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Full Length Research Paper

Morphological and Biochemical Study of Cataractous Nucleus in Diabetics versus Non-diabetics

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Abstract

The number of people with diabetes mellitus is increasing in developing countries and cataracts is the most common causes of blindness in these subjects. Whereas mechanisms related to glucose toxicity contribute significantly to the development of the eye complications under conditions of diabetes, which accumulate sorbitol that leads to osmotic changes resulting in cataract formation. The objective of this investigational study is to determine the relevance of the human lens induction elements in early cataract formation in Sudanese diabetics compared them to non-diabetics at morphological and biochemical level. Sixty cataractous lenses of 60 patients were collected from the operation rooms immediately after Extracapsular cataract extraction sugary with intraocular lens (EECCE+IOL). The colours of the specimens observed and coded. Measurements; including diameter and thickness of the lenses were done under the surgical microscope. The collected lenses were put in small containers with potassium fluoride, phosphate buffer solution with formalin and kept at 4°C. Biochemical studies were done using the enzymatic determination method. Four colour were detected; light yellow, dark yellow, light brown and dark brown. The light yellow colour found in 16.7% of diabetics and 10.0% of non-diabetics at 50 and 60 years of age. The dark yellow colour (16.7%) and the light brown (46.7%) were equal in both diabetics and non diabetics, in patients at 70 and 80 years of age. The dark brown colour was more in non-diabetics (26.7%) than diabetics (20.0%) at 80-90 at 80and 90 years of age. There were slight differences in the diameter and thickness between diabetics and non-diabetics; 8.02-7.97mm diameter and 4.2-4.4mm thickness. There were some differences of lenticular glucose and protein concentrations between the diabetic and non-diabetics (21.2-12.30mg/dl glucose`s) and (1.77g/l-1.56g/l protein`s) respectively. There was a positive correlation between size, colour and age of the catractous lens. Poorly controlled blood sugar in diabetics accelerates the premature lens opacification, so improved diabetic control may reduce the risk of developing lens opacities especially in young.

Keywords: Extracapsular cataract extraction, phosphate buffer solution, glucose, protein, sorbitol

INTRODUCTION

Diabetes Mellitus (DM) is a national and global crisis (Globalization of Diabetes, 2011) with a fast growing public health and economic burden across the world; "diabetes epidemic" (Wild et al., 2004) due to population

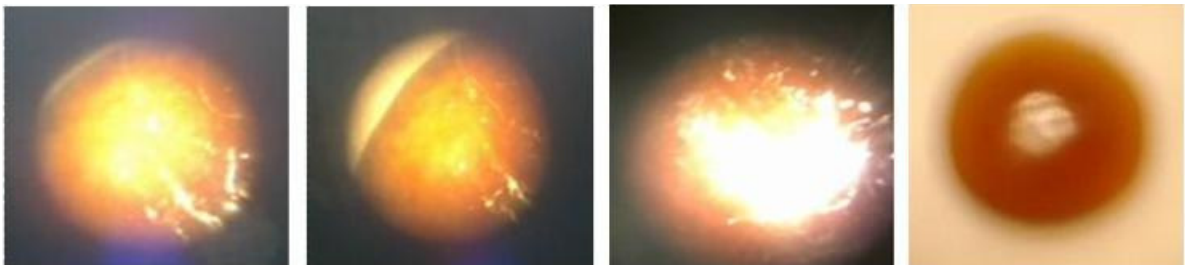

Figure 1. Fresh Enucleated Catractous Lenses

growth, aging and urbanization. The world prevalence of DM for all age-groups worldwide in 2000 was estimated to be 2.8%, but among adults (aged 20–79 years) was 6.4%, affected 285 million, and will increase to 7.7% and 439 million adults by the year 2030. Between 2010 and 2030, there will be a 69% increase in numbers of adults with diabetes in developing countries and a 20% increase in developed countries (Shaw et al., 2010).

