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Central corneal thickness changes and horizontal corneal diameter in premature infants

A prospective analysis

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Abstract

To report observations of horizontal corneal diameter (HCD) and central corneal thickness (CCT) changes in premature infants with stable optic disc cupping and intraocular pressures (IOPs). The HCD and CCT at term serve as a baseline for premature infants.

Sixty-three premature infants were enrolled in a prospective case series. HCD, CCT, and IOP were measured. RetCam images of the optic discs were used to evaluate the cup-disc ratio (CDR) and read by an independent masked observer. Data were collected at between preterm (32–36 weeks) and again at term (37–41 weeks) postconceptual age. Left eye measurements were used for statistical analysis. Left eye findings were combined to construct predictive models for HCD and CCT.

The mean HCD was 9.1 mm (standard deviation [SD] = 0.7 mm) at preterm and 10.0 mm (SD = 0.52 mm) at term. The mean CCT preterm was 618.8 (SD = 72.9) μm and at term 563.9 (SD = 50.7) μm, respectively. The average preterm CDR was 0.31 and at maturity was 0.33. Average IOP of preterm and term was 13.1 and 14.11 mm Hg, respectively. There was significant linear correlation between HCD with the postmenstrual age ($r = 0.40$, $P < .01$) and the head circumference ($r = 0.33$, $P < .05$). Predictive models were constructed for HCD ($R^2 = 0.52$, 0.2 mm/wk) and CCT ($R^2 = 0.23$, −11.4 μm/wk) with postconceptual ages.

The HCD and CCT variation did not affect IOP reading over time. CCT was not correlated with birth parameters and decreased as the infant reached term. Corneal diameter correlated with gestational age at birth and head circumference.

Abbreviations: CCT = central corneal thickness, CDR = cup-disc ratio, HCD = horizontal corneal diameter, IOP = intraocular pressure, SD = standard deviation.

Keywords: corneal diameter, intraocular pressure, premature infants

1. Introduction

In premature infants, the association between corneal thickness and intraocular pressure (IOP) over time is not known with certainty. For adults, corneal thickness is a routine part of the assessment of IOP.[1] In a meta-analysis, Doughty and Zaman[2] reviewed 600 sets of central corneal thickness (CCT) data between 1968 and mid-1999 and found in 134 sets which included IOP measurements. They reported a statistically significant correlation between IOP and CCT, with a 3.4 ± 0.9 mm Hg difference noted for every 10% increase in CCT ($P < .001$, $r = 0.419$) for all eyes irrespective of whether the eyes were normal, glaucoma suspects, or had eye disease including glaucoma. Changes in corneal thickness and corneal diameter in premature infants have been observed to occur.[3–8]

Data available in the published literature on the CCT in premature infants are limited; earlier studies had small sample size[3,4] and more recent larger series report cross-sectional measurements only[5,9,10] (Table 1). Muslubas et al[5] compared 45 premature infants at postconceptual age 33 to 37 weeks with term infants and found CCT of 600 μm vs 586 μm, respectively ($P = .7$). In other studies, a significant change in CCT from preterm to term has been found.[5–8] Further, CCT readings obtained from these studies have varied. This difference in average CCT results may be in part due to the variable instrumentation used in the studies; difficulties in obtaining measurements from infants and possibly racial differences and perinatal factors such as ventilation. Notably, in adults, racial differences in CCT have been reported; Shimmyo et al[21] found mean values of CCT of 550 μm in Caucasians, Asians, and Hispanics compared to 535 μm in African-Americans.

This study was undertaken to investigate prospectively changes in IOP from preterm to term and their relationship to changes in

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Table 1

Studies related to premature and full-term infant cornea.

