Review Paper

The Pathogenesis of Index Myopia in Hyperglycemia in Type 2 Diabetes: A Review

ABSTRACT

Elevated blood glucose or hyperglycemia occasioned by Diabetes Mellitus (DM), compromises the index of refraction of the crystalline lens, due to the osmotic difference between the lens materials and the aqueous medium of the anterior chamber of the eye. Under this circumstance there is a movement of fluid to either direction depending on the concentration gradient in both media. When there is movement out of the lens, into the aqueous, the refractive index of the lens increases, and this situation also causes a sudden change in the refractive power of the lens, leading to index myopia, while a decrease leads to index hyperopia. However, the induced myopia from this sudden fluctuation in the refractive power of the crystalline lens reverses shortly after a prolonged treatment and control of the hyperglycemia, with a combination of hypoglycemic drugs and diet therapy by the physician. The Issuance of spectacle prescription during these fluctuations is suspended until reversal.

Key words:

Aqueous humor; Crystalline lens; Diabetes mellitus; Hyperglycemia; Index myopia; Index hyperopia; Refractive index.

ABBREVIATIONS:

DKA: Diabetic ketoacidosis.

DM: Diabetic mellitus.

mg/dL: Milligrams per deciliter.

1.0. INTRODUCTION:

The aim of this paper is to review the scientific literature relating to refractive changes in index myopia, associated with hyperglycemia in DM and to appraise its significance and implications to the practice of optometry.

According to American Diabetes Association (2014) [1], Hyperglycemia is technically high blood glucose, which happens when the body has too little insulin or when the body can't use insulin properly. It is a serious health problem for diabetics, although one may or may not be diabetic to have hyperglycemia. There are two types of hyperglycemia: fasting and postprandial hyperglycemia. Hyperglycemia can also lead to diabetic ketoacidosis (DKA) or hyperglycemic hyperosmolar

nonketotic syndrome. There are a variety of causes of hyperglycemia in people with diabetes [2]. Upward variation in blood sugar could result, due to hyperglycemia or DM. In fasting blood sugar, a range between 100 – 126 milligrams/deciliter (mg/dL) is considered hyperglycemia; if it's chronically elevated above a certain level above 126mg/dl for a fasting sugar, then it is diabetes [1].

Diabetes is a group of metabolic and systemic diseases in which a person develops hyperglycemia (elevated blood sugar), either because the body does not produce enough insulin, or because cells do not respond to the insulin that is produced [3]. According to the American Diabetes Association recent position statement "Diagnosis and Classification of Diabetes Mellitus", DM is clinically divided into two major types; Type 1 (formally termed insulin-dependent) and Type 2 (formally termed non-insulin dependent) [4]. Others are Gestational diabetes and specific types of diabetes due to other causes, e.g., monogenic diabetes syndromes, diseases of the exocrine pancreas, and drug or chemical-induced diabetes [4]. The classification system went on to include evidence that DM was an etiologically and clinically heterogeneously group of disorders that share hyperglycemia in common [4]. Type 1 DM is the direct consequence of irreversible pancreatic beta-cell destruction in an autoimmune attack by the body, leading to complete dependence on insulin created externally from the patient. Although common in children and young adult may occur at any age [5]. The traditional paradigms of type 2 diabetes occurring only in adults and in type 1 diabetes only in children are no longer accurate, as both diseases occur in both cohorts. Occasionally, patients with type 2 diabetes may present with (DKA) [6]. Children with type 1 diabetes typically present with the hallmark symptoms of acute polydipsia (excessive thirst), polyuria (increase in urine volume and frequency) polyphagia (excessive hunger), weight loss [7], and approximately one-third with DKA.

