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On-Set of Cataract and Accumulation of Copper, Lead and Cadmium in Smokers of Karachi, Pakistan

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Abstract

Background: High prevalence of cataract especially in women, children and urban dwellers and associated blindness is a major problem of Pakistan and low and middle income countries. Prevalence of tobacco use is also very high in Pakistan. The aim of study was to identify association between cigarette smoking and development of cataract in people of Karachi and to determine effect of Lead, Cadmium and Copper in progression of Cataract

Material and methods: 100 Cataract Patients including Smokers and Non-Smokers visiting LRBT Hospital. Karachi was selected randomly. After Surgical Removal, their lenses were analyzed for Cadmium, Lead and Copper Concentration by Atomic Absorption Spectrometer at Pakistan Council of Scientific and Industrial Research

Results: Concentration of Cadmium, Lead and Copper were found to be significantly higher among Lenses of Smokers than Non-Smokers.

Conclusion: Cataract development occurred earlier in heavy smokers with mean age 48.24 years as compared to non-smokers mean age 55.72 years along-with increased accumulation of Cadmium, Lead and Copper in their lenses. The result shows an association between Cigarette Smoking and progression of Cataract

Keywords: Cigarette Smoking; Cataract; Tobacco; DNA; Cadmium

Introduction

Cataract is the major cause of visual impairment and blindness (about 42%) in the world which is the main cause of avoidable blindness [1]. 90% of cases belong to low and middle income countries including Pakistan [2]. Two third of blindness in the world is reported in women [3]. As the old people are increasing due to increased life expectancy number of blind and visually impaired are increasing due to cataract [4], resulting in social burden all over the world [5] especially in Pakistan. The aim of study was to see the relationship of metal toxicity with cataract which is causing blindness in people of Karachi, Pakistan. These people are mostly poor, uneducated and have a lack of access to proper health facilities and affordability.

Prevalence of lens opacity is 20% among adult population of Pakistan [6]. In India the number of people developing cataract are estimated to be 8.25 million by year 2020 [7]. Safe surgical techniques are available which can restore vision. In Pakistan cataract surgery rate was estimated to be 2400/million population per year which is far less than developed countries. Women, uneducated and rural dwellers have decrease access to cataract surgery. Secondly they are not given proper information about the condition [8]. If the miseries cannot be prevented can some of them be delayed so that they may not appear in the life of the individual. Cataract is one of the examples.

Studies have suggested that cigarette smoking is a risk factor for nuclear cataract [9,10], which is the most common type in South Asia [11,12]. Several studies have also established association between cigarette smoking and cataract [9,13-19]. Cigarette smokers are more at risk for developing cataract at an earlier age than nonsmokers [18,19].

Cigarette is composed of tobacco, paper, additives and filter. Approximately 600-1400 additives are used in cigarette manufacturing [20]. Toxic metals are found in cigarettes which cannot be metabolized in humans and have bio-accumulative ability. Metal contents in tobacco depend on soil of agriculture land [21], and its nearby source of contamination [22]. It also depends on how tobacco is being processed [23]. The concentrations of toxic metals, cadmium, lead and copper found in different brands of the world were 1.76-3.20 µg/gm (Mean: 2.71 µg/gm), lead 1.05-3.10 µg/gm (Mean: 2.07 µg/gm) and copper 5.18-17.6 µg/g respectively (Mean: 9.70 µg/gm) [24].

Two types of cells are found in humans and vertebrate lenses. A single layer of cuboidal epithelial cells are present anteriorly which is the only site of lenticular cell division. The lens fiber cells lie posteriorly [25], which lack mitochondria [26]. Nutrients and metabolites reach these fiber cells via gap junctions [27]. The lens has no blood vessels and is multicellular. Aqueous humor is a clear fluid and function like blood for the avascular structures i.e. lens and cornea [28,29]. With the help of active transport anions, cations & other molecules reach aqueous humor against concentration gradient across blood aqueous barrier [30]. Protein transporters help in this process present in cell membrane [31]. A complex network of gap junctions mostly of connexin46 and connex in 50 is essential for normal survival of lens. Any change in these channels may lead to decrease or modified communications [32,33]. Concentration of protein in human eye lens is 400 mg/ml, the major part of it are crystalline which are water soluble [34-36]. Small heat shock proteins are important chaperones found in human lens especially alpha –B crystalline and alpha-A crystallines. Chaperones help in folding of long chains of amino acids and thus prevent aggregation of protein [37], Both crystalline are important for lens transparency [38,39] and survival of lens [40].