Study	Year	Type	Location	Number premature infants	CCT, premature infants	CCT, term	Remark
Choo et al	2018	Longitudinal CCT prem 1st and last ROP screening	Malaysia	63	626 ± 71	568 ± 51 by term	$P < .001$
Grover et al[11]	2016	Measured IOP with CCT of low birth weight infants	USA	45	660.0 ± 65.0 μm		
Hekimoglu et al[12]	2015	Comparing CCT measured with SD-OCT and standard pachymetry in prem at 37.9 wks	Turkey	28	576 ± 69		Found both systems were not interchangeable
Sekeroglu et al[13]	2015	Longitudinal prem CCT at 1st ROP and 4 wks later	Turkey	170	568 ± 22	561 ± 21 at 4 wks later	$P < .001$
Jethani et al[7]	2015	Longitudinal Prem (42) vs Term (43) observed at 8 wks, 20 wks, and 1 y	India	42	578 ± 88 534 ± 57	556.6 530	At 8 wks By 1 y
Acar et al[10]	2015	Cross-sectional prem < 32 wks	Turkey	470	590 ± 58		Ultrasonic pachymetry
Karahan et al[8]	2015	Cross-sectional prem vs term	Turkey		576 ± 16	562 ± 18	$P = .001$
Ozdemir et al[14]	2014	Cross-sectional comparing ROP vs non-ROP	Turkey	187	559 ± 42		No difference in CCT
Gunay et al[9]	2014	Cross-sectional prem on days 1–2	Turkey	100	647 ± 64		
Muslubas et al[5]	2014	Cross-sectional 45 prem vs 45 term	Turkey	45	600 ± 50	586 ± 48	$P = .7$ (NS)
Rushood et al[15]	2012	Cross-sectional 100 term (Saudi)	Saudi Arabia	0		616 ± 61	
Uva et al[6]	2011	Cross-sectional prem (33) vs full term	Italy	33	599 ± 36	576 ± 26	$P < .001$
De Silva et al[16]	2011	Longitudinal prem at birth, 28, 42	Italy	56	794	559 by term	
Kirwan et al[3]	2005	Longitudinal from 31 wks till term	Ireland	35	691	564	
Remon et al[17]	1992	Cross-sectional 152 term babies at days 1–6	Spain	0		585 ± 52	
Portellinha and Belfort[18]	1991	Cross-sectional 74 term babies	Brazil	0		573 ± 52	
Autzen and Bjornstrom[19]	1991	Longitudinal at 1 and 3 wk postnatal	Denmark	13			
Autzen and Bjornstrom[20]	1989	Cross-sectional 30 term babies	Denmark	0		581 ± 47	

CCT and horizontal corneal diameter (HCD). Possible effects of birth parameters and perinatal factors were also examined. Normative data are needed to allow comparative assessment of corneal parameters and IOP particularly for each population as racial variations may occur.

2. Materials and methods

A prospective case series study was conducted. A consecutive cohort of premature infants admitted to the neonatal intensive care unit at the University Malaya Medical Center, Kuala Lumpur from January 1, 2012 to December 31, 2013 was included. Infants were recruited from the retinopathy of prematurity (ROP) screening program if they fulfilled the inclusion and exclusion criteria. Inclusion criteria based on local ROP screening criteria were: infants with a gestational age of 32 weeks or less, birth weight of 1500 g or less, and with an oxygen requirement of 1 month or longer or a duration of ventilation of at least 7 days regardless of the birth weight or gestation criteria. Eyes with other ocular disorders including cataracts, corneal opacity, increased corneal diameter (>10.0 mm) as this is the average diameter for a full-term infant with any larger values seen at term considered an abnormality, and a cup-disc ratio (CDR) >0.5 were excluded. Informed consent was obtained from parent/guardian of each subject and ethics approval was obtained from Hospital Ethics Board and the research adhered to the Tenets of the Declaration of Helsinki.