Type 2 diabetes, previously referred to as "non–insulin-dependent diabetes" or "adult-onset diabetes," encompasses individuals who have insulin resistance and usually relative (rather than absolute) insulin deficiency. Type 2 DM is the most common form of DM [8], it is insidious in onset, and asymptomatic [4]. The main causes of Type 2 DM are a reduction in insulin secretion, a resistance to insulin action or a combination of both [8, 4], and the relative contribution of these two factors varies among patients [8]. It is suggested that insulin resistance occurs as a result of altered mitochondrial function through the electron transport chain [9]. The development of type 2 DM, though with unknown specific etiology, is characterized by a progressive deterioration of glucose tolerance over several years and its pathogenesis is by 4 major metabolic abnormalities: obesity with some degree of insulin resistance, impaired insulin action, insulin secretory dysfunction and increased endogenous glucose output. Commonly, the age of onset for Type 2 DM occurs in the middle age group. This group may not require insulin treatment to survive initially, and often throughout their lifetime [4]. Thus, insulin secretion is defective in these patients and insufficient to compensate for insulin resistance, which may improve with weight reduction and/or pharmacological treatment of hyperglycemia, but is seldom restored to normal. Type 2 diabetes is often associated with a strong genetic influence within the family lineage.

DM affects several organs of the body as well as the oculo-visual apparatus of the eye in several forms. It is a leading cause of visual impairment and blindness [10]. These include Diabetic retinopathy, macula edema, diabetic cataract, glaucoma, extra-ocular muscle palsy and iris changes [10, 11]. There are also, optic neuropathy, iridocyclitis, rubeosis iridis etc, in juvenile diabetes [12]. In uncontrolled diabetes, a general fluctuation in vision could be experienced. The nature of fluctuation depends on the status of the underlying DM and the ocular structure involved. It has long been known that patients suffering from DM may experience transient visual blur. This is usually caused by changes in their refraction [13], although neural factors may also be involved [14]. Blurred vision due to a variation in blood glucose, is a well-known complication of diabetes mellitus. It has been suggested that the predominant cause of refractive changes during hyperglycemia is a change in the shape and/or the refractive index of the lens [15]. Then further documentation showed that

fluctuations in refractive power often accompany changing blood glucose levels [15,16,17]; however, the nature and the aetiology of refractive fluctuations in DM is poorly understood.

There is an alteration of the refractive systems, in form of index myopia. It is an induced or acquired refractive error which occurs due to sudden changes in the refractive index of the intraocular lens. Investigators have observed myopic [16] refractive shift in diabetic patients, which have been related to changing plasma glucose concentration. If undiagnosed, or in a state of hyperglycemia, it could become more myopic [13]. Index myopia is the temporary or transient myopia in hyperglycemia, mostly in type 2 DM. It is a sudden shift in the refractive condition of the eye from emmetropia or hyperopia towards myopia, induced by a change in the refractive index of the crystalline lens, due to DM, as the major underlying etiology [18]. However, it has been suggested that after treatment of the dysregulated DM, the refraction will change towards more hyperopia or less myopia [19].

Other types of induced myopia could result from the exposure to various pharmaceutical agents, transient myopic shift induced by inflammation and inflammatory diseases [20], transient myopia following (blunt) trauma, transient myopia in systemic tuberculosis [21] and other anomalous conditions [22. Another lens complication that is related to DM is the early development of cataract, which is associated with index or transient myopia, present as juvenile cataract. It is the true diabetic cataract or snowflake cataract [23]. It consists of widespread bilateral subcapsular lens opacities of abrupt onset and acute progression, affecting the anterior and posterior cortical layer of the lens, typically in young people with uncontrolled diabetes mellitus. This is rare and may be initial presentation of diabetes [24]. Age-related cataract (nuclear, cortical, and posterior sub-capsular cataract) presents as nuclear sclerosis of the crystalline lens, or other anomalous conditions which induces the most common form of index myopia. This is probably caused by changes (increase) in symmetrical refractive index within the nucleus of the crystalline lens, causing negative spherical aberration and a myopic shift occurring in old people [25]. Studies suggest that approximately half of patients with nuclear cataract have a significant myopic shift and a quarter of patients with cortical cataract have a significant astigmatic shift. Given the high prevalence of age-related cataract, the refractive error induced by a nuclear and cortical cataract is likely to be a major cause of the uncorrected refractive error in the elderly [26]. The change in the refractive index of the lens in the aged, with a slight swelling, is accountable for the cases of so-called second sight. Index myopia of the lens in the aged, however, as it is well known, is usually followed in a short time by formation of a cataract, so that second sight, as a rule, ends in no sight at all. There are a few rare exceptions to this rule, where the second sight is retained for years. Myopia in the aged, as a result of the increase in the refractive index of the lens, may be of rather large amount, Landesberg having reported as high as 10D. Fuchs 9D, Herrnheiser 7D, Weeks 6D, while many other cases of lesser amount have been recorded [27].