The prevalence of adult DM in Sudan was reported in late 1990s to be 3.4% (men, 3.5%; women, 3.4%) (Elbagir et al., 1999; Elbagir et al., 1996); the crude nowadays estimation can reach 5.8%. The Insulin Dependent DM being 31.4% and the None Insulin Dependent DM being 68.6% (Elbagir et al., 1998).

Loss of vision due to cataract formation of the crystalline lens may be the commonest complications of DM apart from diabetic retinopathy; *WHO:* (*Diabetes mellitus; Fact sheet N°138*) and considered a major cause of avoidable visual impairment in diabetic patients (Harding et al., 1993; Kahn et al., 1977; Raman et al., 2010). Many studies have documented an association between diabetes and cataract.The incidence of this diabetic cataract may reach 10.4% (Janghorbani et al., 2000).

MATERIALS AND METHODS

Sixty enucleated catractous lenses of 60 patients who are diagnosed with cataract and planned for Extracapsular cataract extraction sugary with intraocular lens (EECCE+IOL)) were collected along with a detailed case history; then studied morphometricly and biochemically. Half of them from MEC Hospital in Khartoum and the other half from Alwaledain Hospital in Omdorman (Sudan).Thirty of these patients were diabetic (cases) and the other thirty were non-diabetic (controls). (Figure 1)

The extracted lenses were collected from the operation theatre, immediately after extracted from the patients. Then delicately washed with distilled water and the colours of the nuclei were to be observed and graded into four colour grades: Grade 1:light yellow, Grade 2:dark yellow, Grade 3.light brown and Grade 4:dark brown; according to CCRG (Cooperative Catar-act Research Group of America) colour-coding of nuclei (Chylack et al., 1984).

Then the “X-Y” (two different meridians; vertical and horizontal) diameters and the thickness of the lenses were to be measured by Castroviejo Eye Caliper under the operating microscope. Then each nucleolus was to be put in a separate container which contains potassium florid, which was mixed with few milliliters of tissue fixative solution (Formalin, Buffered phosphate hypotonic solution) and preserved at 4℃ temperature. The collected material was studied in “Al Nelain Research Center” and the biochemistry department of the faculty of medicine at Al Nelain University in Khartoum.

Laboratory procedure

Glucose and protein was detected using the enzymatic determination method. Each nucleolus was crushed using glasses rods, 20 µl of the sample were added to 1ml of the protein reagent tube.10 µl of the sample were added to 1ml of the glucose reagent tube. Blank tube, standard tube and the samples were measured using the digital photocolorimeter. The concentration of the sample was calculated by the use of the “concentration of the standard” equation (sample/standard). The result of glucose concentration measured in mg/dl. The results were grouped in intervals 0f 10:- “Group1: 0- 9 mg/dl”, “Group2: 10-19mg/dl”, “Group3: 20-29mg/dl”, “Group4: 30-39mg/dl”, “Group5: 40-49mg/dl”, “Group6: 50-59mg/dl” and “Group7: 60-69mg/dl”. The data was analyzed by Statistical Package for Social Sciences (SPSS) program version 20.

RESULTS

In this cross sectional study; sixty Sudanese patients (n=60); with significantly low visual acuity (6/24 to HM) due to dense cataracts; were examined (Table 1). 34(56.7%) of them were males and 26 (43.3%) were females (Table 2, Figure 2). 30 patients (50%) had diabetes mellitus; the mean duration of their diabetes was 7±1 years; and the other 30 (50%) were non-diabetics. The mean age of the diabetic patients was 61±10 while the mean age of the non-diabetics was 73±10 years. The

Table 1. Diabetics and non-diabetics Visual Acuity

Target eye	Diabetics		Non-diabetics	
	Frequency	Percentage%	Frequency	Percentage%
HM	12	40.0	13	43.3
CF	6	20.0	2	6.7
< 6/25	1	3.3	0	0
< 6/60	9	30.0	12	40.0
PL	2	6.7	3	10.0
Total	30	100.0	30	100.0