Both eyes of the premature infants were examined at 2 different time points, the 1st at "preterm" between age 4 to 6 weeks after birth (postconceptual age between 32 and 36 weeks) and the second at "term" (postconceptual age between 37 and 41 weeks). At each examination, the CCT, HCD, and IOP measurements were taken. Prior to routine ROP screening examination, CCT was measured with the handheld Pacscan 300P USP device (Sonomed Inc, Lake Success, NY) with a 45° angled probe held perpendicular to the corneal surface and an average of 10 readings taken by the 10 contacts and averaged by the probe. Castroviejo calipers, placed on the corneal limbus were used to measure the HCD in millimeters. Following instillation of 1 drop of Gutt Proparacaine HCL (ALCAINE Ophthalmic Solution 0.5%; Mississauga, Ontario, Alcon Canada Inc), a small infant speculum was inserted gently and lifted off the eyeball and when the infant was calm, IOP was measured with the rebound tonometer (iCare II, Helsinki, Finland). The average of 6 readings was given at the end of the examination. The rebound tonometer required contacts to be made on the corneal surface repeatedly to obtain the different readings. The CDR was assessed clinically independently by a masked observer from 2 RetCam II (Clarity

Table 2

Demographics data birth parameters on the preterm infants (n = 63) at enrolment and measured HCD, CCT, IOP, and CDR for left eye at preterm and at term.

	At birth, mean (SD, range)	Preterm (32–36 wks), mean (SD)	Term (37–41 wks)	*P*-value
Gestational age at birth, wks	29.9 (2.17, 23.9 – 35.6)			
Birth weight, g	1243.7 (308.9, 620.0 – 1980.0)			
Birth length, cm	37.5 (4.2, 29.0 – 47.0)			
Head circumference, cm	26.8 (2.4, 21.0 – 31.5)			
Central corneal thickness, μm (SD)		618.8 (72.9)	563.9 (50.7)	<.0001
HCD, mm (SD)		9.11 (0.66)	10.0 (0.52)	<.0001
IOP, mm Hg (SD)		12.87 (3.11)	14.15 (3.33)	.11
Vertical optic CDR (RETCA)		0.32 (0.12)	0.34 (0.13)	.40

CCT = central corneal thickness, CDR = cup-disc ratio, HCD = horizontal corneal diameter, IOP = intraocular pressure, SD = standard deviation.

Table 3

The changes in mean central corneal thickness (CCT), horizontal corneal diameter (HCD), and intraocular pressure (IOP) from preterm to term (n = 63).

Parameter	N	Mean (SD)	Magnitude of changes over time, SD range	*P*-value
CCT, mm	63	−56.49 (48.3)	+20.5 to −187.0	<.0001
HCD, mm	63	0.91 (0.62)	0–2.5	<.0001
IOP, mm Hg	63	0.84 (4.15)	−9.65 to +9.65	.11

Medical Systems, Pleasanton, CA) photographs using the calliper tool.

Routine birth parameter data and postnatal history were extracted from review of the clinical case notes and entered into a database designed for the study. Specifically, the presence of ROP, history of ventilation, oxygen therapy, occurrence of sepsis, and intracranial hemorrhage were noted. Right and left eyes were analyzed independently and statistical analysis undertaken with SAS version 9.3 (SAS Institute Inc, Cary, NC). A *P*-value of <.05 was considered statistically significant. The left eye values in all patients were used for statistical analysis and values were used to construct predictive models. Predictive models were constructed using regression model similar to Tucker et al.[22] These enable a normogram to be constructed for different ages.

3. Results

A total of 148 eyes from 74 infants were examined. A complete data set was obtained from 63 infants and these data were

Table 4

Spearman correlation coefficients (Rho) for birth parameters and age at time of examination with mean central corneal diameter, horizontal corneal diameter, and intraocular pressure (n = 63).