Patients with induced myopia report blurred distance vision [28]. The time course of the distance blur depends upon the agent or the condition that has induced the myopia. Whether other symptoms are present depends upon the cause of the induced myopia. Although this condition is often temporary and reversible, the treatment depends upon the causative agent. This treatment may involve preventing future exposure to the agent, (example in cholinergic pharmaceutical agent-induced myopia), referral to an appropriate practitioner for additional testing and treatment, (like in refractive shifts thought to be due to changes in blood glucose level or nuclear sclerosis of the lens that has advanced to a stage indicating cataract extraction) or other treatment appropriate for the particular causative agent [28].

2.0. LITERATURE REVIEW

2.1. Epidemiology

The prevalence of DM in people over the age of 20 years globally was estimated to be 171 million during the year 2000, and was projected to rise by almost three-fold in the year 2030, due to

population growth, increased life expectancy and altered diets and living [18]. Type 2 diabetes accounts for 90–95% of all diabetes [4]. This is an indication that the number of diabetic patients attending optometric clinic is also likely to increase significantly over the next two decades. Acute hyperglycemia is associated with myopic refraction, but refraction becomes less myopic (or even hyperopic) with lowering in the levels of glycemia [17]. Myopia declines somewhat in population over age 45 years, reaching an average of about 20 percent in 65 year olds and decreasing to as low as an average of about 14 percent of persons in their seventies, from the Beaver Dam, the Baltimore and the Framingham Offspring Eye Studies [29]. This pattern of change shows that the prevalence of myopia appears to decrease because of an intrinsic age-related decrease in the amount of an individual's myopia rather than because of a cohort effect of increasing prevalence over time [29].

Documentations indicated that fluctuations in refractive power often accompany changing blood glucose [15, 17]. Epidemiological studies (Barbados Eye Study and Los Angeles Latino Eye Study) revealed that DM was an independent risk factor for the development of moderate myopia (> -3 D) [30] and low-grade myopia (< -1 D) [31]. Poor metabolic control of DM has also been suggested as a risk factor for myopia [32]. In contrast, in other population studies (Beaver Dam Eye Study, a rural South Indian population) the presence of DM was related to an increased shift towards hyperopia

In a population of adults aged 16-66 years, Fledelius [34] found that the frequency of myopia among diabetes and non-diabetic Danish adults, showed a significantly higher prevalence of myopia among diabetic compared to non-diabetic subjects (38% in diabetics versus 27.5% in non-diabetics). In a further study of metabolically stable diabetics and controls, 40% of the diabetics and 22% of the non-diabetics had myopia, with an onset after the age of 20 years [35]. The mean refractive values of the two groups of diabetic and non-diabetic myopic adults were –2.00D and –3.00D respectively, but late-onset myopia was more prevalent among diabetic patients (40.0% compared to 22.5% in non-diabetics) [35].

In the beginning of hyperglycemia, hyperopia occurrence is observed for a short time because of decrease in lens volume, and myopia occurs when lens volume starts to increase. When blood glucose level reduces rapidly, hyperopia is seen related with decrease in lens thickness and refractive index. After regulation of blood glucose level, lens thickness decreases and hyperopia is seen [15]. Surface curvatures are greater in eyes of diabetics than in normal, but the equivalent refractive index is lower so that lenticular powers are similar [36]. Furthermore, DM was not associated with a shift in ocular refraction in other epidemiological studies (Andhra Pradesh Eye Disease Study, Blue Mountains Eye Study) [37].

