirubinemia and MASLD is intriguing, further research is needed to fully understand the underlying mechanisms and confirm the protective effects of bilirubin in NASH. Additionally, the safety and feasibility of inducing an "iatrogenic Gilbert's syndrome" as a therapeutic strategy need to be carefully evaluated in clinical trials.

Impact of Gilbert's Syndrome on Liver Transplantation

In liver transplantation, the presence of Gilbert's Syndrome (GS) in the donor liver can have implications for post-transplant outcomes, particularly in terms of hyperbilirubinemia[16]. While GS

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liver can be used for transplantation, there is a risk of post-transplant hyperbilirubinemia when the donor liver carries the GS genotype[46]. This underscores the importance of considering GS as a potential factor in post-transplant management and monitoring to ensure optimal outcomes for transplant recipients.

Psychology and Gilbert's Syndrome

A study found that schizophrenic patients with Gilbert's syndrome (GS) exhibited significant decreases in N-acetyl aspartate/creatine-phosphocreatinine (NAA/Cr) and myoinositol/creatine-phosphocreatinine (mI/Cr) ratios in the hippocampus, basal ganglia, and vermis of the cerebellum compared to both healthy subjects and schizophrenic patients without GS, indicating potential differences in brain metabolism associated with schizophrenia and GS co-occurrence.These findings suggest that schizophrenia with GS may represent a more severe subtype with regards to brain metabolism[47].

Also studies show that patients with Gilbert's syndrome (GS) exhibit specific changes in signal intensity on magnetic resonance imaging (MRI), finding that schizophrenia patients with GS showed decreased signal intensity on T1-weighted MRI and increased signal intensity on T2-weighted MRI in various brain regions, suggesting alterations in the frontotemporal cortex, limbic system, and basal ganglia associated with schizophrenia and GS[48].

Discussion

Gilbert's syndrome (GS) is a benign genetic disorder characterized by mildly elevated levels of unconjugated bilirubin. While typically asymptomatic, GS has been associated with various metabolic and cardiovascular conditions, sparking interest in its underlying mechanisms and potential therapeutic implications. This article explores anticipated advancements in GS research, including the discovery of additional genetic variations and molecular pathways, leading to a deeper understanding of GS pathogenesis and the identification of new therapeutic targets. Improved diagnostic and management guidelines, focusing on drug interactions and monitoring, are expected to enhance patient care. Furthermore, investigations into therapeutic strategies that replicate the protective effects of GS, such as inducing unconjugated hyperbilirubinemia, may offer novel treatment options for conditions like non-alcoholic steatohepatitis (NASH) and cardiovascular disease. Additionally, research on the impact of GS in liver transplantation could refine donor selection criteria and post-transplant management, improving outcomes. Lastly, studies on the psychological and neurological effects of GS, particularly its association with schizophrenia, may provide insights into the link between bilirubin

Conclusions

Gilbert's syndrome is a congenital disease of relatively benign deposition in fact it may even be protective as evidenced by reduction in all-cause mortality compared to non GS individuals. However, GS can contribute to significant morbidly in the form of various drug interactions and other clinical interactions. Therefore, it is important to identify GS early and advice the patients on the potential interactions and complications that can potentially arise.

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Abbreviations

GB – Gilbert's Syndrome
MASLD - Metabolic dysfunction associated steatotic Liver disease
MASH – Metabolic dysfunction associated steatohepatitis
NAA/Cr - N-acetyl aspartate/creatine-phosphocreatinine
MRI - magnetic resonance imaging
G-6-PD - glucose-6-phosphate dehydrogenase deficiency
UGT1A1 - UDP-glucuronosyltransferase 1A1
CVD- cardiovascular disease
LDL - low-density lipoprotein
TAG – triacylglycerol
UGT - UDP-glucuronosyltransferase

