Bilirubin Conjugation, Reflected by Conjugated Bilirubin Fractions, in Glucose-6-Phosphate Dehydrogenase-deficient Neonates: A Determining Factor in the Pathogenesis of Hyperbilirubinemia

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ABSTRACT. Background and Objective. Glucose-6-phosphate dehydrogenase (G-6-PD) deficiency is frequently associated with neonatal hyperbilirubinemia, which in severe cases may cause kernicterus and death. Because G-6-PD-deficient individuals frequently undergo acute, trigger-induced hemolytic episodes, increased hemolysis has frequently been implied in the pathogenesis of this neonatal hyperbilirubinemia. However, in Sephardic Jewish G-6-PD-deficient neonates, the rate of hemolysis, reflected by blood carboxyhemoglobin values corrected for inspired carbon monoxide, has been shown to be elevated, not only in those who developed hyperbilirubinemia, but also, to a similar extent, in those who remained only moderately jaundiced. Because at any point, serum total bilirubin values reflect a balance between bilirubin production on the one hand and bilirubin conjugation and elimination on the other, we suspected bilirubin conjugation to be a key factor in the pathogenesis of the hyperbilirubinemia. Physiologically, a fraction of conjugated bilirubin refluxes from the hepatocyte to the serum, and accurate determination of serum conjugated bilirubin fractions can be used to mirror intrahepatic bilirubin. Using this principle, we previously demonstrated a decreased diconjugated bilirubin fraction in hyperbilirubinemic G-6-PD-deficient neonates compared with hyperbilirubinemic G-6-PD-normal controls, suggesting diminished bilirubin conjugation. This conjugated bilirubin pattern probably reflects the recently described interaction between G-6-PD deficiency and the variant promoter for the gene encoding the recently described interaction between G-6-PD and the promoter for the gene encoding the G-6-PD enzyme, UDP glucuronyltransferase, as seen in Gilbert’s syndrome. Therefore, we postulated that efficiency of bilirubin conjugation is a crucial factor in the development of hyperbilirubinemia in G-6-PD-deficient neonates. We hypothesized that those G-6-PD-deficient neonates who develop hyperbilirubinemia would have decreased bilirubin conjugation ability, whereas those with a more efficient conjugating system would have a lesser degree of bilirubinemia.

Methods. Term, healthy, male, G-6-PD-deficient neonates with no other obvious predisposing cause for hyperbilirubinemia were selected at random when their serum diazo total bilirubin values ranged from 171 to 254 μmol/L (10–14.9 mg/dL). At this point, simultaneous with the diazo bilirubin determination, serum was collected and frozen for high-performance liquid chromatography (HPLC) measurement of serum bilirubin fractions. The infants were followed clinically and with serum diazo bilirubin determinations until they either did not exceed a serum diazo bilirubin value of 254 μmol/L (14.9 mg/dL) (nonhyperbilirubinemic) or until bilirubin values rose above this level (hyperbilirubinemic), by a process of self-selection. A method of alkaline methanolation, followed by reverse-phase HPLC, was used to measure unconjugated bilirubin and the mono- and diconjugated fractions of serum conjugated bilirubin. Total HPLC bilirubin and total conjugated bilirubin values were calculated from these measured bilirubin fractions. Patients also were classified according to the serum total conjugated bilirubin value as low bilirubin conjugators (serum total conjugated bilirubin less than median) or as high bilirubin conjugators (serum total conjugated bilirubin greater than median). The data were analyzed by comparing serum conjugated bilirubin fractions between the hyperbilirubinemic and nonhyperbilirubinemic groups and the risk of developing hyperbilirubinemia in the low bilirubin conjugators, relative to that of the high bilirubin conjugators.