2.2. Pathophysiology

The nature and the etiology of refractive fluctuations in DM is poorly understood. However, several authors have advanced several factors and mechanisms. The composition of the aqueous humor depends on the nature of the freshly secreted fluid, the subsequent passive and active solute exchanges across adjacent tissues, and the rate of exit from the eye [38]. The metabolic requirements of tissues such as the cornea, lens, and trabecular meshwork are met by continuous flow of aqueous through the posterior and anterior chambers. Diffusional and metabolic alterations of the aqueous occur constantly. The lens alters the aqueous by using glucose, amino acid, and other solute; releases metabolic products such as lactic acid, and may act as a homeostatic reservoir for amino acid [38]. The glucose of the aqueous humor varies directly with the glucose of the blood. As the concentration of glucose in the aqueous humor increases, the glucose level within the crystalline lens also increases, because the intracellular glucose in the lens is not regulated by insulin [39]. The glucose in the lens is metabolized via the sorbitol pathway, which consists of two enzymes (aldose reductase and sorbitol dehydrogenase) which catalyze the conversion of glucose into its sugar alcohol sorbitol and the further conversion of sorbitol to fructose. These sugar alcohol tend to accumulate within the lens fibers, because they are membrane impermeable. Consequently, an

osmotic gradient between the hypertonic lens and the aqueous humor is built up, resulting in an influx of water from the aqueous humor, producing lenticular swelling. This may lead to a decrease in the radius of curvature and equivalent refractive index of the lens, resulting in changes in ocular refractive power [39,19].

In terms of osmolality, the aqueous humor in a number of mammalian species is slightly hyper osmotic to plasma [40]. The concentration of glucose in the aqueous is approximately 80% of that in the plasma. Glucose likely enters the aqueous by simple diffusion from the plasma. The alpha and gamma lens crystallins normally are present in small amounts in the aqueous humor of eyes with clear lenses. The concentration of these lens crystallins increases in eyes with cataract, consistent with the hypothesis that these proteins leak from the lens [41]. In the anterior chamber, a sudden change or alteration of the refractive index due to this glucose elevation, mostly affects the cornea, crystalline lens, and the aqueous humor. The interplay between the high concentration of sugar (hypertonicity) in the aqueous humor of the anterior chamber and the refractive index of the crystalline lens is a contributing factor to the cause of index myopia. When sudden myopia occurs in diabetes, the lens loses water because of the high level of blood sugar in the anterior chamber; therefore its index of refraction increases [42].

According to an early author Duke Elder [13], the refractive changes in diabetes were due to alterations in the power of the lens, because of osmotic interactions between the lens and aqueous. The mechanisms underlying changes in the shape of the lens with accompanying shifts in refractive power in myopia during hyperglycemia, may be due to the hydration of the lens due to salt retention, occasioned by osmotic changes [39]. However, the profound increase in lens dimensions with DM could be due to an accelerated growth of the lens, but it could also be caused by osmotic swelling of the lens, either as a result of an increase in cell membrane permeability or deficient ion pumping [39]. This laid credence therefore, that hyperglycemia could cause a change in the refractive index of the lens 17].

Later writers had suggested that intralenticular osmotic pressure increased during hyperglycemia, as glucose and its metabolic products especially those derived from the sorbitol pathway, accumulated within the lens [18]. The resultant influx of water has been used to explain either a myopic or a hyperopic change, according to whether shape or refractive index, was considered more important in determining overall refractive power [18]. Others are of the opinion that a myopic shift with decreasing blood glucose concentration in diabetes could be explained by the accumulation of metabolites such as sorbitol [39,43]. It has been suggested that the predominant cause of the refractive changes is a change in the thickness of the lens which promote myopic changes through increase in refractive power [43, 44] or shape of the lens, and/or a change in its refractive index [45]. It is often assumed that a change in the refractive index of the lens could play a role in explaining the refractive changes in patients with DM [45]; however Furushima et al [46], found an increase in lens thickness of 1 mm and a myopic shift of -2 diopters. Kato et al [45], reported a significant increase in lens thickness (0.3 mm) after rapid control of hyperglycemia. There seem to be no agreement on the exact cause of refractive change in unstable diabetes. In several studies that investigated the effect of hyperglycemia on refraction, it was reported that refractive changes in patients with chronic DM were caused by alterations in the lens [47], but the exact contribution of the cornea to these refractive changes is still unknown [47].

