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Correlation of serum coenzyme Q_{10} and bilirubin levels of jaundiced newborns in intermediate risk zone: Is it an etiopathogenic factor in neonatal jaundice?

[Orta dereceli risk bölgesinde yer alan sarılıklı yenidoğanlardaki serum koenzim Q10 ve bilirubin düzeyleri arasındaki ilişki: Koenzim Q10 düzeyi yenidoğan sarılığında bir etyopatojenik faktör olabilir mi?]

Cigdem Karakukcu[1], MD
Musa Karakukcu[2], MD
Peter H. Tang[3], MD, PhD

[1]Department of Biochemistry, Kayseri Education and Research Hospital, 38010 Kayseri, TURKEY
[2]Division of Hematology, Department of Pediatrics, School of Medicine, Erciyes University, 38039 Kayseri, TURKEY
[3]Divisions of Neurology, Pathology, and Laboratory Medicine, Cincinnati Children's Hospital Medical Center, and Department of Pediatrics, School of Medicine, University of Cincinnati, OH 45229-3039, USA

Yazışma Adresi
[Correspondence Address]

Cigdem KARAKUKCU

Department of Biochemistry, Kayseri Education and Research Hospital, 38010 Kayseri, TURKEY
Tel : 00,90 352 336 88 84
Fax : 00,90 352 320 73 13
E-mail: ckarakukcu@hotmail.com

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ABSTRACT

Aim: Jaundice in newborn is caused by neonatal changes in bilirubin metabolism resulting in increased bilirubin production, decreased bilirubin clearance and increased enterohepatic circulation. Although bilirubin is reported to have antioxidant effects in low concentrations, it is toxic at high levels. At high concentration, bilirubin leads to marked alterations in the membrane content of the several classes of phospholipids and cholesterol, which can render the cells more susceptible to lysis and shorten their lifespan. One of the most important properties of coenzyme Q_{10} (CoQ_{10}) is its antioxidant activity; it protects cells from free radicals and increases membrane stability of erythrocytes. For that reason in this study, we aimed to investigate any possible relation between serum bilirubin and CoQ_{10} concentrations in jaundiced newborns in intermediate risk zone.

Materials and Methods: Totally, 44 term jaundiced newborns with elevated indirect bilirubin levels were included to the study. Based on the recommendations of American Academy of Pediatrics newborns were divided into two groups according to their day of age and serum bilirubin concentrations: Group I (n:24); newborns in low intermediate risk zone (low-intermediate) and Group II (n:20); newborns in high intermediate risk zone (high-intermediate). Total serum bilirubin levels were obtained at the time of the routine examination in all newborns. Bilirubin concentrations in serum samples were measured spectrophotometrically and total CoQ_{10} concentration in the same sample of all subjects was measured by HPLC.

Results: Mean total serum bilirubin levels of the Group I and Group II were 11.88±2.58 mg/dL and 17.22±1.69 mg/dL, respectively. Mean serum CoQ_{10} concentration of newborns in Group II was significantly lower according to the newborns in Group I ($p<0.001$). In addition, a significant negative correlation between serum CoQ_{10} concentration and bilirubin was found ($r=-0.676$, $p<0.001$).

Conclusions: The results obtained from 44 fullterm jaundiced newborns indicate that, newborns with higher total serum bilirubin levels in high-intermediate risk group have lower CoQ_{10} concentrations when compared to low-intermediate risk group. Indeed, increase in bilirubin level is correlated with a decrease in serum CoQ_{10} concentration. Low serum CoQ_{10} content in newborns might increase serum bilirubin concentration by leading oxidative stress induced damage to erythrocytes or oxidative and cytotoxic effects of bilirubin might decrease serum CoQ_{10} concentration.