References

1. Berthelot, P.; Dhumeaux, D. New Insights into the Classification and Mechanisms of Hereditary, Chronic, Non-Haemolytic Hyperbilirubinaemias. *Gut* **1978**, *19* (6), 474–480. https://doi.org/10.1136/gut.19.6.474.
2. Memon, N.; Weinberger, B. I.; Hegyi, T.; Aleksunes, L. M. Inherited Disorders of Bilirubin Clearance. *Pediatr Res* **2016**, *79* (3), 378–386. https://doi.org/10.1038/pr.2015.247.
3. Beutler, E.; Gelbart, T.; Demina, A. Racial Variability in the UDP-Glucuronosyltransferase 1 (*UGT1A1*) Promoter: A Balanced Polymorphism for Regulation of Bilirubin Metabolism? *Proceedings of the National Academy of Sciences* **1998**, *95* (14), 8170–8174. https://doi.org/10.1073/pnas.95.14.8170.
4. Huppertz, L. M.; Gunsilius, L.; Lardi, C.; Weinmann, W.; Thierauf-Emberger, A. Influence of Gilbert's Syndrome on the Formation of Ethyl Glucuronide. *Int J Legal Med* **2015**, *129* (5), 1005–1010. https://doi.org/10.1007/s00414-015-1157-7.
5. VanWagner, L. B.; Green, R. M. Evaluating Elevated Bilirubin Levels in Asymptomatic Adults. *JAMA* **2015**, *313* (5), 516. https://doi.org/10.1001/jama.2014.12835.
6. Bosma, P. J.; Chowdhury, J. R.; Bakker, C.; Gantla, S.; de Boer, A.; Oostra, B. A.; Lindhout, D.; Tytgat, G. N. J.; Jansen, P. L. M.; Elferink, R. P. J. O.; Chowdhury, N. R. The Genetic Basis of the Reduced Expression of Bilirubin UDP-Glucuronosyltransferase 1 in Gilbert's Syndrome. *New England Journal of Medicine* **1995**, *333* (18), 1171–1175. https://doi.org/10.1056/NEJM199511023331802.
7. Kamal, S.; Abdelhakam, S.; Ghoraba, D.; Massoud, Y.; Aziz, K. A.; Hassan, H.; Hafez, T.; Abdel Sallam, A. The Frequency, Clinical Course, and Health Related Quality of Life in Adults with Gilbert's Syndrome: A Longitudinal Study. *BMC Gastroenterol* **2019**, *19* (1), 22. https://doi.org/10.1186/s12876-019-0931-2.
8. Bailey, A.; Robinson, D.; Dawson, A. M. DOES GILBERT'S DISEASE EXIST? *The Lancet* **1977**, *309* (8018), 931–933. https://doi.org/10.1016/S0140-6736(77)92226-7.
9. Creeden, J. F.; Gordon, D. M.; Stec, D. E.; Hinds, T. D. Bilirubin as a Metabolic Hormone: The Physiological Relevance of Low Levels. *American Journal of Physiology-Endocrinology and Metabolism* **2021**, *320* (2), E191–E207. https://doi.org/10.1152/ajpendo.00405.2020.
10. Gong, Q.-H.; Cho, J. W.; Huang, T.; Potter, C.; Gholami, N.; Basu, N. K.; Kubota, S.; Carvalho, S.; Pennington, M. W.; Owens, I. S.; Popescu, N. C. Thirteen UDPglucuronosyltransferase Genes Are Encoded at the Human UGT1 Gene Complex Locus. *Pharmacogenetics* **2001**, *11* (4), 357–368. https://doi.org/10.1097/00008571-200106000-00011.
11. Watson, K. J. R.; Gollan, J. L. Gilbert's Syndrome. *Baillieres Clin Gastroenterol* **1989**, *3* (2), 337–355. https://doi.org/10.1016/0950-3528(89)90004-3.
12. Goncharik, I. I.; Kravchenko, I. S. [Gilbert's Syndrome: Pathogenesis and Diagnosis]. *Klin Med (Mosk)* **2001**, *79* (4), 40–44.
13. Bartlett, M. G.; Gourley, G. R. Assessment of UGT Polymorphisms and Neonatal Jaundice. *Semin Perinatol* **2011**, *35* (3), 127–133. https://doi.org/10.1053/j.semperi.2011.02.006.
14. Strassburg, C. P. Hyperbilirubinemia Syndromes (Gilbert-Meulengracht, Crigler-Najjar, Dubin-Johnson, and Rotor Syndrome). *Best Pract Res Clin Gastroenterol* **2010**, *24* (5), 555–571. https://doi.org/10.1016/j.bpg.2010.07.007.
15. Wagner, K.-H.; Shiels, R. G.; Lang, C. A.; Seyed Khoei, N.; Bulmer, A. C. Diagnostic Criteria and Contributors to Gilbert's Syndrome. *Crit Rev Clin Lab Sci* **2018**, *55* (2), 129–139. https://doi.org/10.1080/10408363.2018.1428526.
16. Fretzayas, A.; Moustaki, M.; Liapi, O.; Karpathios, T. Eponym. *Eur J Pediatr* **2012**, *171* (1), 11–15. https://doi.org/10.1007/s00431-011-1641-0.