The C-terminal extension of Alpha B crystalline is responsible for recognizing & selecting of unfolded protein substrate. Removal of C-terminal extension in Alpha B crystalline reduces the chaperone

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activity. In alpha-A crystalline C terminal hinge loop is flexible & takes part in zinc binding [41]. In most of the ocular diseases including cataract, oxidative stress and metabolites of polyunsaturated fatty acids play a major role [42]. Oxidative stress leads to lipid peroxidation, protein denaturation, damage to DNA and mitochondria [43,44]. Antioxidants help in removing free radicals and try to maintain cell function [43,45,46]. Toxicity of metals is mainly due to generation of reactive oxygen & nitrogen species (oxidative stress). These metals may combine with enzymes & proteins having thiol groups. Several antioxidant enzymes contain sulfhydryl groups at their active site. Metals inactive these site due to binding with sulfhydryl group. Heavy metals compete with other metals for same binding sites [47]. Even heavy metals can replace already bound metals and thus their concentrations increases in eye [48], Once heavy metals bound it becomes difficult to displace them [49]. Increased rate of telomere shortening in human lens cells due to oxidative stress and per oxidative damage to lens cell membranes results in lipid peroxidation, which are the triggering mechanism of cataractogenesis [50].

Cadmium is known to cause its deleterious effects by deactivating DNA repair activity [51]. Cigarette smoking results in 50% increase in oxidative DNA damage in smokers as seen by increase in excretion of DNA repair product 8-Hydroxydeoxyguanosine in urine [52].

Present work was intended to find out association of cigarettes smoking (air pollution) & accumulation of bivalent metal ions in Lens of Human's eye resulting in opacification of lens (cataract). The study was conducted in Karachi which is the largest city of Pakistan having a population of more than 18 million. Prevalence of tobacco use in the forms of cigarettes, cigars, home rolled tobacco leaves called berri and lime mixed tobacco and additives called gutka is very high, approximately 40% of adult population of Karachi. No such study determining the prevalence and association of cigarette smoking with cataract has been carried out in Karachi.

Materials and Methods

Cross Sectional study design was selected because of convenience and practicality as it is difficult to follow up individual patient and chances of drop out were high. Selection of samples was carried out from the Out Patient Department (OPD) of Layton Rahmatullah Benevolent Trust (LRBT) Hospital after taking permission from ethical committee. The hospital is highly reputable charity based and is serving the people for decades and is being visited by patients from all over Karachi and Sindh. The research work was done at the Institute of Environmental Sciences, University of Karachi. Laboratory analysis was done at Pakistan Council of Scientific and Industrial Research (PCSIR).

Random sampling method was used. A total of 100 patients were selected for the study after a detailed interview using validated questionnaire about their personal data & health, residence & its surrounding environment & smoking habits, general physical and ophthalmic examination and blood glucose analysis to assess their eligibility based on inclusion and exclusion criteria. As far as it could be ascertained no one selected were occupationally exposed to metals. Socio-economic status of patient could not be determined as most of the patients were uneducated, daily wages workers and reluctant to answer questions regarding financial conditions. 75 patients having nuclear cataract with the history of heavy smoking for the last 20 years were selected. They were categorized into two groups in accordance to avoid recall bias (Half to One Pack i.e. 10-20 cigarettes/day & One or more Pack i.e. >20 cigarettes/day), Similarly 25 patients having cataract but no history of cigarette smoking or tobacco chewing were selected as control. Out of 100 cataract patients 70 were male and 30 were female. Every patient was explained about the study and its usefulness. They were also assured that their participation has nothing to do with their line of management and surgical procedure and their extracted lenses were otherwise going to be discarded. The confidentiality of their particulars was also assured. Those who agreed a written consent was taken.

Lens samples were collected by Extra Capsular Cataract Extraction (ECCE) surgical technique. Lens samples were collected in sterilized glass bottles which were washed with nitric acid and then by deionized water. The weights were carefully recorded & then specimens were stored at -20°C till analyzed.