Key words: Coenzyme Q_{10}, jaundice, newborn

ÖZET

Amaç: Yenidoğan döneminde görülen sarılık, artmış bilirubin üretimi, azalmış klirens ve artmış enterohepatik dolaşım nedeniyle meydana gelen bilirubin metabolizması değişikliklerinden kaynaklanmaktadır. Bilirubin düşük konsantrasyonlarda antioksidan özellik gösterirken, yüksek düzeylerde toksiktir. Yüksek konsantrasyonlarda bilirubin, fosfolipid ve kolesterol gibi hücre membran içeriklerinde değişikliklere neden olabilir, ki bu durum hücreleri lizise daha duyarlı hale getirir ve ömürlerini kısaltır. Koenzim Q_{10}'in en önemli özelliklerinden birisi antioksidan aktivitesidir. Bu aktivitesi ile hücreleri serbest radikallerden korur. Ayrıca eritrositlerde membran stabilizasyonunu artırıcı etki gösterir. Bu çalışmada biz, orta dereceli risk bölgesinde yer alan sarılıklı yenidoğanlarda, serum bilirubin ve koenzim Q_{10} düzeyleri arasındaki ilişkiyi araştırmayı amaçladık.

Gereç ve Yöntemler: Çalışmaya toplamda 44 term sarılıklı yenidoğan alındı. Amerikan Pediatri Akademisi'nin önerileri doğrultusunda bebekler yaş ve bilirubin değerlerine göre iki gruba ayrıldı: Düşük-orta risk zonundaki bebekler Grup I (n:24); yüksek-orta risk zonundaki bebekler Grup II (n:20) olarak adlandırıldı. Tüm bebeklerin serum total bilirubin konsantrasyonları rutin kontrolleri esnasında ölçüldü. Aynı serum örneklerinde bilirubin (spektrofotometrik) ve CoQ_{10} (HPLC ile) düzeyleri çalışıldı.

Bulgular: Serum total bilirubin düzeyi ortalamaları sırasıyla Grup I ve Grup II'de 11.88±2.58 mg/dL ve 17.22±1.69 mg/dL idi. Ortalama serum koenzim Q_{10} düzeyleri Grup II'de, Grup I'e göre düşük bulundu ($p<0.001$). Ayrıca koenzim Q_{10} düzeyleri ile bilirubin düzeyleri arasında negatif bir korelasyon tespit edildi ($r=-0.676$, $p<0.001$).

Sonuç: Toplamda 44 term sarılıklı yenidoğanla yapılan bu çalışmanın sonuçlarına göre, yüksek-orta risk zonundaki sarılıklı bebekler düşük-orta risk zonundaki bebeklere göre daha düşük serum koenzim Q_{10} düzeylerine sahiptirler. Ayrıca bilirubin düzeyindeki artışla birlikte serum koenzim Q_{10} konsantrasyonu azalmaktadır. Düşük serum koenzim Q_{10} düzeyi eritrositlerde oksidatif stres aracılı hasarı artırarak bilirubin konsantrasyonlarını arttırmış veya bilirubinin oksidatif ve sitotoksik etkilerine bağlı olarak koenzim Q_{10} düzeyi azalmış olabilir.

Anahtar Kelimeler: Koenzim Q_{10}, sarılık, yenidoğan

Introduction

Neonatal jaundice attributable to physiological immaturity usually appears between 24-72 hours of age, peaks by 4-5 days in term and 7th day in preterm neonates and disappears by 10-14 days of life. It is predominantly indirect and levels usually do not exceed 15 mg/dL. It comes out because of an imbalance between the production and elimination of indirect bilirubin, with a multitude of factors and conditions affecting each of these processes [1].

In the last 10 years, *in vitro* and *in vivo* studies have demonstrated that bilirubin exhibits potent anti-oxidant properties preventing the oxidative damage triggered by a wide range of oxidant-related stimuli [2,3]. Conversely, at higher levels bilirubin has toxic effects and induces membrane oxidation. Binding to the membrane interferes with its stability and leads to marked alterations in the membrane content of the several classes of phospholipids and cholesterol, which can render the cells more susceptible to lysis and shorten their lifespan [4,5]. However it's not clear if bilirubin has oxidant or antioxidant effects at intermediate levels.