Index myopia occurs due to sudden changes in the refractive index of the lens. In uncontrolled diabetes, a general fluctuation in vision due to changes in refractive power of the lens by as much as 3 or 4 Diopters could be experienced, and this results in blurred vision. Such changes do not occur when the disease is well controlled. The blood glucose concentration is regulated within narrow limits in healthy individuals, but these limits are disrupted in patients with diabetes [48]. It is mostly witnessed in two pathologic states, diabetes and cataract. In diabetes the lens loses water because of

the high level of blood sugar in the anterior chamber, and therefore its index of refraction increases. In the cataract patient, the lens becomes increasingly hard because of the constant lamination of lens fibers being pushed to the center of the lens. The hard inner core increases the index of refraction of the entire lens structure, thereby increasing the converging power [42]. Myopic refractive shifts with changing blood glucose, could result from morphological changes in the cornea, crystalline lens, axial length or retinal thickness [15]. Index myopia may be caused by an increase in the refractive index of the cornea, aqueous, or the lens; or to a decrease in the refractive index of the vitreous [27]. Well authenticated cases of any considerable amount of myopia due to an increase in the refractive index of the aqueous humour have not been reported. Parsons [27], stated that to produce myopia of 1.50 D. to 2.0 D would require that the aqueous have an index equal to that of the cornea. "The myopia of diabetes cannot be explained by increase in the aqueous index. The aqueous would have to contain 20 percent of sugar in order that its refractive index is raised to that of the cornea, a result which would only cause myopia of 1.50 D in a previously emmetropic eye" [27].

Sudden changes in refraction are a well-recognized feature of hyperglycemia. These refractive changes tend to be of a low magnitude and present during adulthood. The development of refractive abnormalities in response to hyperglycemia is characterized by rapid onset, followed by prolonged regression [49]. In evaluating refractive disorders in patients with DM, Furushima [50], observed that the blood glucose returned to normalcy, with reversal of myopia towards hyperopia. Recovery of the refractive error back to baseline without any more fluctuation takes about approximately twice as long with oral hypoglycemic medication as with insulin [51]. This suggests that the hyperopia indicated a recovery of the myopic changes accompanying the reversal of hyperglycemia. A tendency towards myopia has always been associated with elevations in blood glucose [19]. From the summaries of the results of the three studies by Gwinup and Villareal, Furushima et-al and Steffes, it is perhaps surprising that cycloplegic refraction, results in such a large refractive change when insulin secretion was completely suppressed in these subjects, resulting in very high blood glucose levels as seen in Table 1 [52].

Table 1. Results from three studies showing refractive error changes after induced hypo- or hyperglycemia.

Author	Mean Change in blood glucose concentration (mM/l)	Mean change in refractive error (D)	Comments
Gwinup and Villareal.	+8.4	-0.50	None
Furushima et al.	+11.2	-2.00	Cyclopegic refraction, insulin suppression in non-DM subjects.
Steffes	- 2.8	-0.25	One subject

Source: Huntjens & O'Donnell (2006) [52].

3.0. DIFFERENTIAL DIAGNOSIS

A differential diagnosis for the establishment of a tentative diagnosis of index myopia due to hyperglycemia, considering the common features of blur vision in diabetic retinopathy, diabetic cataract, index hyperopia, and index myopia.

Diabetic retinopathy exhibits a miotic pupil [53], while significantly smaller pupils were found in people with proliferative diabetic retinopathy [18]. The pupil diameter becomes smaller with increasing duration of diabetes mellitus [54]. The miotic pupils, even in dim illumination, and poor dilation with mydriatic agents, could be attributed to an autonomic neuropathy partially denervating both the

sphincter and the dilator muscles [55]. In diabetic retinopathy, there are two major vascular changes to the retina, which are the most common effect of DM with subsequent loss of vision: (1) Non proliferative diabetic retinopathy involves the formation of small areas of balloon-like swelling in the retina's tiny blood vessels (microaneurysms). There is leakage of fluid into the retinal macular (macular edema), loss of their ability to transport blood, blockage with deprivation of vascular supply to the retina and the formation of macular ischemia. This is the most common reason why people with diabetes lose their vision. (2) Proliferative diabetic retinopathy involves the proliferation of new blood vessels, which grow along the inside surface of the retina and into the vitreous, with likely leakages and bleeding into it. The accompanying scar tissue can contract and cause retinal detachment leading to permanent vision loss [55,56]. In some patients diabetic retinopathy is asymptomatic, and only retinal examination can reveal it.