In the Lens sample bottle 3 ml of 65 % Conc. Nitric Acid HNO_3 was added and left for 30 minutes at ambient temperature. The digested lens material was transferred into a 50 ml beaker. In the sample bottle 2 ml conc. Nitric Acid was again added to remove any leftover & transferred to the beaker. The sample was heated on a hot plate (sand bath) and temperature was gradually increased to 140°C until decomposition was completed and the mixture was almost dry. The decomposed sample was cooled to ambient temperature. 3-5 ml deionized water was added to beaker and beaker was shaken well to dissolve the decomposed material of lens and then transferred to 25 ml calibrated volumetric Flask. The beaker was again rinsed twice with 10 ml deionized water & then transferred to the volumetric flask. Deionized water was added to the volumetric flask to make it 25 ml, and then used for metal analysis by spectroscopic analysis. Blank samples were also prepared by similar method under identical conditions. Blanks were used to eliminate any possible contamination due to digestion process. The prepared samples of lenses were analyzed for Cadmium, Lead and Copper. Hitachi Atomic Absorption Spectrophotometer (Z-8000) with Zeeman Effect back ground correction was used for analysis equipped with a graphite furnace, a microprocessor and a built in printer.

Results

Table 1 shows socio-demographic characteristics of study participants. Mean age of data set was 50.11 with SD 4.32 ±. More than half (56%) were in 40-50 year age group. Nearly three quarter (70%) of participants was male and smoker (75%). Among smokers nearly half (40%) were smoking cigarettes more than 20 cigarettes daily.

Table 2 shows concentrations (ppm) of Cu, Cd, and Pb in lenses of study participants in relation with age, sex and frequency of cigarette smoking. Mean concentration of copper, cadmium and lead level were higher in age group of 40-50 years. Mean concentration of copper, lead and cadmium level were higher in male, the mean concentration of these elements was also higher among those smoking more than 20 cigarettes/day.

Table 3 shows mean and standard deviation of Cu, Cd and Pb, levels in smokers and non-smokers lenses of study participants. Among smoker, mean concentrations of lead, cadmium and copper were 2.74, 0.11 and 2.74 µg/gm of wet tissue weight respectively. Among non-smokers mean concentration of lead, cadmium and copper were 0.65, 0.11 and 0.96 µg/gm of wet tissue respectively.

To establish, whether difference of metal concentration was statistically significant, Independent Sample T-Test was conducted on SPSS. Reason of choosing Independent T-Test was the parametric versus continuous nature of Data (Smoker / Non-Smoker versus Metal Concentration) and relative robustness of the test.

Comparing mean concentration of lead, it was found that a statistically significant difference of lead concentration was found between smokers and non-smokers with t=8.395 and p-value to be

0.000 lower than 0.05 (95% Confidence Interval) as shown in Table 4 (extracted from SPSS)

Again comparing mean concentration of cadmium, it was found that a statistically significant difference of cadmium concentration was found between smokers and non-smokers with t = 6.58 and p-value to be 0.000 lower than 0.05 (95% Confidence Interval) as shown in Table 5 (extracted from SPSS)

Lastly comparing mean concentration of copper, it was found that a statistically significant difference of copper concentration was found between smokers and non-smokers with t = 4.726 and p-value to be 0.000 lower than 0.05 (95% Confidence Interval) as shown in Table 6 (extracted from SPSS)

Table 7 shows difference between mean ages of cataract development in smokers and non-smokers. Nuclear Cataract Development was seen at an earlier age in smokers (Mean: 48.24 years) while at a lower age in Non-Smokers (Mean: 55.72 years)

Characteristics	Percentages (%)
Mean Age (years)(SD) Age (Years)	
40-50	56
51-60	44
Gender	
Male	70
Female	30
Smoking Status	
Smoker	75
Non-Smoker	25
Frequency of Smoking(n=75)	
10-20 cigarette/day	60
> 20 cigarette /day	40

Table 1: Socio-demographic characteristics of study participants.