Oxidative reactions form an essential part of all biological systems, but toxic effects of the derivatives of these reactions depend on a critical balance between the oxidative stimulus and the antioxidant defense mechanisms available. The cytotoxic effect of circulating free radicals can enhance lipid peroxidation of the cell membranes and this can only be controlled through the intermediary of antioxidant substances [6-8]. As the antioxidant defense mechanisms are not developed enough, newborns, especially premature are at high risk of free radical oxidative damage [9-12].

Coenzyme Q_{10} (CoQ_{10}) a vitamin-like substance found in every cell, hence the name ubiquinone, is vital in the production of energy. Physiologically, CoQ_{10} has four major roles. *i*. It is essential in mitochondrial energy (ATP) production through redox activity in the respiratory chain, transporting electrons between enzymes. *ii*. It is assigned to the extramitochondrial redox activity in the cell membrane and endomembranes. *iii*. CoQ_{10} also functions as an antioxidant, inhibiting lipid peroxidation and scavenging free radicals. The reduced form readily gives up electrons to neutralize oxidants and displays its strongest antioxidant activity [13]. *iv*. Finally, it plays an important role in membrane stabilization and fluidity [13,14].

In this study we aimed to investigate serum CoQ_{10} concentrations of jaundiced newborns who have moderately high bilirubin levels (newborns in intermediate risk zone) and any relation between CoQ_{10} and bilirubin.

Materials and Methods

Subjects

Based on the recommendations of American Academy of Pediatrics (AAP) according to day of age and serum bilirubin concentrations of newborns as shown in a nomogram [15], 44 jaundiced, full term (38-42 gestational weeks) infants in the intermediate risk zone were included in this study. Jaundiced newborns in high and low risk zone were excluded. According to the nomogram newborns were divided into two groups: infants in low intermediate risk zone were considered as Group I (n:24) and in high intermediate risk zone were considered as Group II (n:20).

The infants did not show any pathologic abnormalities and all had an APGAR score on the 5th minute ranging eight to ten. All the infants were being breastfed and had no etiological factor for hyperbilirubinemia; all had non-hemolytic, physiologic or idiopathic hyperbilirubinemia. Infants with any blood group (Rh or ABO) incompatibility, glucose 6-phosphate dehydrogenase deficiency, positive Coombs test; any congenital malformation, serious illness requiring oxygen therapy and any medication, birth asphyxia, sepsis, and infants those received any phototherapy; infants with maternal disease like diabetes were excluded from the study. The Ethical Committee of the Medical Faculty of Erciyes University approved the study (05/48).

Total serum bilirubin levels were obtained at the time of the routine examinations in all newborns. Postnatal age at the time of total serum bilirubin measurement was recorded.

Venous blood from newborns was collected into a Vacutainer® Tube (Becton Dickinson) without any anticoagulant for measurement of bilirubin levels. Blood samples were processed within 1 hour of collection and centrifuged at 2000x*g* for 10 min. Serum bilirubin concentrations (sum of indirect and direct bilirubin with no inclusion of δ-bilirubin*)* were analyzed spectrophotometrically (VITROS 5,1 FS Chemistry System, Ortho Clinical Diagnostics). Remaining part of the serum was collected in a capped polypropylene tube and stored at 4°C until analysis for CoQ_{10}.

Serum CoQ_{10} determination and sample analysis

Serum CoQ_{10} level was determined by HPLC as previously described by Tang et al. [16]. CoQ_{10} and coenzyme Q_9 (CoQ_9) (internal standard) were obtained from Sigma. Methanol, ethanol, 1-propanol, 2-propanol, hexane, sodium acetate, and glacial acetic acid were obtained from Fisher Scientific. All chemicals were HPLC grade and were used without further purification. Dade® immunoassay comprehensive tri-level controls were from Dade International.

