Turner syndrome (TS) is one of the most frequently reported chromosomal abnormalities. Its prevalence is approximately 40 in every 100,000 live female births [1, 2]. The syndrome is characterized by the total or partial loss of one of the X-chromosomes, with 1 intact sex chromosome in phenotypic females, being the only monosomy compatible with life [3-6]. The karyotype is either X-monosomy (45, X) or mosaic-type, 45X, 46XX. Other mosaicism might be with 45, X/46, XY karyotype; thus, the presence of an Y-chromosome can be seen in 5% to 10% of cases, and carries a risk for subsequent gonadoblastomas [7]. Partial deletions of X-chromosome can also cause TS [8, 9]. Apart from genetics, patients with TS display characteristic phenotypical findings. These clinical features (stigmata) are required for the diagnosis of TS along with the cytogenetic changes [10]. The most common phenotypical findings are short stature and delayed puberty, and primary ovarian insufficiency, affecting nearly 90% of all patients with TS [3, 10]. Other physical findings are variable but can be present. These are neck webbing, edematous hands and feet, broad shield-like chest, characteristic craniofacial alterations (small mandible, rotated ears, high arched palate, low posterior hairline), and even nail abnormalities (hypoplasia, hyperconvexity).

Multisystemic involvement is typical in TS [11]. The manifestations of TS are not exclusively consequential to estrogen deficiency; other factors contribute to the phenotype as well. TS can be associated with congenital cardiovascular (left-sided cardiac anomalies, such as aortic coarctation, bicuspid aortic valve [12, 13]), and renal malformations (for example, horseshoe kidney [14]), representing a major cause of morbidity and mortality, and the associated excess risk is increasing with the advancement of age ([15]). GH replacement therapy is also warranted because it is shown to facilitate normal growth and metabolic health in affected girls. Patients are at increased risk for autoimmune and endocrine (mostly related to the thyroid gland: Hashimoto thyroiditis and hypothyroidism) disorders [2]. The phenotypical findings and characteristic features can be present even in patients with mosaicism.
Autoimmune conditions might also be involved in the contribution to hepatobiliary pathology. Though the role of sex chromosomes is implicated in the development of the cerebral cortex, the intellectual capabilities of patients are usually normal [16, 17]. Nonetheless, proper estrogen concentrations are beneficial for cognition and memory, thus further highlighting the importance of proper replacement. The syndrome is often associated with decreased self-esteem and psychological disturbances, both benefiting from estrogen replacement therapy (ERT) [18]. By writing our paper, we sought to emphasize the importance of estrogen hormone substitution in patients with TS, as implicated in current guidelines [5, 6].

Etiology of Hepatic Alterations in TS

Several endocrine derangements were shown to predispose patients to steatosis of the liver [19-21]. Thus, nonalcoholic fatty liver disease (NAFLD) is frequently associated with hypogonadism as well [22, 23]. NAFLD is frequently associated with metabolic syndrome and is otherwise defined by the presence of excess intrahepatic fat deposits, not attributable to the consumption of alcoholic beverages [24, 25].

The relationship between liver and endocrine abnormalities seems to be bidirectional [19]. Patients with TS often display multiple endocrine derangements and hepatic steatosis; likely, their hypogonadism is both an exacerbating factor behind the liver abnormalities as well as being slightly aggravated by hepatic dysfunction. Another possible underlying cause of endocrine origin is the presence of hypothyroidism, which often accompanies TS. Patients with TS also display a somewhat increased likelihood of both celiac disease (gluten-sensitive enteropathy) and inflammatory bowel diseases (Crohn disease and ulcerative colitis). These conditions might also enhance the risks for hepatic alterations, with distinct patterns. A recent study conducted by Voss et al. on the UK Biobank samples investigated the characteristics of immune-mediated gastrointestinal diseases on hepatobiliary laboratory findings [26]. Whereas mild hypertransaminasemia (elevated alanine aminotransferase [ALT] and aspartate aminotransferase) is mostly seen in celiac disease, the elevation of gamma-glutamyltransferase is mostly seen in inflammatory bowel diseases (both Crohn and ulcerative colitis) cases. All of these intestinal inflammatory diseases show an association with elevated levels of alkaline phosphatase. As implicated, patients might also require GH administration. Short stature is a common phenotypical finding in TS, seen in up to 95% of patients. Girls affected by TS usually require GH replacement therapy, which is shown to be effective in alleviating their hindered growth [6, 18, 27]. Furthermore, GH is essential for optimal metabolic health and nutrient homeostasis and thus can be beneficial for the often encountered fatty liver disease and obesity. Adequate levels of GH aid the repartitioning of fat mass to lean mass and thus can improve glucose homeostasis and metabolic syndrome.