In diabetic cataract, the change in vision is slow and takes a little time for the sclerosis of the lens nucleus, lens opacifications and lens thickening to occur [55], The lens also ages at an accelerated rate of an average of 15 years in adult person. People who have had DM for longer and those with poor glucose control are at higher risk of developing diabetic cataracts [55]. There are two major types of diabetic cataracts: (1) True diabetic cataract, the more frequent adult-onset diabetic cataracts, similar in appearance to nuclear sclerosis cataracts [57], but appear mainly in older middle-aged patients with Type 1 and Type 2 DM [58], with early symptoms of persistent refractive changes, glare, and monocular diplopia or polyopia, slightly more permanent and may end up requiring cataract surgery [59] (2) The 'snowflake' cataracts, characterized by flake opacities and fine white punctuate spots in the anterior and posterior subcapsular areas of the lens [60], are reversible once the hyperglycemic condition is reversed.

Index hyperopia occurs prior to the manifestation of the diabetes or after the reversal of the condition is achieved. With the variation of blood glucose, there is a tendency to hyperopia with decreased sugar. Hyperopia is associated with hypoglycemia with regards to the effect of chronic changes in plasma glucose [13]. Hyperopia seems not to occur as an initial phenomenon in diabetes but to follow myopic change [61] The development of hyperopia or the reversal of myopia have been correlated with a fallen blood sugar, usually associated with treatment of hyperglycemia and especially if this is rapid [13]. A hyperopic shift in refractive error in diabetes, occurs almost exclusively in those patients receiving intensive glycemic control with insulin [62]. Acute changes in plasma glucose for 1- 2 months will cause hyperopia [15]. Recovery of the refractive error back to baseline without any more fluctuating, takes about 6-10 weeks when treated with insulin. Accommodation significantly reduces with DM and this is one reason why such patients can reportedly experience more headaches, blurred vision and vertigo upon attempting to read [63]. The increase in the blood sugar level, leads to a decrease in the amplitude of accommodation (AoA) [63].

Index myopia is presented with a blur at far [28] without accommodation, correctable with a tentative concave spherical lens. The refractive changes are too short, sudden and transient especially at far and exhibits a very rapid fluctuations within a short period of diabetic onset. [19]. In index myopia, the refractive power of the eye tends to vary directly with the blood sugar; with increased sugar to myopia [1]. Its reversal with a fallen blood sugar is usually associated with treatment of hyperglycemia. The refractive error back to baseline without further fluctuation takes about approximately twice as long with oral hypoglycemic medication as with insulin [64]. Index myopia is associated with hyperglycemia with regards to the effect of chronic changes in plasma glucose [13].

4.0. RISK FACTORS TO INDEX MYOPIA

4.1. Direct /Major Risk Factor

HYPERGLYCEMIA: Predisposition to hyperglycemia, especially in type 2 DM can lead to index myopia. A fasting blood glucose over 100 mg/dL may indicate an impaired glucose tolerance (IGT). A

blood glucose of 126mg/dL and above on two occasions indicates diabetes. Random blood glucose value of 200mg/dL or more is indicative of diabetes [65]. If untreated, 70% of people with impaired glucose tolerance (pre-diabetes) will progress to diabetes. An HbA1c of 6.5% is recommended as the cut-off point for diagnosing diabetes. There is a positive relation between hyperglycemia and myopic shift. The patients with HbA1c above the median value (8.8%) have a 60% increased risk of a myopic shift compared to the other patients. Poor metabolic control of glucose over a period of at least two to three months increases the risk of a long-term myopic shift.[66]. 30% of all eyes have negative refractive values in refractively adult patients. The highest myopia prevalence of about 40% is seen in the age group 26-45 years. The diabetics show a shift towards negative refractive values (37.9% with myopia), as compared to non-diabetics (27.5%) [67].