17. Gil, J.; Sąsiadek, M. M. Gilbert Syndrome: The *UGT1A1* *28 Promoter Polymorphism as a Biomarker of Multifactorial Diseases and Drug Metabolism. *Biomark Med* **2012**, *6* (2), 223–230. https://doi.org/10.2217/bmm.12.4.
18. Whitmer, D.; Gollan, J. Mechanisms and Significance of Fasting and Dietary Hyperbilirubinemia. *Semin Liver Dis* **1983**, *3* (01), 42–51. https://doi.org/10.1055/s-2008-1040670.
19. Pashankar, D.; Schreiber, R. A. Jaundice in Older Children and Adolescents. *Pediatr Rev* **2001**, *22* (7), 219–226. https://doi.org/10.1542/pir.22-7-219.
20. Hirschfield, G. M.; Alexander, G. J. Gilbert's Syndrome: An Overview for Clinical Biochemists. *Annals of Clinical Biochemistry: International Journal of Laboratory Medicine* **2006**, *43* (5), 340–343. https://doi.org/10.1258/000456306778520034.
21. Vítek, L.; Tiribelli, C. Gilbert's Syndrome Revisited. *J Hepatol* **2023**, *79* (4), 1049–1055. https://doi.org/10.1016/j.jhep.2023.06.004.
22. Schwertner, H. A.; Vítek, L. Gilbert Syndrome, UGT1A1*28 Allele, and Cardiovascular Disease Risk: Possible Protective Effects and Therapeutic Applications of Bilirubin. *Atherosclerosis* **2008**, *198* (1), 1–11. https://doi.org/10.1016/j.atherosclerosis.2008.01.001.
23. Erlinger, S.; Arias, I. M.; Dhumeaux, D. Inherited Disorders of Bilirubin Transport and Conjugation: New Insights Into Molecular Mechanisms and Consequences. *Gastroenterology* **2014**, *146* (7), 1625–1638. https://doi.org/10.1053/j.gastro.2014.03.047.
24. Gollan, J. L.; Knapp, A. B. Bilirubin Metabolism and Congenital Jaundice. *Hosp Pract* **1985**, *20* (2), 83–106. https://doi.org/10.1080/21548331.1985.11702995.
25. Horsfall, L. J.; Nazareth, I.; Pereira, S. P.; Petersen, I. <scp>G</Scp> Ilbert's Syndrome and the Risk of Death: A Population-based Cohort Study. *J Gastroenterol Hepatol* **2013**, *28* (10), 1643–1647. https://doi.org/10.1111/jgh.12279.
26. Goel, A.; Aggarwal, R. Unconjugated Hyperbilirubinemia: A Blessing in Disguise? *J Gastroenterol Hepatol* **2013**, *28* (11), 1687–1689. https://doi.org/10.1111/jgh.12375.
27. Mölzer, C.; Wallner, M.; Kern, C.; Tosevska, A.; Schwarz, U.; Zadnikar, R.; Doberer, D.; Marculescu, R.; Wagner, K.-H. Features of an Altered AMPK Metabolic Pathway in Gilbert's Syndrome, and Its Role in Metabolic Health. *Sci Rep* **2016**, *6* (1), 30051. https://doi.org/10.1038/srep30051.
28. Kundur, A. R.; Santhakumar, A. B.; Bulmer, A. C.; Singh, I. Mildly Elevated Unconjugated Bilirubin Is Associated with Reduced Platelet Activation-Related Thrombogenesis and Inflammation in Gilbert's Syndrome. *Platelets* **2017**, *28* (8), 779–785. https://doi.org/10.1080/09537104.2017.1280146.