Table 2. Gender of Diabetics and Non-diabetics

Gender	Diabetics	Non-diabetics	Total
Males	15 (50%)	19 (63.3%)	34 (56.7%)
Female	15 (50%)	11(63.7%)	26 (43.3%)
Total	30 (100%)	30 (100%)	60 (100%)

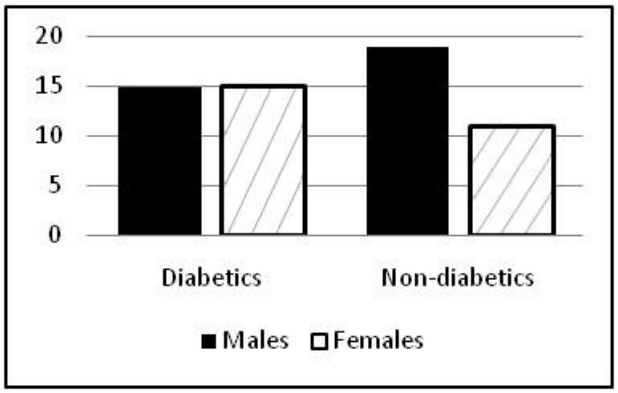

Figure 2. Gender of Diabetics and Non-diabetics

Table 3. Frequency of Cataract vs Age of Diabetics and Non-Diabetic

Age in years	Diabetics		Non-diabetics	
	Frequency	Percentage	Frequency	Percentage%
30 - 39	2	6. 7 %	0	0.0 %
40 - 49	2	6. 7 %	0	0.0 %
50 - 59	8	26. 7 %	1	3.3 %
60 - 69	9	29.9 %	8	26.7 %
70 - 79	8	26.7 %	15	50.0 %
80 - 89	1	3.3 %	6	20.0 %
Total	30	100 %	30	100 %

age of the diabetic patients who developed significant cataract was found to be less than non-diabetic patients by more than one decade (12 years) (Table 3).

10% of the diabetic group has type 1 DM and 90% with type II DM (Table 4). The majority of these diabetics (63.3%) had poor control while only (36.7%) were of reasonably good control (Figure 3).

Only 63.3% of the diabetics were using diabetic's medications (40% on insulin, 23.3% on oral hypoglycaemic drugs and the rest (36.7%) were on no regular treatment (Table 5). Male to Female ratio was 1:1in diabetics and 1:1.3 in non-diabetics (Table 2, Figure1).

In respect to the types of cataract, in the diabetics; posterior sub capsular was more frequent (36.7 %) followed by nuclear sclerotic type (26 %) then the mixed type (23.3%) and the least one is the cortical cataract (13.3%),while the nuclear type is more in non-diabetic patients, which was 40% and then posterior subcapsular

Table 4. Type of diabetes

Type of DM	Frequency	Percentage %
Type 1	3	10%
Type II	27	90%
Total	30	100%

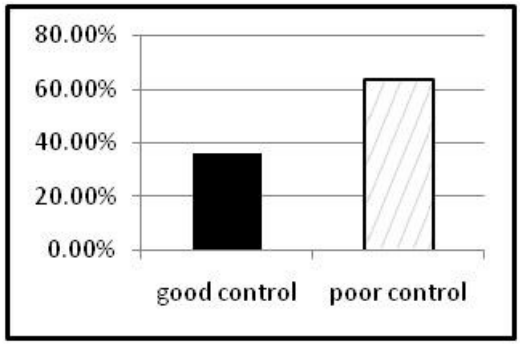

Figure 3. Diabetic control

Table 5. Diabetic`s Medication

Medication	Frequency	Percentage %
Oral hypoglycaemic agent	12	40%
Insulin	7	23.3%
No treatment	11	36.7%
Total	30	100%