Results. Neonates were sampled at 53 ± 12 and 58 ± 12 hours for the subsequently hyperbilirubinemic and nonhyperbilirubinemic groups, respectively (NS). Initial (ie, at the time of sampling) serum total diazo bilirubin values (mean ± SD) were almost identical for the subsequently hyperbilirubinemic and nonhyperbilirubinemic groups (214 ± 27 μmol/L [12.5 ± 1.6 mg/dL] vs 212 ± 19 μmol/L [12.4 ± 1.1 mg/dL], respectively, NS), as were the HPLC-determined serum total bilirubin values (162 ± 32 μmol/L [9.5 ± 1.9 mg/dL] vs 160 ± 16 μmol/L [9.4 ± 0.9 mg/dL], respectively, NS). However, despite similarity in the simultaneously drawn serum diazo bilirubin values, HPLC-determined conjugated bilirubin fractions (mean [range]), measured from the same serum samples, were lower in those infants who ultimately became hyperbilirubinemic than in those who remained nonhyperbilirubinemic: total conjugated bilirubin 0.82 (0–2.07) μmol/L vs 1.24 (0.6–11.0) μmol/L; monoconjugated bilirubin 0.80 (0–2.07) μmol/L vs 1.24 (0.60–1.23) μmol/L; and diconjugated bilirubin 0.00 (0.00–0.42) μmol/L vs 0.11 (0–1.78) μmol/L. The diconjugated bilirubin fraction was especially affected; 18 (69%) neonates in the subsequently hyperbilirubinemic group had no detectable diconjugate compared with 8 (36%) in the nonhyperbilirubinemic neonates. Conversely, more of those neonates with serum total conjugated bilirubin fraction less than the median value of 1.06 μmol/L (0.06 mg/dL) developed hyperbilirubinemia than those with greater than the median value.

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Glucose-6-phosphate dehydrogenase (G-6-PD) deficiency is associated with a high incidence of neonatal hyperbilirubinemia that may, in severe cases, cause kernicterus and death. Because of the association between G-6-PD deficiency and acute, drug-induced hemolytic episodes, acute hemolysis has been implicated frequently in the pathogenesis of the hyperbilirubinemia. However, the associated jaundice appears even when all known triggers of hemolysis are avoided. Using carboxyhemoglobin measurements corrected for inspired carbon monoxide as an accurate index of bilirubin production, it was found that bilirubin production in G-6-PD-deficient neonates was increased to a similar extent not only in those who developed hyperbilirubinemia, but also in those who did not.

Because at any point, serum bilirubin levels reflect a balance between bilirubin production on the one hand and bilirubin conjugation and elimination on the other, we proposed that decreased bilirubin conjugation would be crucial to the pathogenesis of excessive jaundice in G-6-PD-deficient neonates. Physiologically, a fraction of conjugated bilirubin refluxes from the hepatocyte to the serum, and accurate determination of serum conjugated bilirubin fractions can be used to mirror intrahepatocytic bilirubin. Using this principle, we have demonstrated previously a decreased serum diconjugated bilirubin fraction, reflective of diminished bilirubin-conjugating ability in hyperbilirubinemic G-6-PD-deficient neonates, compared with hyperbilirubinemic G-6-PD normal controls. This decreased bilirubin conjugation may be the functional manifestation of the recently described gene interaction between G-6-PD deficiency and the variant promoter for the gene encoding the bilirubin-conjugating enzyme UDP glucuronosyltransferase 1, as seen in Gilbert’s syndrome.

In the current study, we assessed bilirubin conjugation by analyzing unconjugated and conjugated bilirubin fractions in serum sampled from G-6-PD-deficient neonates while they were still moderately jaundiced with serum bilirubin values in a fixed range. After sampling, the patients either developed hyperbilirubinemia (serum total diazo bilirubin \( \geq 256 \mu\text{mol/L} \) (15 mg/dL)) or remained in the nonhyperbilirubinemic range (serum total diazo bilirubin \(< 256 \mu\text{mol/L} \) (15 mg/dL)) by a natural selection process. This study design enabled us to compare conjugated bilirubin fractions from sera with similar total bilirubin values in neonates in the two groups. In addition, we determined the risk of developing hyperbilirubinemia in G-6-PD-deficient neonates with lower, versus higher, bilirubin-conjugating capacity, as determined by serum total conjugated bilirubin lesser or greater than median, respectively.