Characteristics Age(years)	Copper (Cu) mean(SD) ppm	Lead (Pb) mean(SD) ppm	Cadmium (Cd) mean(SD) ppm
40-50 (n=56)	2.06(1.82)	2.84(2.40)	0.11(0.14)
51-60(n=44)	1.40(1.46)	1.43(1.07)	0.05(0.092)
Gender			
Male(n=70)	2.06(1.89)	2.66(2.28)	0.11(0.14)
Female(n=30)	1.08(0.77)	1.2(0.63)	0.03(0.03)
Frequency of cigarettes smoking			
10-20 cigarettes/day (n=45)	1.47(1.06)	1.79(0.43)	0.06(0.08)
More than 20 cigarettes/day (n=30)	2.89(2.45)	4.17(2.76)	0.19(0.16)

Table 2: Cu, Pb and Cd Concentrations (mean & SD) in ppm with respect of age, gender and frequency of cigarette smoking

Groups	Lead mean (SD)	Cadmium mean (SD)	Copper mean (SD)
	(Lens) µ g/gm.	(Lens) µ g/gm	(Lens) µ g/gm
Groups 1 Smoker (n=75)	2.74 ± 2.12	0.11 ± 0.13	2.04 ± 1.87
Groups 2 Non-Smoker (n=25)	0.65 ± 0.23	0.01 ± 0.00	0.96 ± 0.33

Table 3: Cu, Pb and Cd concentration (mean & SD) in smokers and non-smokers of study participants (ug/gm of tissue weight)

		Levene's Test for Equality of Variances		t-test for Equality of Means		
		F	Sig.	t	df	Sig. (2-tailed)
Pb ug/gm	Equal variances assumed	8.876	.004	4.911	98	.000
	Equal variances not assumed			8.395	79.332	.000

Table 4: Result of Independent Sample T-Test for Lead Concentration

		Levene's Test for Equality of Variances		t-test for Equality of Means		
		F	Sig.	t	df	Sig. (2-tailed)
Cd ug/gm	Equal variances assumed	24.951	.000	3.825	97	.000
	Equal variances not assumed			6.580	74.148	.000

Table 5: Result of Independent Sample T-Test for Cadmium Concentration

		Levene's Test for Equality of Variances		t-test for Equality of Means		
		F	Sig.	t	df	Sig. (2-tailed)
Cu ug/gm	Equal variances assumed	13.995	.000	2.833	98	.006
	Equal variances not assumed			4.726	86.565	.000

Table 6: Result of Independent Sample T-Test for Cadmium Concentration

	Minimum	Maximum	Mean	Std. Deviation
Smokers	40	60	48.24	3.705
Non-Smokers	47	60	55.72	3.208

Table 7: Descriptive Statistics of Age in Smoker and Non-Smokers

Discussion

Study data reveals the potential role of cigarette smoking in the development of cigarette smoking in the development of cataract. The smokers are increasing in developing countries as in Pakistan especially among women and children [53]. Two thirds of blindness cases in the world is reported in women [3], as women stay most of the time at home in Pakistan, smoking will lead to health problems in infants and children due to passive smoking [54,55].

Cigarette smoke is composed of toxic substances like toxic aldehydes, aromatic hydrocarbons, nitrosamines, benzopyrenes and free radicals. A single puff of cigarette smoke contains 1014 free radicals of low molecular weight [55-57], Smoking causes deposition of many metals in human tissues and lead to harmful effects even at lower levels [58]. Elinder et al. [59] reported 1.76 µgm Cd/cigarette and Friberg et al. [60] reported 1.56-1.96 µgm Cd/cigarette. They mentioned two reasons for high level of Cd in tissues of smokers. Firstly Cd level is high in cigarettes as compared to food. Secondly absorption of Cd is much higher from respiratory tract (25-50%) when inhaled as compared to gastrointestinal tract (1-10%) when ingested with food as a contaminant. Metals after being absorbed from respiratory tract reaches the blood and then into the aqueous humor against concentration gradient across blood aqueous barrier [30] as

they are bio accumulative and non-degradable they start depositing in tissues due to long half-life like cadmium 10-30 years [61].