Hepatobiliary Histological Changes in TS

Hepatic manifestations are frequent in TS [28]. These are usually mild, with a moderate propensity to progress with age. The reported prevalence of these alterations ranges from 20% to 80%. A large cohort study of adults with TS found that 36% of patients at 33 years had liver test abnormalities, with an annual incidence increase of 3.4% in 5 years [29]. Liver enzyme changes or even liver steatosis (fatty liver) can present in children, even before the recognition of TS [29]. This phenomenon indeed questions the possible role of estrogen deficiency as a key underlying factor behind hepatobiliary alterations. Before puberty, the levels of circulating female sex steroid hormones are only a fraction of what is seen in later life [30-32]. Thereby, it is plausible that the etiology of liver derangements is multifactorial and cannot be contributed to estrogen deficiency alone. Probably the changes are consequent to an interplay of environmental, lifestyle, and epigenetic and genetic risk factors, predisposing to metabolic and hepatic dysfunction [33, 34].

The hepatic damage seen in TS might range from mild elevation of liver-related laboratory parameters, with minimal to no change in liver histology, to cirrhosis and nodular regenerative hyperplasia [33, 35]. Because these require historical sampling to diagnose, hitherto no large cohort studies were evaluating the prevalence of more severe liver architectural changes in TS. A schematic overview of possible hepatic pathology is depicted in Fig. 1.

Marked architectural changes, such as cirrhosis, nodular regenerative hyperplasia (NRH), and multiple focal nodular hyperplasias (FNH), were also observed in TS. These might originate from primary vascular involvement (in a later section of our paper, we briefly discuss the associated vascular abnormalities in TS) [35]. The typical picture of NRH is multiple small parenchymal nodules, and conserved portal tracts, without annular fibrosis [36]. NRH is thought to be an adaptation to microcirculatory disturbances, resulting in altered intrahepatic perfusion. NRH is thus a combination of hepatocyte atrophy in areas of decreased perfusion, with compensatory hepatocyte hyperplasia in areas with preserved blood flow [33, 35, 36].

FNH is similarly regarded as hyperplasia of hepatocytes in foci, resulting from the uneven portal perfusion of the liver parenchyma. Areas with the finding of the histological picture of FNH are generally well perfused, unlike the rest of the organ. FNH is characterized by the presence of large nodules, with, or without intranodular fibrosis, alternating with fibrotic areas, with abnormal vasculature and bile ductules [35, 37, 38]. The nodules in FNH might become larger and progress with time, as described by Roulot et al [35]. Abnormalities of the intrahepatic portal veins included thrombosis, intimal thickening, and even complete obstruction and replacement by fibrous tissue, containing several vessels. These are frequently encountered in the presence of liver parenchymal alterations and are regarded as features of obliterative portal venopathy [35, 39]. Cirrhosis without a known cause for chronic liver disease might represent the final stage of the vascular abnormalities seen in TS. In severe cases, patients might require transplantation [40].

Although estrogen deficiency alone cannot explain the previously mentioned hepatic changes, it is likely to be a contributing factor. Estrogen-deficient states often correlate with liver pathology, for example, after oophorectomy or in postmenopausal women [41-43]. As implicated previously, low levels of estrogen hormones can be associated with excess liver adiposity (not only in TS [44], oophorectomized [43], and postmenopausal women [41], but also in men with defective aromatase activity [45]). Thereby in these states,
Estrogen substitution can potentially ameliorate fatty liver disease. However, the exact cause of hepatic findings is not yet elucidated. Estrogen deficiency in itself is not sufficient to cause liver steatosis because the development of NAFLD is highly likely to be multifactorial and dependent on environmental and lifestyle factors as well.