29. Ishizaka, N.; Ishizaka, Y.; Takahashi, E.; Yamakado, M.; Hashimoto, H. High Serum Bilirubin Level Is Inversely Associated With the Presence of Carotid Plaque. *Stroke* **2001**, *32* (2), 580–583. https://doi.org/10.1161/01.STR.32.2.580-b.
30. Vitek, L.; Bellarosa, C.; Tiribelli, C. Induction of Mild Hyperbilirubinemia: Hype or Real Therapeutic Opportunity? *Clin Pharmacol Ther* **2019**, *106* (3), 568–575. https://doi.org/10.1002/cpt.1341.
31. Bakrania, B.; Du Toit, E. F.; Wagner, K.-H.; Headrick, J. P.; Bulmer, A. C. Pre- or Post-Ischemic Bilirubin Ditaurate Treatment Reduces Oxidative Tissue Damage and Improves Cardiac Function. *Int J Cardiol* **2016**, *202*, 27–33. https://doi.org/10.1016/j.ijcard.2015.08.192.
32. Cure, E.; Yuce, S.; Cicek, Y.; Cumhur Cure, M. The Effect of Gilbert's Syndrome on the Dispersions of QT and P-Wave Dispersion: An Observational Study. *Anadolu Kardiyoloji Dergisi/The Anatolian Journal of Cardiology* **2013**. https://doi.org/10.5152/akd.2013.180.
33. Schonfeld, E. A.; Brown, R. S. Genetic Testing in Liver Disease. *Clin Liver Dis* **2017**, *21* (4), 673–686. https://doi.org/10.1016/j.cld.2017.06.001.
34. ULLRICH, D.; SIEG, A.; BLUME, R.; BOCK, K. W.; SCHRÖTER, W.; BIRCHER, J. Normal Pathways for Glucuronidation, Sulphation and Oxidation of Paracetamol in Gilbert's Syndrome. *Eur J Clin Invest* **1987**, *17* (3), 237–240. https://doi.org/10.1111/j.1365-2362.1987.tb01242.x.
35. Nakagawa, T.; Mure, T.; Yusoff, S.; Ono, E.; Harahap, I. S. K.; Morikawa, S.; Morioka, I.; Takeshima, Y.; Nishio, H.; Matsuo, M. Acetaminophen Administration in a Patient with Gilbert's Syndrome. *Pediatrics International* **2012**, *54* (6), 934–936. https://doi.org/10.1111/j.1442-200X.2012.03602.x.
36. Kawato, Y.; Aonuma, M.; Hirota, Y.; Kuga, H.; Sato, K. Intracellular Roles of SN-38, a Metabolite of the Camptothecin Derivative CPT-11, in the Antitumor Effect of CPT-11. *Cancer Res* **1991**, *51* (16), 4187–4191.
37. Kawato, Y.; Furuta, T.; Aonuma, M.; Yasuoka, M.; Yokokura, T.; Matsumoto, K. Antitumor Activity of a Camptothecin Derivative, CPT-11, against Human Tumor Xenografts in Nude Mice. *Cancer Chemother Pharmacol* **1991**, *28* (3), 192–198. https://doi.org/10.1007/BF00685508.
38. Tolomeo, M.; Colomba, C.; Meli, M.; Cascio, A. Hepatotoxicity Caused by Mebendazole in a Patient with Gilbert's Syndrome. *J Clin Pharm Ther* **2019**, *44* (6), 985–987. https://doi.org/10.1111/jcpt.13033.
39. Kumar, A.; Aggarwal, V. Celiac Disease in Association with Gilbert's Syndrome. *The Indian Journal of Pediatrics* **2018**, *85* (9), 814–815. https://doi.org/10.1007/s12098-018-2674-4.