4.2. Indirect Risk Factors

4.2.1. Non-modifiable Risk Factors

GENETICS AND FAMILY HISTORY: One may be predisposed to hyperglycemia in DM, If a parent or sibling has the condition. The influence of family medical history vary to a certain degree. According to American Diabetes Association, a person whose parents have type 1 diabetes has about 10 to 25% chance of developing that disease, and someone whose both parents have type 2 diabetes has a 50% chance of developing that disease. In one study, researchers found that 73% of people with type 2 diabetes had moderate to high family risk factors [68].

AGE: There is an association between increase in age and the risk of hyperglycemia in DM. The older one is the greater the likelihood of developing type 2 DM. About 18% of people over the age of 65 years have diabetes, while 8% of those between the ages of 21 and 64 have the condition [65].

Sex: Men account for 53% of the adult cases of diabetes in U.S, according to the National Institutes of Health (NIH). Although little or no research has been conducted to explain this trend. One factor may be the documented increase in recent years of low testosterone levels (male hypogonadism), which scientists have linked to insulin resistance [69].

RACE: People of certain race including blacks and Hispanics, are at risk of developing hyperglycemia than others. For example, autoimmune type 1 diabetes is more common in white people, while type 2 is more common in people of other races and ethnicities. Alaska natives and American Indians have three times the risk of predisposal to developing diabetes, African Americans have 1.7 times the risk, while Hispanic/Latino have two times the risk [65].

4.2.2. Modifiable Risk Factors

OBESITY: Overweight predisposes one to obesity, which is a risk factor to hyperglycemia. For every 2.2 pounds over ones target weight, there is an increase risk of developing diabetes by 4.5% [70]. Researchers found that 40% of people with type 2 diabetes had obesity. The Diabetes Prevention program, reported a 58% reduction chance of prediabetes turning into type 2 diabetes in weight loss and increased physical activity; and a 71% reduction chance for people 60 years or older [71].

DIET: Poor dietary and eating plan affect blood sugar level. Consuming excess free sugars is associated with weight gain for adults and children. According to WHO recommendations, intake of free sugars should be less than 10% of total daily energy intake for both adults and children, and ideally should be less than 5%. [72]. American Diabetes Association recommends that at high risk for developing type 2 DM, structured programmes that emphasizes regular dietary strategies (such as reduced intake of fat) to reduce calories and the risk for developing diabetes should be adopted. Reducing the amount of total fat intake to less than 30% of total energy intake helps prevent unhealthy weight gain in the adult population [72]. Also, the risk of developing non communicable diseases (NCDs) is lowered by reducing saturated fats to less than 10% of total energy intake, trans fats to less than 1% of total energy intake, and replacing both with unsaturated fats [72].

INACTIVITY: Sedentary/physical inactivity elevates blood sugar level. Regular physical activities, 30 minutes 3-4 times a week, can reduce your risk of diabetes by 42%, Exercise improves the body use of insulin [65]. The global target of a 10% relative reduction in physical inactivity is therefore strongly associated with the global target of halting the risk in diabetes. In all WHO regions and across all country income groups, women were less active than men, with 27% of women and 20% of men classified as insufficiently physically active [73].

LIFESTYLE: Poor compliance with a healthy lifestyle influences hyperglycemia.
Tobacco use and exposure remain the cause of 6 million preventable deaths per year globally, accounting for 6% of all female and 12% of all male deaths in the world. More than 5 million of those deaths are the result of direct tobacco use while more than 600,000 are the result of non-smokers being exposed to second hand smoke. 80% of the world's one billion smokers live in low and middle-income countries [74].

HIGH BLOOD PRESSURE: Hyperglycemia could occur due to poor management of high blood pressure. Those with high blood pressure (140/90mm Hg or higher), stand a 20 percent higher risk of developing diabetes [65].

MEDICATION: Most drugs are associated with the risk of developing hyperglycemia. Some fall within the categories of anti-hypertensive, anti-cardiovascular diseases, anti-psychotic, immunosuppressive agents, highly active antiretroviral therapy and other drugs. "Atypical" antipsychotic agents are 50% more likely to result in diabetes [75]. There is a high prevalence of post-transplantation diabetes, observed in 13.4% of patients following solid-organ transplantation (16.6% for tacrolimus versus 9.8% for cyclosporine) [76]. The Multicentre AIDS Cohort Study found that 14% of HAART treated men developed diabetes, with an annual rate of 4.7 per 100 person-years as against 1.4/100 person-years for seronegative controls [77]. It has been shown that an excess risk of 9% of progression to diabetes in those taking statins, an anti-cardiovascular risk drug [78]. The Atherosclerosis Risk in Communities (ARIC) study found that the risk of diabetes was increased by 28% in those taking a beta-blocker for hypertension over a 6-year period, as compared with other medications [79].