**METHODS**

**Clinical Material**

At the Shaare Zedek Medical Center, a subgroup of infants born to mothers of Sephardic-Jewish descent, whose families immigrated from Asia Minor, and who thus were at high risk for G-6-PD deficiency and its associated hyperbilirubinemia, was screened for the enzyme deficiency on the first day of life. G-6-PD-deficient neonates were hospitalized routinely for observation for a minimum of 72 hours after birth, with serum total bilirubin determinations performed as clinically indicated. Discharge was delayed if total serum bilirubin values were rising and approaching criteria for phototherapy (below). Discharged newborns were followed by our staff, using our laboratory facilities, as outpatients, until it was clear that serum bilirubin values had stabilized. The compliance rate in our population was excellent, and we were confident that we were aware of virtually all neonates who develop excessive bilirubinemia. Nursery protocol included the institution of phototherapy as part of hospitalization in G-6-PD-deficient term neonates if the serum total bilirubin value was \( \geq 256 \mu\text{mol/L} \) (15.0 mg/dL) in the first week of life. Exchange transfusion was performed if these values rose to \( \geq 342 \mu\text{mol/L} \) (20 mg/dL) and if infants were unresponsive to phototherapy.

**Study Protocol**

The study protocol was approved by the Shaare Zedek Medical Center’s institutional review board. Candidates for the study, chosen arbitrarily from the G-6-PD-deficient population, included otherwise healthy, term, male newborns, free of any other identifiable factor known to exacerbate jaundice such as cephalhematoma, maternal diabetes, Coombs’ positive hemolytic anemia, or sepsis. Infants were managed according to the routine protocol. When an infant who met criteria for entry into the study was estimated by clinical judgment to have a rising serum total bilirubin value ranging from 171 to 254 \( \mu\text{mol/L} \) (10.0–14.9 mg/dL), serum for high-performance liquid chromatography (HPLC) analysis of bilirubin fractions of infants was obtained along with routine total diazo bilirubin serum. Neonates were entered into the study only if their serum diazo bilirubin value was found to be 171 to 254 \( \mu\text{mol/L} \) (10.0–14.9 mg/dL). If the serum diazo bilirubin value was lower than the range for inclusion in the study, that infant was allowed to be included at a later time should he meet the criteria using a new serum HPLC sample, obtained with a later serum total diazo bilirubin value, to proceed. Serum for HPLC bilirubin determinations were sampled concurrently in all cases. The subsequent management of enrolled newborns was identical to that for the routine clinical protocol. The infants were followed until they either did not exceed a serum bilirubin value of 254
**RESULTS**

The serum samples were collected between July 1994 and April 1996. A total of 48 male neonates were entered into the study, of whom 26 subsequently developed serum total diazo bilirubin values \( \geq 256 \mu mol/L \) (15.0 mg/dL) (hyperbilirubinemic) and 22 remained nonhyperbilirubinemic. There were no significant differences in the clinical characteristics of the neonates; birth weights (mean \( \pm SD \)) were 3066 \( \pm 470 \) g and 3324 \( \pm 392 \) g, and gestational ages 39.1 \( \pm 1.0 \) and 39.6 \( \pm 1.2 \) weeks for the hyperbilirubinemic and nonhyperbilirubinemic groups, respectively. In both groups, 77\% were exclusively breast-fed. Neonates were delivered vaginally in 92\% and 95\% of the subsequently hyperbilirubinemic and nonhyperbilirubinemic groups, respectively.

Serum total diazo bilirubin values (mean \( \pm SD \)) at the time of sampling were almost identical (214 \( \pm 27 \) \( \mu mol/L \) [12.5 \( \pm 1.6 \) mg/dL] and 212 \( \pm 19 \) \( \mu mol/L \) [12.4 \( \pm 1.1 \) mg/dL] for the subsequently hyperbilirubinemic and nonhyperbilirubinemic groups, respectively), whereas the time of sampling was 53 \( \pm 12 \) h and 58 \( \pm 10 \) h, respectively (NS). Maximal serum diazo total bilirubin values in the hyperbilirubinemic group, before the onset of phototherapy, were 282 \( \pm 26 \) \( \mu mol/L \) (16.5 \( \pm 1.5 \) mg/dL), although therapy probably did not allow the bilirubin values to reach their natural peak. Measured and calculated HPLC determined values for the major bilirubin components are displayed in Table 1, and those for the conjugated bilirubin fractions are shown graphically in Fig 1. It should be noted that despite similarity in the total and unconjugated bilirubin values in both groups at the time of sampling, the total conjugated and its mono- and diconjugated bilirubin fractions, measured from the same serum sample as the former, were significantly lower in those neonates who subsequently developed hyperbilirubinemia than in those who remained nonhyperbilirubinemic. The diconjugated bilirubin fraction was especially affected; whereas only one neonate in the subsequently hyperbilirubinemic group had undetectable levels of monoconjugated bilirubin, 18 (69\%) neonates in that group had no detectable diconjugate. In contrast to the latter, in the nonhyperbilirubinemic group, only 8 (36\%) had undetectable diconjugated bilirubin levels (\( P < .05 \)).