Parameter	Mean CCT		Mean HCD		Mean IOP	
time of examination	Preterm	Term	Preterm	Term	Preterm	Term
GA						
R	−0.34	−0.06	0.22	0.26	−0.19	−0.16
P	.005	.64	.08	.04	.14	.19
Age at time 1						
R	−0.42		0.62		−0.16	
P	.0005		.0001*		.18	
Age at time 2						
R		−0.10		0.35		−0.21
P		.43		.005		.11
Birth weight						
R	−0.37	−0.29	0.51	0.26	−0.18	−0.17
P	.003	.02	.0001*	.04	.15	.19
Birth length						
R	−0.42	−0.28	0.47	0.39	−0.05	−0.12
P	.007	.02	.0001*	.001	.71	.31
Head circumference						
R	−0.24	−0.13	0.50	0.27	−0.12	−0.10
P	.05	0.30	.0001*	.03	.34	.43
Mean CCT						
R	1.00	1.00	−0.30	−0.04	0.18	0.10
P			.016	.74	.16	.93
Mean HCD						
R	−0.30	−0.04	1.00	1.00	−0.14	−0.07
P	.016	.74			.28	.56
Mean IOP						
R	0.17	−0.01	−0.14	−0.07	1.00	1.00
P	.16	.94	.28	.56		

BL = birth length, BW = birth weight, CCT = central corneal thickness, GA = gestational age (weeks), HCD = horizontal corneal diameter, IOP = intraocular pressure, R = correlation.
R = Correlation which is moderate ($R \geq 0.5$) and strong ($R \geq 0.7$).
*Significant value.