Table 6. Type of Cataract in Diabetics and Non-Diabetic

Type of cataract	Diabetics	Non-diabetics
Posterior subcapsular	36.7 %	26.7 %
nuclear	26 %	40%
mixed	23.3%	26.7 %
cortical	13.3%	6.7%

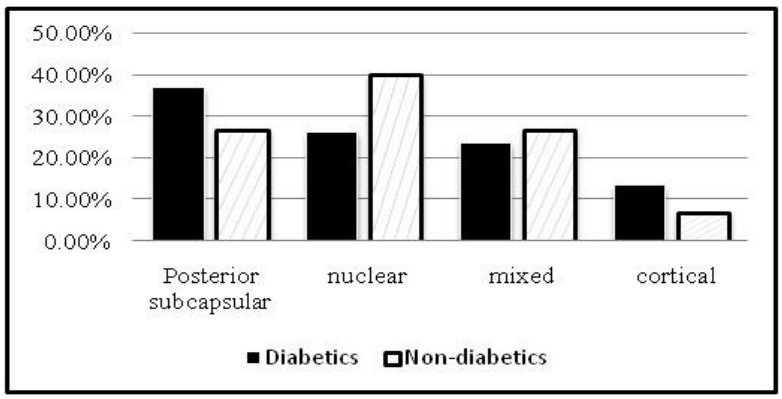

Figure 4. Type of Cataract in Diabetics and Non-Diabetic

(26.7 %), mixed (26.7 %) and cortical cataract (6.7%) (Table 6, Figure 4).

Regarding the colour`s grades of the enucleated cataractus lenses; and the relationship between these

Table 7. Colour grades of the enucleated catractous lenses vs age

Colour grades	Age in years	Diabetic	Non-diabetic
light yellow	50-60	16.7%	10.0%
dark yellow	60-70	16.7%	16.7%
light brown	60-80	46.7%	46.7%
dark brown	80-90	20.0%	26.7%

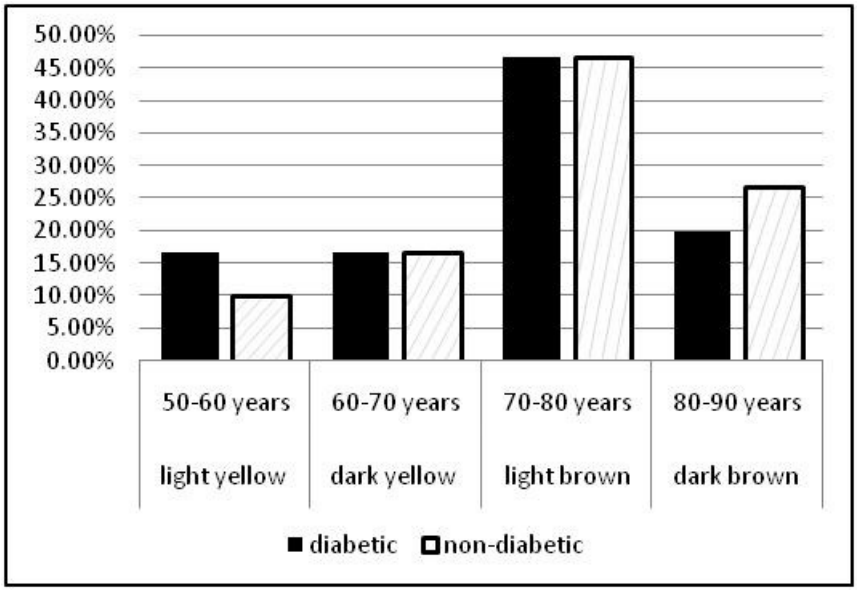

Figure 5. Colour grades of the enucleated catractous lenses vs age

Table 8. Diameter of the cataractus nucleus in Diabetics and Non-Diabetic

Diameter mm	Diabetics		Non-diabetics	
	Frequency	Percentage	Frequency	Percentage
6.5 - 6.9	3	10	2	6.7
7 - 7.4	2	6.7	3	10
7.5 - 7.9	7	23.3	8	26.7
8 - 8.4	5	16.7	6	20
8.5-8.9	7	23.3	6	20
9 - 9.4	4	13.3	4	13.3
9.5 9.9	2	6.7	1	3.3
Total	30	100	30	100