Biliary involvement of various types has been reported in TS. These include sclerosing cholangitis, primary biliary cholangitis (PBC), biliary atresia, and paucity of the bile ducts. Concentric fibrosis of small intrahepatic bile ducts, without inflammation, was reported frequently. These lesions resemble primary sclerosing cholangitis (PSC). It is noteworthy that TS patients have a greater propensity for developing inflammatory bowel diseases, which are associated with an increased prevalence of PSC [46, 47]. Although PSC mostly involves extrahepatic bile ducts, in TS, only the intrahepatic bile ducts develop lesions. Furthermore, those cases of TS, where there is evidence of biliary pathology, are generally not associated with cooccurring inflammatory bowel disease. Thus it is plausible that the pathogenesis of biliary ductal fibrosis differs from that which is seen in the case of PSC.

Bile duct fibrosis is frequently seen in those patients, who have arteriolar damage in the proximity of the biliary ducts. Therefore, it might represent a consequent manifestation of vascular compromise. It also raises the question of whether the presence of biliary duct alterations without overt liver architectural changes might represent a milder degree of vascular involvement.

The atresia of intrahepatic biliary ducts was described in pediatric TS patients. A possible explanation is abnormal angiogenesis might underlie the deranged development of bile ducts. Cholangitis and ductopenia are frequently encountered in patients with PBC, as well as in TS. Though the prevalence of PBC in TS is not known, the picture of biliary involvement share commonalities. TS patients have a greater risk of developing autoimmune disorders; thus, there were reports of PBC in TS as well. It should also be emphasized that PBC patients also display an increased risk for developing other immune-mediated inflammatory disorders. TS is characterized by the partial or total loss of an X chromosome, and a study reported X-monosomy in women with PBC to be more common [48].

Likely, the X chromosome contains genes involved in immune tolerance. The loss of an X chromosome thus could predispose TS patients to the breakdown of self-tolerance and the subsequent development of immune-mediated diseases. So far, only 1 homeobox-containing gene has been identified, with a clear implication for TS phenotype. SHOX or short-stature homeobox gene is found in the pseudoautosomal region (PAR1) of X chromosomes. As implicated, it is involved in the short stature phenotype of TS patients. Its role in the development of immune-mediated diseases or liver dysfunction is not yet described.

So far, detailed information on the long-term follow-up of TS patients with hepatic involvement is lacking. A smaller cohort study, published by Roulot and colleagues, with an

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Figure 1. Contributing factors behind Turner hepatobiliary abnormalities. CIMT, carotid intima-media thickness, CV, cardiovascular; FNH, focal nodular hyperplasia; NAFLD, nonalcoholic fatty liver disease; NRH, nodular regenerative hyperplasia.
average follow-up time of 9 years found mostly favorable outcomes [35]. Mild liver involvement did not deteriorate into an overt disease in most cases. More serious complications were observed in 3 patients, all of them displaying hepatic architectural changes. One patient died from uncontrolled refractory ascites, pleural effusion, and heart failure. Another patient required liver transplantation 6 years after the diagnosis of hepatic involvement. The patient suffered from bleeding from esophageal varices and intractable cholestasis. The third patient experienced recurrent variceal bleeding, necessitating surgical portocaval shunting [35]. Therefore, serious complications seldom occur in TS and are only observed in those with hepatic architectural alterations.

Diagnostic Workup of Patients With Liver Abnormalities

The detailed diagnostic algorithms and discussion of chromosomal alterations in TS are outside the scope of this work. Nonetheless, we summarize the main aspects in our paper. An excellent overview of diagnostic considerations was published in 2018 by Shankar and Backeljauw [49]. Even though TS is widely recognized, there is often a marked delay in the diagnosis of the condition [3]. For a rapid overview of the general characteristics of TS, please refer to Table 1.

In patients with known TS and abnormal hepatic enzyme values, other possible underlying causes of liver enzyme derangements (alcohol abuse, medications, infections by hepatitis or herpesviruses, metabolic diseases, alpha-1 antitrypsin deficiency, Wilson disease, autoimmune liver diseases [PBC and PSC, respectively], and autoimmune hepatitis) should be tested for and excluded. Most of the time, the clinical picture is characterized by cholestatic enzyme elevations, with normal or mildly elevated transaminases (serum glutamic oxaloacetic transaminase and serum glutamic pyruvic transaminase, or ALT and aspartate aminotransferase in US terminology) [29, 33, 39, 50]. The history of the patients and the previous laboratory studies might provide valuable insight for the clinicians.