The median value for serum total conjugated bilirubin at the time of sampling for the entire patient sample was 1.06 \( \mu mol/L \) (0.06 mg/dL). Of the 24 neonates with serum total conjugated bilirubin val-

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**Data Analysis**

Measured HPLC values for unconjugated, monoconjugated, and diconjugated bilirubin fractions were used to calculate values for total bilirubin and total conjugated bilirubin. For the purpose of the study, hyperbilirubinemia was defined as a maximal serum total bilirubin diazo level \( \geq 256 \mu mol/L \) (15.0 mg/dL) at any time during the first week of life. Those whose maximal serum total bilirubin value did not exceed 254 \( \mu mol/L \) (14.9 mg/dL) during this time were regarded as nonhyperbilirubinemic. In addition, those whose serum total conjugated bilirubin values less than the median value for this parameter were defined as low bilirubin conjugators, whereas those with serum total bilirubin values greater than the median value were defined as high bilirubin conjugators. The data were analyzed by comparing serum conjugated bilirubin fractions between the hyperbilirubinemic and nonhyperbilirubinemic groups, and the risk of developing hyperbilirubinemia in the low bilirubin conjugators, relative to that of the high bilirubin conjugators. Mean values \( \pm SD \) and median value (range) were calculated for parametric and nonparametric data, respectively. Continuous variables were compared using Student’s t test or the Mann-Whitney rank sum test, whereas categorical variables were analyzed using analysis of Fisher’s exact test, as appropriate. Significance for the above tests was defined as \( P < .05 \). Relative risk and 95\% confidence interval (CI) were calculated to assess the risk of the low conjugators developing hyperbilirubinemia relative to the high conjugators, the latter defined as relative risk \( = 1 \). Significance for this test was achieved when the 95\% CI were wholly \( > 1 \) or \( < 1 \).
ues less than median, 17 (71%) subsequently became hyperbilirubinemic compared with 9 of 24 (37.5%) of those with serum total conjugated bilirubin values greater than median (relative risk: 1.89; 95% CI: 1.06–3.36; \(P = .04\)). Furthermore, 22 of 26 (84.6%) neonates with no detectable diconjugated bilirubin, compared with 8 of 22 (36.4%) neonates with any measurable diconjugate, developed hyperbilirubinemia (relative risk: 2.33; 95% CI: 1.31–4.14; \(P = .002\)).

### DISCUSSION

The results of our study show that those G-6-PD-deficient neonates who developed higher maximal serum total bilirubin values had significantly lower serum conjugated bilirubin fractions than those who remained only moderately jaundiced. Conversely, those with lower serum total conjugated bilirubin values at the time of sampling were at higher risk for the subsequent development of hyperbilirubinemia. The serum bilirubin profile demonstrated in the subsequently hyperbilirubinemic G-6-PD-deficient neonates (high total and unconjugated fraction, with low total conjugated, monoconjugated, and especially diconjugated fractions) is reminiscent of that seen in conditions of partial deficiency of the bilirubin conjugating enzyme UDP glucuronosyltransferase, such as Gilbert’s Syndrome. These data support functionally the concept of the gene interaction demonstrated recently between G-6-PD deficiency and the variant promoter for the gene encoding this enzyme, UDP glucuronosyltransferase. The primary site of the pathogenesis of the hyperbilirubinemia therefore appears to be localized to a deficiency in bilirubin conjugation. As a result, G-6-PD-deficient neonates who become hyperbilirubinemic have bilirubin conjugation ability which is even more inefficient than that of the physiological immaturity of conjugation normally found in neonates. Those with an excessively immature bilirubin eliminating capacity are more likely to develop hyperbilirubinemia than those with a more mature ability. This mechanism may exist to a certain extent in all neonates but may be exacerbated in the G-6-PD deficiency state because of increased hemolysis and the resultant additional bilirubin load. In addition, the monoglucuronide preponderance in biliary excretion that must have resulted may have in itself exacerbated the enterohepatic circulation and added to the total bilirubin pool; in vitro studies have shown that hydrolysis of monoglucuronide back to unconjugated bilirubin occurs at rates four to six times faster than for diglucuronide.