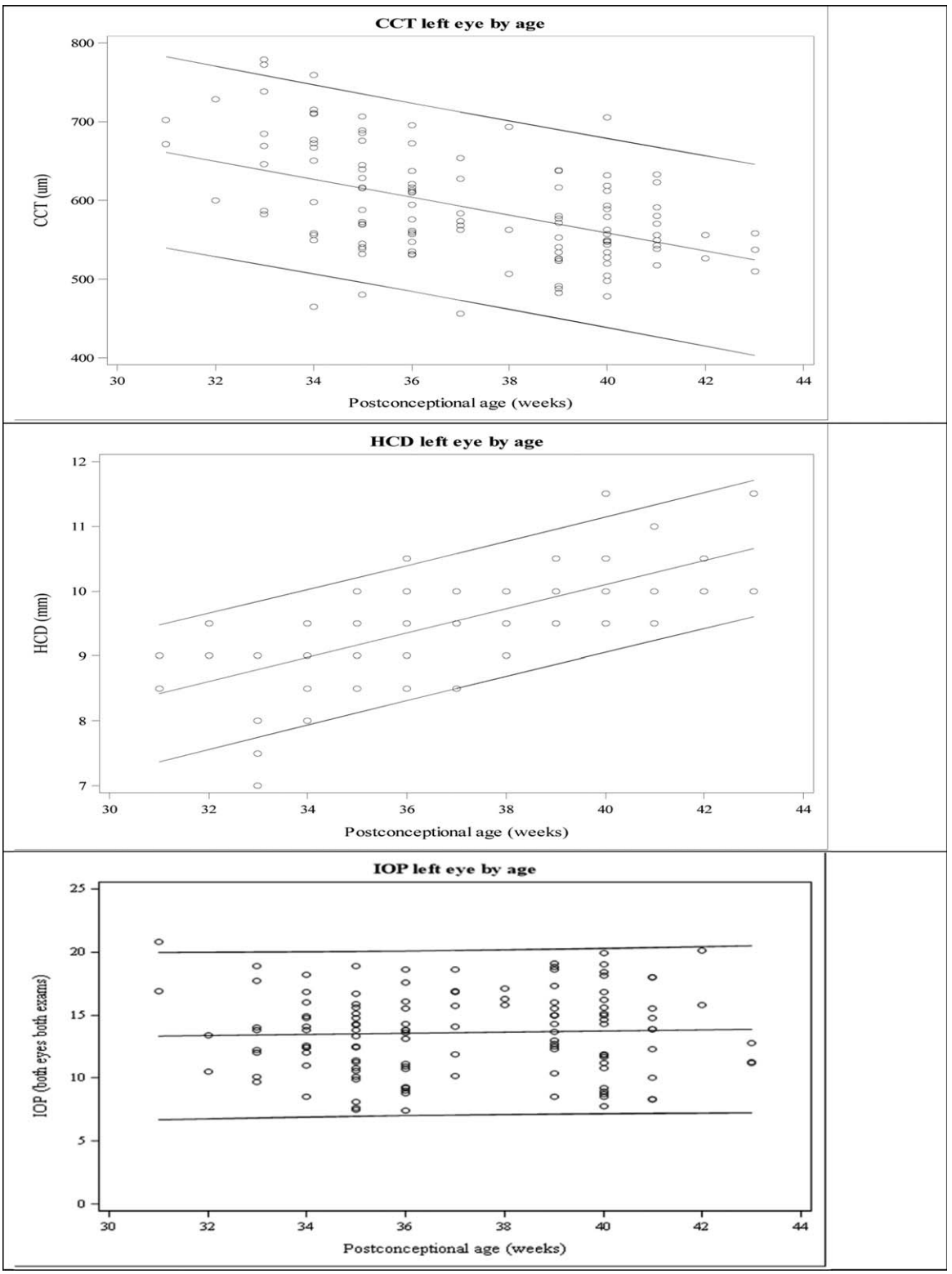

Figure 1. Scatterplots for central corneal thickness (CCT), horizontal corneal diameter (HCD), and intraocular pressure (IOP) from the study cohort of premature infants. Intraocular measure, IOP ($P = .67$) did not change significantly at different age but CCT and HCD were significantly ($P < .001$) correlated with postconceptional age (weeks). The 2 outer lines represent upper and lower limits of 95% confidence interval from the predicted value represented by the line in between the 2.

included for analysis as the remaining 11 infants did not have complete data. Demographic data and measurements for the HCD, CCT, IOP, and CDR for the right eye for the 63 infants analyzed are shown in Table 2 and the mean changes in Table 3.

In the analysis of correlation with birth factors (Table 4), a moderate positive correlation was found between HCD and birth weight ($\rho = 0.51$, $P < .0001$) and head circumference ($\rho = 0.50$, $P < .0001$). A weak negative correlation was found between CCT

and birth weight ($\rho = -0.35$, $P = .003$), birth length ($\rho = -0.42$, $P = .007$), and head circumference ($\rho = -0.24$, $P = .05$).

Predictive models for all the measured values were constructed from regression plots for our population of infants (Fig. 1). This model will be a useful guide to detect infants with abnormally high or low values. The HCD was calculated to increase at rate of 0.2 mm/wk ($R^2 = 0.52$, $P < .001$) and CCT decreased at rate of 11.4 μm/wk ($R^2 = 0.23$, $P < .001$).

4. Discussion

Premature infants are born with organ and tissues that have not had time to mature in their physiologic environment. Observational studies on premature infants[4,5,10,21] have found that they have thicker central corneas compared to adult corneas. In our cohort of premature infants, the mean HCD was 9.1 mm (standard deviation [SD] = 0.7 mm) at preterm and 10.0 mm (SD = 0.52 mm) at term. The mean CCT preterm was 618.8 μm (SD = 72.9) and at term 563.9 (SD = 50.7)μm, respectively. Both HCD ($P < .0001$) and CCT ($P < .0001$) changes occurred from preterm to term and these changes were significant. There were no significant changes in IOP and vertical CDR over both periods in the study.

The normal values for full-term infants may not be applicable to infants who are born prematurely. Acar et al[10] who compared 33 premature infants with 33 full-term infants found that CCT differed significantly between the 2 groups ($P < .001$). Various studies[2,3,5,9,10] on premature infant corneal thickness reported CCT values between 564 and 616 μm where the measurements were taken at different corrected age. This shows a need for a normogram (Fig. 1) for different populations of infants.