Even though fatty liver disease is frequently associated with TS, this entity is also prevalent in the general population. We should emphasize that, particularly, NAFLD is on the rise recently because the consumption of spirits was decreasing before the recent COVID-19 pandemic [51, 52]. However, at least temporarily, the number of drinkers rose during the lockdowns and restrictions in 2020 and 2021 [53, 54]. Infections with hepatotropic viruses are also becoming scarce because of immunization and sanitation practices; thereby, some other lifestyle factor is likely to be the underlying cause.

Possible diagnostic difficulty in determining hepatobiliary alterations might be the presence of various risk factors. Apart from alcoholic beverages, excessive fructose and sugar consumption can aggravate hepatic enzyme abnormalities and liver steatosis [55-57]. Thereby, careful assessment of other risk factors is required. Even though clinicians ought to inquire about additional contributing factors, the self-reported habits of patients (regarding alcohol, nutrition, and medications) are not always reliable. Excess adiposity and liver steatosis can also be underlying causes of deranged laboratory findings. Furthermore, liver steatosis and mild hypertransaminasemia are very common in the population, thereby not specific to TS [58, 59].

ERT: Modes of Administration

Unless contraindicated, women with TS should be given estrogen therapy, not only for optimizing sexual development and health and enhancing skeletal mass but also for improving quality of life and metabolic parameters [5, 60]. Practicing physicians are encouraged to prefer transdermal estrogen patches as opposed to the oral route of administration or contraceptive pills. One should not disregard the elevated risk of venous thromboembolism with contraceptive pills, particularly ethinyl-estradiol. The exact length of estrogen replacement can be debated. It would be plausible to replicate the natural course of estrogen throughout the lifespan, thereby ceasing treatment at roughly 50 years of age (corresponding to the average age of menopause).

Table 1. Overview of general characteristics of Turner syndrome

| Epidemiology            | 40 in every 100 000 live female births |
|-------------------------|----------------------------------------|
|                         | Only monosomy compatible with life     |
|                         | Risk does not increase with the advanced age of the mother |
|                         | Diagnosis can be delayed in mild cases |
| Karyotype               | 45 XO is most common, mosaicism possible—usually with less severe symptoms |
|                         | Partial deletions of X chromosome are possible |
|                         | Total monosomy is associated with increased risk of spontaneous abortions |
| Typical phenotype       | Stature: height and growth is reduced, increased upper-to-lower segment, broad chest, wide-spaced nipples. |
|                         | Facial features: dental deformations, malocclusion, micrognathia |
|                         | Lymphatic abnormalities: lymphedema of hands and feet, webbed neck, short posterior hairline, possible cystic hygroma in newborn, lung hypoplasia |
|                         | Cardiovascular: About one-half of the patients might have cardiovascular abnormalities: coarctation of the aorta, bicuspid aortic valve, increased risk of hypertension of renovascular origin |
|                         | Metabolic: Increased body fat, visceral fat, propensity for developing metabolic syndrome |
| Reproductive            | Rudimentary streak ovaries, deficient follicles. Infertility, primary amenorrhea, impaired development of secondary sexual characteristics |
| Therapy                 | Estrogen replacement therapy (preferred application is transdermal, mimicking the natural course of estrogen-hormone fluctuations), GH therapy for stature |
|                         | Treat comorbidities (eg, hypothyroidism) when indicated |
| Outcome                 | Usually favorable, normal life expectancy if there are no complications. Increased risk of X-linked diseases |
The Relationship of Cardiovascular and Hepatic Alterations in TS

Cardiovascular morbidity is the most threatening health problem for adults with TS, contributing to the increased mortality rates. Increased risks for cardiovascular malformations, renal abnormalities, and hypertension predispose patients to increased risk for aortic dilatation and dissection [28, 61]. Extrahepatic vascular alterations are represented by coarctation of the aorta, bicuspid aortic valve, cerebral aneurysms, and gastrointestinal telangiectasias. These are not uncommon in TS. The abnormalities of thoracic vessels are seen in up to half of the patients with TS [28]. The abnormalities of the aorta are more frequently encountered in patients with overt architectural changes in the liver parenchyma. Estrogen replacement (with higher than usual doses) can also reduce the markers of cardiovascular risk in TS [62, 63].