Diabetics mean = 0.81 ± 0.8 Non-diabetics mean = 0.75837 ± 0.75837

colour`s grades and the age in all patients (diabetics and non-diabetics) (Table 7, Figure 5) show that the light yellow colour (grades1) which represent 16.7% in diabetic and 10.0% in non-diabetics was found among patients who were between 50 and 60 years of age. The dark yellow colour (grades 2) found to be equal in both diabetics and non diabetics; 16.7% each; among patients who were between 60 and 70 years of age. The light brown (Grade3) found to be equal in both diabetics and non diabetics; 46.7% each; which it was common among patients who were between 70 and 80 years of age. The dark brown colour (grades 4) was more in non-diabetics (26.7%) than diabetics (20.0%) at the age between 80-90.

The mean diameter of the extracted nuclei in diabetic was 8.02mm and in non-diabetic was 7.97mm, and their mean thickness in diabetics was 4.2mm and in non-diabetics was 4.4mm (Table 8).

The readings of glucose concentration were high in diabetics (mean concentration of 21.24 mg/dl) than in non-diabetics (mean concentration of 12.30mg/dl), which is statistically significant. Most of non-diabetics had low glucose concentration in the first three degrees of reported glucose concentration; 0-9, 10-19, 20-29 mg/dl,

Table 9. Glucose Concentration of the cataractus nucleus in Diabetics and Non-Diabetic

Glucose concentration mg/dl	Diabetics		Non-diabetics	
	Frequency	Percentage	Frequency	Percentage
0-9	3	10	17	56.7
10-19	5	16.7	7	23.3
20-29	4	13.3	6	20
30-39	6	20	0	0
40-49	4	13.3	0	0
50-59	1	3.3	0	0
60-69	7	23.3	0	0
Total	30	100	30	100

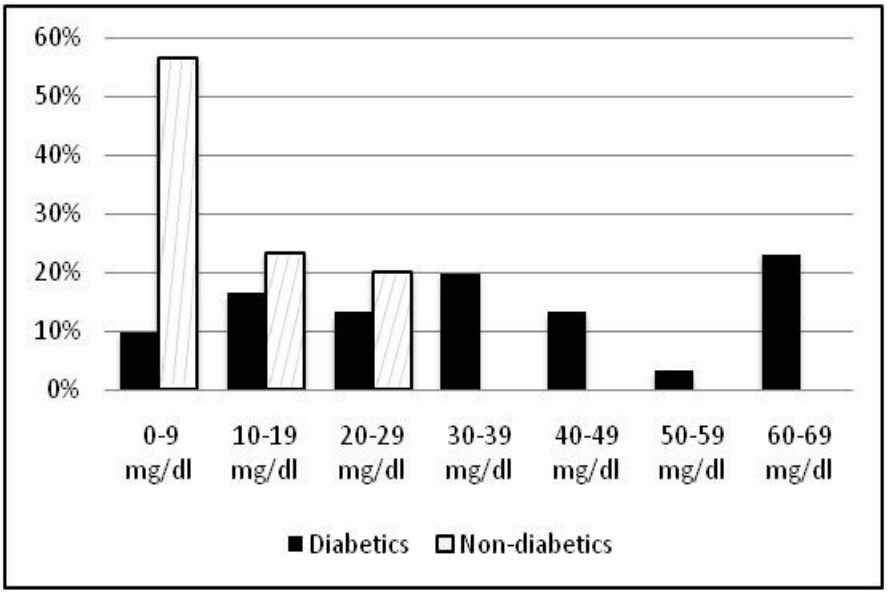

Figure 6. Glucose Concentration of the cataractus nucleus in Diabetics and Non-Diabetic