This active transport is the main mechanism of aqueous humor formation [62] and this process along with protein transporters move the cations/metals into the aqueous humour. No mechanism exist for regulation of concentration of toxic divalent metals like cadmium & lead in cells as seen for essential metals and they bind with Divalent Cation transporter-1 to reach cell by hindering essential metal transport into cell [63], In this way these toxic metal concentration increases in human eye including lens [64]. Aqueous humor passes through the lens because of presence of a large number of Jap Junctions [65], these junctions establish cellular communication between adjacent cells and are formed by Connexin Hemichannels [66]. These hemichannels have regulated gating mechanism which is essential for cell survival [67]. Important Lens Fiber Connexin is CX43, CX46 and CX50 [68].

Connexin protein Alpha l (Connexin 46) are necessary for keeping the lens transparent and Connexin protein alpha 8 (Connexin 50) is important for transparency & growth of Lens [69], so if the metals are responsible for any structural or functional abnormality in Connexin hemichannels then they have an association in decrease in lens transparency and lens growth. Cigarette Smoking also by increasing the intraocular pressure may help in increased deposition of metals in aqueous humour & in lens [70]. Metals decreases Connexin proteins [67] and produces oxidative stress by producing reactive radicals which can affect Connexin protein [71]. Cadmium at a very low concentration 50-100 nM affect the sulfhydryl group of hemichannel opening, causing narrowing & even closure of hemichannels [67] It also decreases the number of gap Junctions in each cell [72], These structural and functional changes of Connexin hemichannel will impair transfer of antioxidant enzymes to reach nuclear region of lens thus decreasing antioxidant level and retention of toxic metabolites causing oxidative damage [65,73]. Even mutations can occur in Connexin like in Connexin 50 (W45 S and G46 V) affecting hemichannels and cell viability of lens [74]. Cadmium is a known carcinogen and may be responsible for such mutations. The disturbances in hemichannels also decrease the transport of antioxidants like reduced glutathione into the center (nucleus) affecting lens transparency and flexibility [75].

Lens contains antioxidant enzymes [76-78] Now the question is does smoking Cigarettes have any role in producing an imbalance in the above system. Metals present in Cigarette are responsible for producing reactive oxygen species [79,80]. As metals have a long half-life deposition in tissues occur [61] the radicals produced can cause peroxidation of Lipids, biomolecules degradation and breakup of DNA strand [81]. Cumulative damage to mitochondria can occur due to oxidative damage which is important for providing energy and cell survival [82], these metals can directly bind to antioxidant enzymes like Glutathione & increases their inactivated form to get deposited in lens [83]. Metals combine with protein and enzymes having thiol group impairing their function directly and also indirectly as antioxidant enzymes such as reduced Glutathione, which keeps thiol groups in reduced form responsible for transparency of lens [84]. Decrease level of antioxidant enzymes lead to oxidative damage to lens epithelial cells even at low concentration affecting Na/K ATPase, Cytoskeletal proteins & membrane permeability [85] and even lead to apoptosis [86]. The decrease antioxidant enzymes also make Lens epithelia vulnerable to damaging effect of transforming Growth Factor –beta (TGF-beta) [87]. Metals also inactivate several antioxidant enzymes by binding with sulfhydryl group which is their active site.

The C-terminal extension of Alpha B crystallines is responsible for recognizing & selecting of unfolded protein substrate. Removal of C-terminal extension in Alpha B crystalline reduces the chaperone activity. When proteins develop damage, Alpha crystalline binds to them. A fixed amount of Alpha Crystalline is present in humans at birth, so if they reduce due to smoking cataract can develop. In alpha-A crystalline C terminal hinge loop is flexible & takes part in zinc binding. Cu, Cd & Pb can replace Zn From the hinge region & cause impaired Flexibility [41].

Epithelial cell abnormalities were also observed in lenses when cultured in lead for short term. Significant changes were multiple layering of epithelial cells and nuclei abnormalities. Changes in structural proteins of lens were observed when further exposed to oxidative stress; leading to opacification [87], Cadmium gets deposited in lens and decreases the viability of lens epithelial cells. This is also indicated by increase in apoptic cells. LDH (lactic dehydrogenase) releases from HLECs (Human Lenticular epithelial cells) which is related to the amount of cadmium. Cadmium increases oxidative stress, peroxidation of lipids and MAPK pathway activation. α-Tocopherol and N-acetylcysteine decreases toxicity of cadmium in HLECs [88].