The HPLC-EC system consisted of a Model 582 Solvent Delivery Module (ESA), an AS1000 variable-loop auto sampler (Thermo Separation Products), an analytical column, an ESA CouloChem II Model 5200A EC detector, and a computer/controller with ChromQuest software (Thermo Separation Products). The analytical

column was a reversed-phase Microsorb-MV column. A reversed-phase C18 guard column was used to protect the analytical column. The injection volume was set at 100 µL for each sample. The mobile phase for the isocratic elution of CoQ_{10} was prepared as follows: sodium acetate trihydrate (6.8 g), 15 mL of glacial acetic acid, and 15 mL of 2-propanol were added to 695 mL of methanol and 275 mL of hexane. The pH of the mobile phase was 6, and the flow rate was 1mL/min. To prepare a 5 mg/L working solution of CoQ_{10}, we dissolved 10 mg of CoQ_{10} in 10 mL of hexane and diluted this solution to 100 mL with 1-propanol. The solution was thoroughly vortex-mixed until completely dissolved. A working solution was then prepared by dilution with 1-propanol to 5 mg/L. The concentration of the working solution was then calculated by reading the absorbance on a spectrophotometer (275 nm wavelength; 1-cm quartz cuvette), using a molar absorptivity (e) of 14 200.

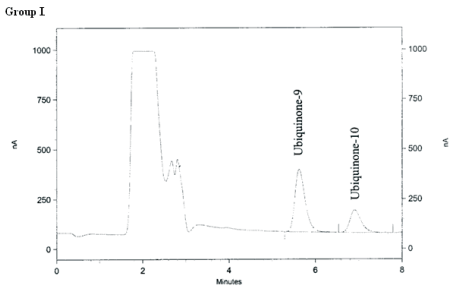
The samples were analyzed in duplicate. A 100 µL aliquot of the sample was placed in a 1.8 mL capped polypropylene tube containing 100 µL of internal standard solution. The sample was then mixed with 600 µL of cold 1-propanol. All tubes were vortex-mixed for 2 min on a mechanical vortex-type mixer and centrifuged for 10 min at 2000x*g*. The resulting supernatant was separated from the precipitate and transferred to a glass autosampler tray. A 100 µL aliquot of 1-propanol extract from a vial was injected into an automated HPLC. The ChromQuest software obtained peak height and area measurements for each injection. The CoQ_{10}:CoQ_9 peak-height ratios were used to calculate the CoQ_{10} concentrations of the frozen control samples and patient samples.

Statistical analysis

Data were presented as mean±SD for parametric variables in groups. Qualitative variables were assessed by a Chi-square test. Parametric variables were compared by Student's *t*-test. Pearson correlation coefficient was calculated between serum CoQ_{10} and bilirubin levels. p-value of <0.05 was considered to be statistically significant. Data was analyzed using the SPSS® for Windows computing program (Version 13.0).

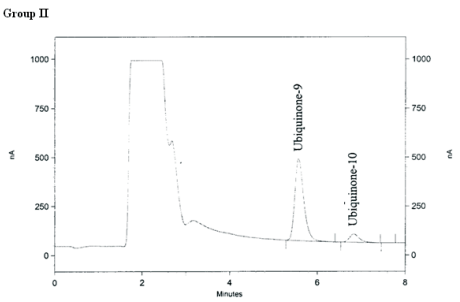
Results

In Group I and Group II sex (8/12 girls/boys and 11/13 girls/boys, respectively) (p>0.05) and age of days in newborns were similar (5.4±2.4 and 4.6±1.6 days, respectively) (p>0.05). Mean serum bilirubin level of the Group II was 17.22±1.69 mg/dL, which was significantly higher from those of the Group I (11.88±2.58 mg/dL) (p<0.001). Mean serum CoQ_{10} level of the Group II was 0.36±0.09 µg/mL and serum CoQ_{10} level of Group I was 0.59±0.19 µg/mL. The difference was also found to be statistically significant (p<0.001) (Table 1). Representative chromatograms of newborns in both groups are demonstrated in Figure 1.