Table 10. Protein Concentration of Diabetics and Non-Diabetic

Protein concentration g/dl	Diabetics		Non-diabetics	
	Frequency	Percentage	Frequency	Percentage
0.1-0.5	2	6.7%	4	13.3%
0.6-1.0	6	20.0%	8	26.7%
1.1-1.5	7	23.3%	4	13.3%
1.6-2.0	8	26.7%	5	16.7%
2.1-2.5	3	10.0%	4	13.3%
2.6-3.0	4	13.3%	2	6.7%
3.1-3.5	0	0%	3	10.0%
Total	30	100%	30	100%

especially in the very low category (0-9 mg/dl glucose concentration: 56.7%). Glucose was detected in all nuclei of the diabetic patients (Table 9), and the maximum concentration was found in those nuclei from older patients (60-69 years; 23.3%). There was a positive relationship between the glucose concentration in the diabetics and their age.

The mean protein concentration of the cataractus nuclei in diabetics was 1.77g/l and in the non-diabetics was 1.56g/l; there were slight differences between each group, but statistically were not significant (Table 10, Figure 6, Figure 7).

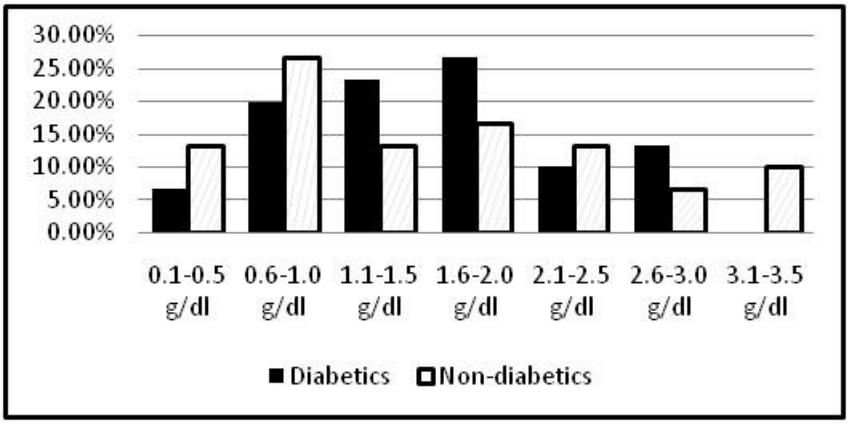

Figure 7. Protein Concentration of Diabetics and Non-Diabetic

DISCUSSION

The crystalline lens is one of the components of ocular refractive media which transmit and refract light. It is the only component whose refractive power can be varied, and many morphological, metabolic and biochemical changes take place in the human lens throughout life; increase in size, weight, hardness and biochemical constituents (Smith, 1992; Martin, 1993; Spector et al., 1978). The lens reacts for any pathological insult by losing its transparency, which has been attributed to a very complex biological arrangement both at microscopic and molecular levels (Taylor et al., 1996) and to be cataractous. Therefore cataract can be defined as an opacification or loss of transparency in the crystalline lens of the eye (Shaikh and Janjua, 1997).

Diabetes mellitus is associated with a 5-fold higher prevalence of cataracts (Obrosova et al., 2010; Zatechka et al., 2003). Cataracts can be an uncommon initial manifestation of type 1 diabetes mellitus (Uspal and Schapiro, 2011), and suddenly developing bilateral cataracts can be the first unusual manifestation of any type of diabetes mellitus (Uspal and Schapiro, 2011). The pathogenesis of diabetic cataract development is still not fully understood (Pollreisz and Schmidt-Erfurth, 2010), although being one of the major causes of blindness in developed and developing countries (Albulescu and Zolog, 2011). The morphological and biochemical investigational studies of cataractous lens get less interest among resent young researchers, however they are very important to know the relevance elements that induce cataract formation; especially early cataract formation in diabetics.