It is unlikely that additional stages of the bilirubin elimination process, such as bilirubin uptake by the hepatocyte, or excretion of the conjugated product into the biliary tree also are involved in the pathogenesis of the hyperbilirubinemia. Deficiency of hepatic uptake of bilirubin, possibly related to deficiency of ligandin (Y protein) could lead to increased serum total bilirubin values and decreased conjugated bilirubin fractions. However, in this situation, both the mono- and the diconjugated fractions should be expected to be decreased to a similar de-

### TABLE 1

Details Relating to HPLC Bilirubin Values, Taken at the Time of Entry into the Study, in the Two Study Groups

<table>
<thead>
<tr>
<th>Bilirubin Fraction</th>
<th>Patient Groups</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hyperbilirubinemic</td>
<td>Nonhyperbilirubinemic</td>
</tr>
<tr>
<td>Total bilirubin*</td>
<td>162 ± 32</td>
<td>160 ± 16</td>
</tr>
<tr>
<td>(\mu\text{mol/L})</td>
<td>9.5 ± 1.9</td>
<td>9.4 ± 0.9</td>
</tr>
<tr>
<td>(\text{mg/dL})</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unconjugated bilirubin*</td>
<td>161 ± 32</td>
<td>158 ± 16</td>
</tr>
<tr>
<td>(\mu\text{mol/L})</td>
<td>9.4 ± 1.9</td>
<td>9.1 ± 0.9</td>
</tr>
<tr>
<td>(\text{mg/dL})</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total conjugated bilirubin**</td>
<td>0.82 (0–2.07)</td>
<td>1.24 (0.60–11.0)</td>
</tr>
<tr>
<td>(\mu\text{mol/L})</td>
<td>0.05 (0–0.12)</td>
<td>0.07 (0.04–0.64)</td>
</tr>
<tr>
<td>(\text{mg/dL})</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monoconjugated bilirubin**</td>
<td>0.80 (0–1.85)</td>
<td>1.24 (0.6–9.23)</td>
</tr>
<tr>
<td>(\mu\text{mol/L})</td>
<td>0.05 (0–0.11)</td>
<td>0.07 (0.04–0.54)</td>
</tr>
<tr>
<td>(\text{mg/dL})</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diconjugated bilirubin**</td>
<td>0 (0–0.42)</td>
<td>0.11 (0–1.78)</td>
</tr>
<tr>
<td>(\mu\text{mol/L})</td>
<td>0 (0–0.02)</td>
<td>0.01 (0–0.10)</td>
</tr>
<tr>
<td>(\text{mg/dL})</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Values (parametric) are expressed as mean ± SD.
** Values (nonparametric) are expressed as median (range).
NS, not statistically significant.
degree. In fact, there was a predilection for the diconjugated bilirubin component, as evidenced by a large number of neonates having unmeasurable levels of diconjugated bilirubin. It is unlikely that decreased bilirubin excretion played a part in the pathogenesis of the jaundice, because neonates with an inefficient excretory system would be expected to have higher serum conjugated bilirubin fractions, along with higher total serum bilirubin values, than those with more efficient excretory function. In fact, in our patients, higher conjugated bilirubin fractions were related inversely to maximum total serum bilirubin values and vice versa.

There was no correlation between the level of erythrocyte G-6-PD enzyme activity and the unconjugated or conjugated serum bilirubin levels. However, in G-6-PD Mediterranean, levels of the enzyme are so low that there is probably little value to this type of analysis.