During maturation to term, a general trend toward thinner corneal thickness has been found although different methods of measurement were employed in these studies (pachymetry and ultrasound). We found a similar trend for each individual infant over the course of this study. To date, 6 longitudinal studies[3,7,13,16,19] have reported a range of mean values (Table 1). These differences may reflect the differences in racial groups as well as the mean gestational age of the infants in different cohorts.

The increased thickness of preterm corneas has been postulated to be due to on-going differentiation,[3] poor function of corneal endothelium that does not dehydrate effectively enough and the effects of mechanical ventilation and prolonged closure of eyelids.[23] Notably, the change in corneal thickness in our cohort was found to be insignificant in the ventilated group. Apart from presence of sepsis ($P = .009$), the other postnatal factors studied were also not significant. Birth parameters also did not influence corneal thickness change. CCT had a small negative correlation with HCD in this study ($R = -0.30$, $P = .016$).

In our cohort, variation in HCD and CCT was found to correlate with birth parameters. These findings are consistent with those from other studies. In this study, there was significant moderate ($r \geq 0.5$ positive correlation seen between HCD and age at 1st examination ($r = 0.62$), birth weight ($r = 0.51$), and head circumference ($r = 0.5$). Premature infants were found to have very rapid growth of the HCD over the observation period averaging 0.9 ± 0.6 mm over an average period of 5 weeks between the 4th week of life and term in our study. Throughout the period IOP did not change significantly (Fig. 1). The CDR was also observed to be minimally changed between the 2 time points. It can therefore be assumed that in this group of infants, the increase in HCD was attributable to growth of the infant, rather than changes in IOP.

The findings in our cohort revealed significant negative correlation was observed between CCT and gestational age, age at examination, birth weight, birth length, and head circumference which was weak (Table 4). In Muslubas' cohort, CCT changed with birth weight and gestational age.[5] However, Karahan et al[8] found that CCT did not correlate with gestational age or birth weight in their cross-sectional study. The CCT in Sekeroglu et al[13] was negatively correlated with gestational age and birth weight. Ng et al[24] was the only other study that found strong negative association between IOP and postconceptive age, head circumference, body weight, and body length. As only 1 study did not find any negative correlation,[8] it is probable that CCT varies with birth parameter and decreases over time as the infant develops to term. These could be attributed to improved corneal endothelial function to maintain corneal deturgescence and the remodeling of corneal collagen.

Corneal thickness has been associated with glaucoma risk[25] in adults. A thin cornea may result in underestimation of the actual IOP measured by the Goldmann applanation tonometer. However, these differences may not apply to infants as these indentation tonometers (Goldmann applanation tonometer and Perkins tonometer) were not used in the measurements of IOP in premature infants due to the small palpebral apertures at this young age as well as the difficulty in setting up the infant to a slit-lamp microscope. Different instruments produced differing results. Only 1 study on infants, Uva et al[6] found that the main factor affecting IOP readings was CCT.

Karahan et al's[8] comparative study on premature and full-term infant CCT, IOP was not correlated in premature infants. Earlier reports in 1980 to 1990, Autzen and Bjornstrom[19,20] and Portellinha and Belfort[18] also did not find any significant correlation between IOP with age or birth weight in their sample of full-term and premature infants. This was also seen in our cohort. From the study result shown, it can be observed that despite a significant change in CCT in our population, there was no significant change in the IOP measured with the rebound tonometer used (iCare II). Therefore, it can be safely assumed that there is no need to measure CCT when taking IOP measurements in premature infants using this instrument.

The predictive model constructed with data from our cohort serves as a guide for these parameters which is similar to what Tucker et al demonstrated with their cohort of infants with combined data from both eyes, for corneal diameter. However, in our predictive model, we have included corneal thickness, IOP, and vertical corneal diameter for the local population.

The small sample size and limitation of measurements to 2 time points was a limitation of this study. Having a larger number of study patients may reveal more influence from postnatal factors on the differences of corneal parameters observed.

Author contributions

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