Recent basic research studies have emphasized the role of the polyol (sorbitol-aldose reductase) pathway in the initiation of the diabetic cataract process (Albulescu and Zolog, 2011; Brownlee, 2001) and the important contribution of increased the Aldose Reductase enzyme activity (Obrosova et al., 2010; Zhu, 2013; Brogard et al., 1992). Early anti-hyperglycemic therapy and maintenance of stable blood glucose level may reverse acute diabetic cataract (Beyer-Mears and Cruz, 1985) or prevent it from getting worse (Jin et al., 2012) by improving the distorted lens hydration done by the rapid changes in blood sugar (Butler, 1994; Bettelheim et al., 1998).

Researchers commented on the role of the oxidative damage and modifications of the lens crystallins proteins (Bloemendal et al., 2004) *(alpha-, beta- and gamma-crystallins)* and glycation proteins as being associated with lens aging and earlier diabetic cataract formation (Liu et al., 2005; Boscia et al., 2000; Pokupec et al., 2003; Dhar et al., 2002; Lyons et al., 1991). Anathanaryanan JPH (2004, India) documented a significantly higher glycation levels in hypermature senile cataract (Anathanaryanan, 2004).

The lenticular proteins during the path of their above modification processes showed increased colouration effects due to increased crystallin protein pigmentation; this is what responsible for the decrease of blue colour sensation in older people; a phenomena known as “Blue-deprivation” (Spector, Roy and Stauffer,1975).

To our knowledge this investigational study is first one of its type in Sudan. It revealed insignificant difference in sex between diabetics and non- diabetics patients (Table 2, Figure1). The significant diabetic cataracts that warrant surgery found early in the 4th decade (age 30-40) and increase with age (Table 3). In the current study; the mean age of the diabetic cataract patients was found to be 61±10 which was identical with the Indian “Sankara Nethralaya, 2010” study by Raman and his colleagues (Janghorbani et al., 2000) and higher than Janghorbani (Nottingham, 2000) group, which showed a mean age of 49.2years (Chylack et al., 1984). The mean age of the non-diabetics cataracts patients was 73±10 years. This point clearly showed the deference in the two groups; between the early onset of cataract in diabetic patients and late onset in non-diabetic cataracts ones.

In the present work, in which most of the diabetic patients were poorly controlled (63.3%); by taking in-

proper diabetic medication or none; the risk for diabetic cataract was more (Table 5, Figure 2), a fact which found to be in agreement with the old oxford-Pirie`s study (1965) (Pirie Epidemiological and Biochemical Studies of Cataract and Diabetes, 1965), Patterson`s experimental research (1952) (Patterson, 1952) and fairly recent (2010) Indian-Raman`s work (Janghorbani et al., 2000).

All types of cataract (nuclear, cortical, posterior subcapsular and mixed cataracts) were found in both in diabetic and non-diabetics, with the subcapsular cataract being more frequent in diabetics and nuclear cataract in non- diabetics (Table 6, Figure 3). This finding was in agreement with the Beaver Dam Eye Study (Klein et al., 1998) and Blue Mountains Eye Study which shown that Posterior subcapsular cataract was to be statistically significantly associated with diabetes (Mitchell et al., 2003). The nuclear cataracts were more frequent in older non-diabetic patients an observation which is in agreement with Leske (USA) study that showed the incidence of nuclear opacities greatly correlated with older ages (senile cataract) (Leske et al., 2002). Our results were in disagreement with the "American Cooperative Cataract Research Group (CCRG) Classification of human senile cataractous changes" (Chylack et al., 1984), which showed the preponderance of mixed cataracts and the relative scarcity of other pure cataracts like the nuclear one.