40. Hjelkrem, M.; Morales, A.; Williams, C. D.; Harrison, S. A. Unconjugated Hyperbilirubinemia Is Inversely Associated with <scp>non-alcoholic Steatohepatitis (NASH)</Scp>. *Aliment Pharmacol Ther* **2012**, *35* (12), 1416–1423. https://doi.org/10.1111/j.1365-2036.2012.05114.x.
41. Han, H.; Yu, Q.; Qin, N.; Song, B.; Meng, Y.; Feng, Z.; Li, Z.; Chen, L. Non-Linear Associations of Circulating Total Bilirubin Concentration with the Risk of Nonalcoholic Fatty Liver Disease and All-Cause Mortality. *Ann Hepatol* **2024**, *29* (2), 101177. https://doi.org/10.1016/j.aohep.2023.101177.
42. Barañano, D. E.; Rao, M.; Ferris, C. D.; Snyder, S. H. Biliverdin Reductase: A Major Physiologic Cytoprotectant. *Proceedings of the National Academy of Sciences* **2002**, *99* (25), 16093–16098. https://doi.org/10.1073/pnas.252626999.
43. Keshavan, P.; Deem, T. L.; Schwemberger, S. J.; Babcock, G. F.; Cook-Mills, J. M.; Zucker, S. D. Unconjugated Bilirubin Inhibits VCAM-1-Mediated Transendothelial Leukocyte Migration. *The Journal of Immunology* **2005**, *174* (6), 3709–3718. https://doi.org/10.4049/jimmunol.174.6.3709.
44. Li, L.; Grenard, P.; Van Nhieu, J. T.; Julien, B.; Mallat, A.; Habib, A.; Lotersztajn, S. Heme Oxygenase-1 Is an Antifibrogenic Protein in Human Hepatic Myofibroblasts. *Gastroenterology* **2003**, *125* (2), 460–469. https://doi.org/10.1016/S0016-5085(03)00906-5.
45. McCarty, M. F. '"Iatrogenic Gilbert Syndrome"'– A Strategy for Reducing Vascular and Cancer Risk by Increasing Plasma Unconjugated Bilirubin. *Med Hypotheses* **2007**, *69* (5), 974–994. https://doi.org/10.1016/j.mehy.2006.12.069.
46. Leong, J.; Serrano, M.-S. A Case of Acquired Gilbert's Syndrome. *Clin Pediatr (Phila)* **2017**, *56* (12), 1164–1166. https://doi.org/10.1177/0009922816668632.
47. Miyaoka, T.; Yasukawa, R.; Mizuno, S.; Sukegawa, T.; Inagaki, T.; Horiguchi, J.; Seno, H.; Oda, K.; Kitagaki, H. Proton Magnetic Resonance Spectroscopy (1H-MRS) of Hippocampus, Basal Ganglia, and Vermis of Cerebellum in Schizophrenia Associated with Idiopathic Unconjugated Hyperbilirubinemia (Gilbert's Syndrome). *J Psychiatr Res* **2005**, *39* (1), 29–34. https://doi.org/10.1016/j.jpsychires.2004.05.003.
48. Wake, R.; Miyaoka, T.; Tsuchie, K.; Kawakami, K.; Nishida, A.; Inagaki, T.; Horiguchi, J. Abnormalities in MRI Signal Intensity in Schizophrenia Associated with Idiopathic Unconjugated Hyperbilirubinemia. *Australian and New Zealand Journal of Psychiatry* **2009**, *43* (11), 1057–1069. https://doi.org/10.3109/00048670903107526.