Detector 1 Results (Reprocessed)

Name	Retention Time	Start Time	Stop Time	Area	Height	ISTD concentration	Units
Ubiquinol-10						0.000 BDL	ug/mL
Ubiquinone-9	5.623	5.29	6.54	5162163	314346	0.000	ug/mL
Ubiquinone-10	6.908	6.57	7.61	2031912	113590	0.963	ug/mL



Detector 1 Results (Reprocessed)

Name	Retention Time	Start Time	Stop Time	Area	Height	ISTD concentration	Units
Ubiquinol-10						0.000 BDL	ug/mL
Ubiquinone-9	5.572	5.28	6.41	5893042	418486	0.000	ug/mL
Ubiquinone-10	6.828	6.54	7.44	649002	41650	0.265	ug/mL

Figure 1. Representative CoQ10 (Ubiquinone-10) chromatograms of newborns in Group I and Group II.

Table 1. Demographic parameters and serum CoQ_{10} and bilirubin levels of the newborns.

	GROUPS		
	Group I (n:24)	Group II (n:20)	p
Age (day)	5.4±2.4	4.6±1.6	>0.05
Sex (female/male)	8/12	11/13	>0.05
Bilirubin (mg/dL)	11.88±2.58	17.22±1.69	<0.001
Serum CoQ10 (µmol/L)	0.59±0.19	0.36±0.09	<0.001

Indeed a significant negative correlation was found between serum CoQ_{10} and bilirubin levels (r=-0.676, p<0.001) (Figure 2). Serum CoQ_{10} decreased as bilirubin levels increased in jaundiced newborns.

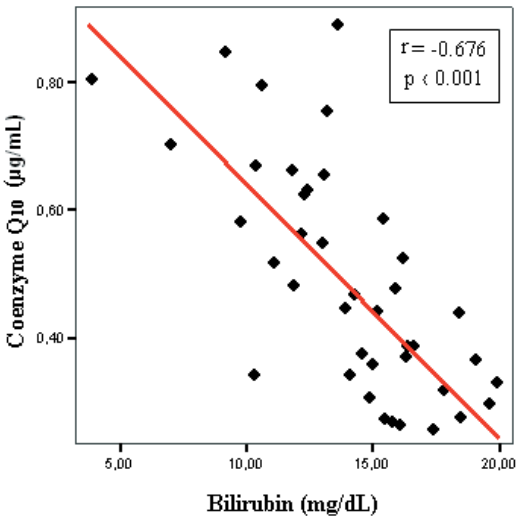


Figure 2. Correlation between serum CoQ10 and bilirubin levels of groups.

Discussion

There are some studies investigating serum/plasma CoQ_{10} levels in newborns [17-19]. To the best of our knowledge, this is the first study contributing serum CoQ_{10} and bilirubin concentrations in jaundiced newborns. In this study, we found lower serum CoQ_{10} levels in high-intermediate risk group newborns compared to the low-intermediate risk group. In addition, there was a negative correlation between CoQ_{10} and serum bilirubin concentrations. Serum CoQ_{10} decreased as bilirubin levels increased. This finding is in accordance with one of our recent studies in which toxic effect of moderately high serum bilirubin (in high-intermediate risk zone) was demonstrated in jaundiced newborns, as evidenced by DNA strand breaks by the use of alkaline comet assay. DNA damage of jaundiced newborns was significantly higher in hyperbilirubinemic newborns before phototherapy [20].

Although very high levels of bilirubin are known to be toxic, there is continued uncertainty about the risks and benefits of moderate serum bilirubin values in high- and low-intermediate risk zone [21]. Over the years, the antioxidative property of bilirubin has been firmly established [22] owing to its effect in preventing conditions like asthma [23], atherosclerosis [24], and experimental autoimmune encephalomyelitis [25]. In newborns, it is unclear that which levels of bilirubin has oxidant or antioxidant effects.