Some authors described more complex cardiovascular phenotypes. These were even observable in otherwise asymptomatic patients. Via the combination of echocardiography and magnetic resonance imaging, it was found, that nearly 75% of adult TS patients have dilated ascending aorta, and this could be associated with the increased diameter of other major arteries (brachial and carotid arteries) [62, 64, 65].

Carotid intima-media thickness and arterial diameters are increased in TS, compared with healthy control subjects [28, 62, 63-67]. One proposed explanation was estrogen deficiency. Supporting this concept is that estrogen replacement seems to attenuate these alterations, thus reducing carotid intima-media thickness in young women with TS. Additionally, proper ERT had beneficial effects on several metabolic parameters, further optimizing cardiovascular risk (high-density lipoprotein cholesterol, triglycerides, glucose levels, hemoglobin A1c) [63, 68].

TS subjects display increased cardiovascular mortality, mostly from aortic dissection. This is regarded as the leading cause of early mortality in TS patients with cardiovascular alterations. The risk of aortic dissection was recently reported as being 12 times higher in TS than in healthy individuals [64]. In addition to structural abnormalities, there is also an increased prevalence of ischemic heart disease [66].

Previously, highly sensitive 3-dimensional cardiovascular magnetic resonance imaging techniques were used to evaluate aortopathy in adult TS patients. Findings indicated accelerated ascending aortopathy, with marked growth of aortic diameter during the 2.4 years of follow-up [65]. It is yet not known whether changes in other vascular areas might also be seen with age. As mentioned previously, with increasing age, patients have more tendency to develop liver architectural and circulatory changes. Thereby, possibly these findings share a common etiological origin.

Abnormalities and malformations of the venous system, like agenesis or hypoplasia of the portal venous system, may also be seen in TS women [65]. The eponymous Druveilhier-Baumgarten disease corresponds to presinusoidal portal hypertension because of congenital hypoplasia of the intrahepatic portal system [69]. Examination revealed no cirrhosis, but severe parenchymal atrophy, causing liver dysfunction.

Thromboembolic events are more common in TS patients [69]. There is also evidence for increased levels of von Willebrand factor, factor VIII, fibrinogen, and C-reactive protein. The factor V Leiden mutation is frequent as well [69]. These disorders could favor the development of oblitative portal venopathy, observed in the liver of some TS patients [70, 71]. The risk for deep venous thrombosis and portal vein thrombosis is also enhanced in TS [72].

Controversial Effects of ERT

The administration of exogenous estrogen substitution is known to cause (cholestatic) liver enzyme abnormalities [39, 73]. On the other hand, estrogen deficiency is also detrimental to liver health. Thus, in TS, hormone replacement therapy can improve the laboratory derangements [50]. There is no evidence for the role of either excess weight or ERT causing liver test alterations in TS [33, 35]. Estrogen-induced liver toxicity has been also regarded as a cause of deranged liver tests. This theory was never proven and eventually was discarded. Proper hormone replacement therapy in fact can facilitate the normalization of abnormal transaminase and gamma-glutamyltransferase laboratory studies in these patients [18, 74]. By comparing 3 different routes of estrogen administration, it was found that combined oral contraceptives predisposed patients to higher blood pressure and lipid profile abnormalities. Transdermal patches were indeed associated with elevated liver enzymes and hemoglobin A1c compared with estrogen-only pills [6]. Nonetheless, it is accepted, that the cessation of ERT is not warranted purely based on deranged liver function.

Moreover, as TS patients are more inclined to develop thromboembolic events, and, administration of female sex hormones can aggravate the formation of clots, clinicians should not exceed physiologic levels of estrogen. Regular follow-up laboratory studies are recommended.

Conclusions

Summarizing the evidence, one can conclude that the exact etiology of the liver abnormalities is not yet elucidated and can almost rule out exogenous estrogen replacement agents as an underlying cause. More studies reported improvement in cholestatic laboratory values and mild improvement in transaminases in TS, after the initiation of ERT [5, 6]. It should be emphasized that hormone replacement is warranted in TS patients, and regular follow-ups of laboratory studies on the liver and cardiovascular risk parameters are recommended [27].

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Data Availability
Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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