Except eye whole human body has skin layer for heat regulation of body. Even weak heat exposure makes it susceptible to potential damage. Only sclera and retina has blood flow. One possible role of aqueous humor dynamics and heat regulation of eye contributing in development of lens opacity could be as mentioned below. Aqueous humor produced by ciliary processes enters the posterior chamber circulates around the lens and reaches the anterior chamber via pupil and also passes through the lens via gap junctions as seen in lens circulation model. The temperature of eye is highest posteriorly, 36.8°C in retina and gradually decreases anteriorly. Cornea is the least warm part of eye, 33.3°C. Aqueous humor circulation in human eye transfer heat from inner eye to the corneal surface heating the cornea Without aqueous humor circulation temperature of cornea is lower (33.3°C) as compared to with aqueous humor circulation (33.73°C) [89]. While aqueous humor passes through lens it is a suggested that transfer of heat to lens takes place, then this absorbed heat helps in producing convection current transferring heat from lens to cornea. Corneal surface losses heat to ambient air mainly by evaporation and by convection and irradiation. Metals present in aqueous humor by absorbing infra-red radiation achieve a higher energy level which augments the metal binding with protein leading to structural and functional changes in lens especially in gap junctions obstructing aqueous humor flow through lens and this may further increase the temperature of lens (especially the posterior and nuclear region) and anterior chamber. Stagnation of aqueous humor flow increases oxidative stress and radical formation augmenting the protein denaturation [90], as the lens loses the role of heat transfer from retina to cornea; it develops opacity to minimize damage to retina due to effect of Infra-red radiations. D L Epstein et al. [91], studied the effect of cataractous lens protein on aqueous humor dynamics. They observed a 68% decrease in outflow when they perfused the anterior chamber with 1% of homogenate of cataractous lens as compared to lens homogenate. This is indicative of that cataractous lens proteins can obstruct aqueous outflow pathways. This obstruction was partly relieved by normal saline and chymotrypsin. Cumming RG et al. [92], conducted Blue Mountain Eye Study. In this study they used a detailed questionnaire taking smoking history of 3654 participants. They also took the photographs of their lenses to categorize them according to different types of lens opacities. They found that nuclear and post subcapsular cataract was more common in smokers. Hiller R et al [93], also found a positive association of developing nuclear cataract with

cigarette smoking similar to this result they found that risk of cataract increases with increasing number of cigarettes smoked daily. Erie JC et al [94], measured the concentration of heavy metals in 30 eyes of 16 human subjects with an aim to establish a reference range. The analysis was done by Mass Spectrometry. The mean concentration of lead and cadmium in lens were found to be 13 ± 18 ng/g and 20 ± 18 ng/g of dry weight respectively. Ragab et al. [95], found significantly higher level of lead in early onset cataract (51-60%) as compared to late onset cataract. The result of my study shows that the smokers developed nuclear cataract at an earlier age (mean age 48.24 years) than the non-smokers (mean age 55.72 years) and the lead level is significantly higher in smokers than non-smokers. Debra A. Schaumberg et al [96], although in their cohort study looked for Lead level in tibia & patellar bone & in blood but also followed ophthalmic examination of participants and they found higher Lead level as a risk Factor for Cataract. R Neal et al. [97], also found in their study that exposure of Lead in rats resulted in changes in crystalline of lens resulting in lens opacity. The study also supports the results of this study as higher Lead level was found in smokers lens than non-smokers and smokers had a mean age of cataract less than the non-smokers. Graziano et al [98], found that tobacco exposure affect almost all macromolecules related to structure and/or function of cell due to Oxidative damage. The study is also supportive of the result of this study as the onset of cataract is earlier in smokers and weight of lens is also lesser in smokers. Smokers had a mean age of cataract less than the non-smokers. Nazar S. Haddad et al [99], also found 50% higher level of lead in smoker's lens (1.5 µg/g of lens) as compared to non-smokers (1µg/g of lens). I found much higher level of lead (2.74 µg/g) in smokers than non-smokers (0.65 µg/g). This could be because of differences in quality of tobacco & additives used in the two different areas & also because of environmental exposure. Osman Cekicet 1998 [100], in their study looking for Cu, Cd & Pb deposition in lenses of smokers & non-smokers found significantly higher levels of all three metals in smokers than non-smokers.

The results suggest that smoking has an association with early cataract development in smokers of Karachi.

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