At high concentrations bilirubin has toxic effects to erythrocytes, because it promotes an accelerated aging of human erythrocytes by inducing loss of membrane lipids [5]. Increased oxidative stress after birth due to inadequate antioxidant defense mechanisms, excess amount of oxygen radicals, etc., can lead to lipid peroxidation of the erythrocyte membranes and cause increased bilirubin production in newborns [26]. One of the most important roles of CoQ_{10} is membrane stabilization. The membrane stabilizing property of CoQ_{10} has been postulated to involve the phospholipid-protein interaction that increases prostaglandin (especially prostacyclin) metabolism [27]. Therefore, CoQ_{10} deficiency in infants can either be itself the cause of idiopathic hyperbilirubinemia by making erythrocyte membrane more susceptible to fragility without any hemolytic disease such as Rh or ABO incompability or erythrocyte membrane defects.

Many procedures have been reported for the analysis of CoQ_{10} in human plasma/serum [27,28]. The total CoQ_{10} concentration may be obtained by the simultaneous detection of both the reduced ($CoQ_{10}H_2$=ubiquinole) and oxidized CoQ_{10} [28,29]. However, reduced form is very unstable [30,31] and for routine clinical use total CoQ_{10} determinations of many samples a better strategy is to oxidize the reduced form to CoQ_{10} before or during the extraction [29]. The oxidation has been performed in this study with precolumn guard cell. When the guard cell is at an oxidation potential between 500-1000 mV, the reduced CoQ_{10} is converted completely to the oxidized CoQ_{10} and the oxidized CoQ_{10} remained unchanged. In recent studies redox status of CoQ_{10} in jaundiced newborns can be investigated to lighten the oxidative state in hyperbilirubinemia.

More than 90% of the CoQ_{10} content in human serum exists in its reduced form, [31,32] and the total amount of CoQ_{10} in human plasma (the sum of the reduced and oxidized forms) for normal, healthy persons is in the range of 0.4 to 2.0 µg/mL [31]. There is no evidence of maternal-fetal transport of CoQ_{10} as evidenced by markedly reduced CoQ_{10} levels in cord blood samples. This state suggests placental impermeability of CoQ_{10} [33]. Noia et al. showed CoQ_{10} levels in pregnants in the third trimester (1.18±0.27 µg/mL) were different from fetal plasma (0.3 µg/mL). The CoQ_{10} plasma level does not increase with gestational age but increases after birth [17]. Huertas at al. investigated plasma and erythrocyte membrane CoQ_{10} levels in newborn infants and found a significant increase during their first 72 hours of life [34]. Human breast milk contains appreciable amounts of CoQ_{10}. The mean concentration of CoQ_{10} was 0.27±0.18 µg/L (ranging from 0.06 to 1.67 µg/L) [35]. Maternal dietary intake of CoQ_{10} can increase breast milk amounts and may decrease the incidence of idiopatic neonatal hyperbilirubinemia. Fetal transportation of oral CoQ_{10} supplementation in pregnancy and during breastfeeding can be subjects of new studies.

In conclusion, newborns in high-intermediate risk zone have lower serum CoQ_{10} levels. Because of the lower serum CoQ_{10} content of infants compared to adults [29,36]

erythrocyte membrane of infants may be more susceptible to fragility. Low serum CoQ_{10} content in newborns can increase bilirubin concentration by leading oxidative stress induced damage to eryhtrocytes. And also any oxidant like bilirubin at high levels can damage erythrocyte membranes resulting in a vicious cycle that can even lead to higher bilirubin levels in newborns. Therefore, CoQ_{10} supplementation during pregnancy and breastfeeding can perhaps prevent newborns to be subjected to higher bilirubin levels. Further studies are needed to identify the basic role of CoQ_{10} mechanism in jaundice.

Conflict of Interest:

The authors declare no conflict of interest.

Acknowledgement:

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