It could be argued that because the time of sampling in the hyperbilirubinemic group was on average 5 hours earlier than that for the nonhyperbilirubinemic group, and that because infants who develop severe hyperbilirubinemia have a greater rate of bilirubin increment, this time factor may have affected bilirubin conjugation maturation and therefore the values of the serum conjugated bilirubin fractions. However, the difference in times of sampling between the two groups was not significant. Based on the rate of rise up to the point of sampling, the serum total bilirubin values in the hyperbilirubinemic group could be expected to rise by only 1.2 mg during the 5-hour period. Because the total conjugated bilirubin values were only ~0.5% of the total bilirubin in the hyperbilirubinemic group, any change in the conjugated bilirubin component over the 5-hour period would have been minimal.

Although this was not a cohort study, we believe that little bias could have entered the selection or follow-up process. The neonates were selected while their serum bilirubin values were within a fixed range and before progression into hyperbilirubinemic or nonhyperbilirubinemic subgroups. The nursery staff are extremely sensitive to the high risk of developing serious hyperbilirubinemia in these G-6-PD-deficient neonates and are liberal in ordering serum bilirubin values during both hospitalization and follow-up, rather than relying on clinical judgment. Again, because the study population was not cohorted, neither the incidence of hyperbilirubinemia nor the median total conjugated bilirubin value in this selection of neonates should be regarded as representative of this entire G-6-PD-deficient population. The lower cutoff point for serum total diazo bilirubin was 171 μmol/L (10 mg/dL), because at levels lower than this, conjugated bilirubin levels may be so low as to exclude useful analysis. Because phototherapy most likely had a dampening effect on the peak serum bilirubin values in the hyperbilirubinemic neonates and prevented these values from reaching their natural peak, peak serum total bilirubin values were not used for analysis.

The upper limits of physiologic jaundice are frequently defined as serum total bilirubin value of 221 μmol/L (12.9 mg/dL), based on the value for the 95th percentile in the Collaborative Perinatal Project, conducted between 1959 and 1966 and encompassing 35 000 neonates. However, it is unlikely that neonates with exaggerated physiologic jaundice up to a serum bilirubin value of 256 μmol/L (15 mg/dL) would be at any risk for neurologic damage from bilirubin encephalopathy. For the purpose of the study, therefore, we were more conservative in defining hyperbilirubinemia and used a serum bilirubin cutoff point of ≥256 μmol/L (15 mg/dL). This value is equivalent to the 97th percentile for both the Collaborative Perinatal Project and a subsequent study of >2000 neonates studied in the 1980s.

The reverse-phase HPLC method we used is extremely sensitive and accurate for the measurement of unconjugated, monoconjugated, and diconjugated bilirubin fractions in serum. Indeed, reverse-phase HPLC determinations are regarded as the standard for bilirubin measurements. It should be taken into account that the HPLC method of bilirubin determination may frequently give considerably lower total bilirubin readings than does the conventional, less accurate diazo method on the same serum sample because of the presence of a diazo positive material, distinct from bilirubin and its ester conjugates, which frequently is found in serum samples containing conjugated bilirubin.

In conclusion, we have shown that deficient bilirubin conjugation, reflected by serum conjugated bilirubin values, is a cardinal factor in the pathogenesis of G-6-PD deficiency associated neonatal hyperbilirubinemia. In G-6-PD-deficient neonates who conjugate bilirubin less efficiently, hyperbilirubinemia is more likely to result. In contrast, those neonates with higher neonatal bilirubin conjugation ability are less likely to develop clinically significant hyperbilirubinemia. It is unknown at present whether the previous observations related to hemolysis and bilirubin production, the variant promoter for the gene encoding UDP glucuronosyltransferase, or the deficient serum conjugated bilirubin fractions described above are unique to Sephardic Jews with G-6-PD Mediterranean or whether they have global implications for the hundreds of millions of people worldwide estimated to have G-6-PD deficiency. Additional study of the pathophysiology of this process may lead to improved therapeutic or prophylactic interventions in the clinical management of G-6-PD deficiency associated neonatal hyperbilirubinemia.

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