We adopted deferent and easy "colour coding*"* system for the lenses than that found in the literature (creamy, yellow, honey and brown (Dorairaj et al., 2002); as these previous grades were a pit confusing. Our results demonstrated that the dark yellow (16.7%) and the light brown (46.7%) cataract colours were found to be equal in both diabetics and non diabetics among patients between 60-80 years; 60-70years as dark yellow and 70-80 as light brown. There was relationship between cataract colour and the age; this study demonstrated that the deepening of the colour took place with increased age regardless the presence or absence of DM. The dominancy of the deepest colour "dark brown" among non-diabetics (26.7%) over diabetics (20.0%) at the higher ages showed that this is a trend of senile cataracts (80-90 years) rather than diabetic effect on the cataractous lens (Figure 4). This strengthens the above observation; relationship between colour and age, which was in strong agreement with (Dorairaj et al., 2002). In younger diabetics patients (age: 50-60 years) the light yellow colour of the catraactous lens was predominant (16.7%) than the non-diabetics (10.0%) (Table 7, Figure 4); this observation was in agreement with Lurze and Dresnick (1991) comment.

This current investigational study demonstrated a slight non-significant deference between the mean diameter of the extracted nucleus in diabetics (8.02 mm) and non-diabetics (7.97mm). Also this comment was applicable to the mean thickness of the extracted nuclei in both above groups; as we also demonstrated slight non-significant deference between the mean thickness of the extracted nuclei in diabetics and non-diabetics; 4.2 mm and 4.4 mm respectively. These measurements were within the range of the measurements found by Dorairaj and colleagues (8.5 mm mean diameter and 4.5; mm mean thickness) (Dorairaj et al., 2002; Huntjens and O'Donnell, 2006). Although these measurements were slightly non-significant but still give the impression that the diabetic nuclei are slightly bigger than the non-diabetics; in agreement with the comments by Huntjens (2006), Brown-Hungerford (1982) and Huggert (1953). The Japanese data by Ayaki and his group (1993) reported very low figures; 6.51 mm mean diameter and 2.96 mm mean thickness (Ayaki et al., 1993). No clear explanation of these Ayaki`s low figures, although both study sample sizes were near to each other, except if there is any ethnic variations.

In this current biochemical part of the study we demonstrated the presence of glucose in all diabetic`s nuclei with a mean concentration of 21.24mg/dl and in non-diabetics the mean concentration was 12.30mg/dl. This observation was in agreement with Pirie`s who noticed higher levels of sorbitol, glucose, and fructose in the diabetic cataractous lenses than that of a non-diabetics (Pirie Epidemiological and Biochemical Studies of Cataract and Diabetes, 1965), Quite possible parallel to the high levels of glucose concentrate in the aqueous humour of the diabetics (Davies et al., 1984). To note that; although sorbitol detection may be of value in the formation of diabetic cataracts than glucose, we could not assess sorbitol levels due to some logistic problems as there was shortage in supplying the 'sorbitol detection reagent'. According to Yoshikka (Japan), "the content of glucose correlated positively with that of sorbitol"; this comment strengthens our glucose result (Yoshioka et al., 1991).

This study showed slightly high level (12%) in proteins concentration in diabetic cataract lenses than in non-diabetics, as the mean concentration of this lenticular protein in diabetics was 1.77g/l and the mean concentration in non-diabetics was 1.56g/l. Zhu and colleagues documented even higher level of proteins in diabetics and little higher in age-related cataract lenses than non- diabetics (Zhu et al., 2013). This in contrary to (Anthrayose and Shashidhar, 2004), (Agarwal et al., 1976) and (Bagchi, 1959) results who showed a reduction in the total protein concentration in senile and diabetic cataract as compared to normal lenses.

CONCLUSION

Diabetes Mellitus activates some biochemical oxidative stress substances like glucose and proteins that early compromise the transparency and measurements of the crystalline lens in younger persons, similar to ageing process. Those with poorly controlled diabetes are more

likely to have a diabetic cataract, a process which can be reversible in early stage by restricted diabetic control.

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Disclaimers

The authors hold no financial or conflict of interest.

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