STEROID: Excessive use of steroids can raise the blood sugar. Steroids (synthetic steroids) are potent anti-inflammatory agents normally utilized in the treatment of both acute and chronic illness. Their frequent use have many side effects, which includes osteoporosis and diabetes. The diabetogenic effects of steroids are a limiting factor to their clinical use. 75% of steroid-induced diabetics were females as compared to only 25% males. The percentage of males and females among diabetics, likely induced by steroid are 41.7% male and 68.8% female, while non-diabetics are 58.3% male and 31.2% females [80]. 0.4% of childhood diabetes was ascribed to medication, and 55 of 56 children in this category were on steroids. Monogenic diabetes was diagnosed in only 0.2% of children [81].

CHOLESTEROL: Abnormal cholesterol and triglyceride levels trigger hyperglycemia. If your total cholesterol is over 200 mg/dL, triglycerides over 150mg/dL, HDL lower than 60mg/dL, and LDL over 100mg/dL, your risk to develop diabetes is increased [65].

ENVIRONMENT: Some environmental conditions are risk factors to hyperglycemia in DM. These include chemical contaminants in food or water, occupational exposures to various toxins, air pollutants, unhealthy food environment etc. The exposure to air pollutants like traffic-related pollutants (particulate matter (PM) and nitrogen dioxide (NO_2)) have been strongly associated with higher incidence rates of type 2 diabetes, in a dose dependent manner. The highest exposures carry a >20% increase in type 2 DM prevalence after adjusting for other risk covariates [82]. There is a higher likelihood of developing Type 2 DM by 19% and 40% per 10 micrograms per cubic meter

(µg/m3) increase in NO2 and PM, respectively [83]. However, the risk of type 2 DM decreased by 37% among those with highest access to healthy food environment than those with least [84].

EMOTIONAL STRESS: Hyperglycemia can be triggered by work place fatigue, family conflict, depression, hostility, anxiety, sleeping problems, anger etc. Depression increases the risk of type 2 DM by 37% [85]. The risk for incident diabetes is 60% higher in the depressed than the non-depressed [86].

5.0. CONTROL, MANAGEMENT AND TREATMENT OF INDEX MYOPIA

5.1. Prevention:

In Index myopia, careful monitoring and control of elevated blood glucose is the key to the prevention and control [64]. In addition; regular glucose check, moderation and adjustment in diet, changes in lifestyle and regular exercises could prevent it. Type 2 DM is milder than in Type 1, therefore controlled primarily by diet, weight reduction, regular exercises and oral hypoglycemic agents [87], although insulin may also be required when diet and oral drug therapy fail to induce blood glucose homeostasis.

5.2. Inter Specialty Referrals:

The need for Inter specialty referrals cannot be over emphasized. Optometrists and ophthalmologists are under obligation to refer patients with index myopia to the physicians or endocrinologists for further medical attention and management, vis-à-vis in suspected type 2 DM. The treatment of Index myopia is based on the understanding of its pathogenesis, as a complication from hyperglycemia in DM, and its transient and reversible nature. Furthermore, the understanding of The American Diabetes Association's 2017 guideline [88] on the management of diabetes, which includes psychological health, access to care, expanded and personalized treatment options, and the tracking of hypoglycemia in people with diabetes, can only be adequately achieved through referrals to the experts. However other allied or associated professionals (dieticians, counselors etc), competent in exploring modern options in handling DM, could play an effective role in other aspects of management like: counseling, dieting and lifestyle modifications as well as hypoglycemic medications.

5.3. Control Using Hypoglycemic Agents:

The reversal of hyperglycemia reverses the refractive fluctuations, which in turn normalizes vision. The control of elevated blood sugar is achieved through the use of single or combination of different oral hypoglycemic drugs, which dosage is determined by the range of the fasting blood sugar, and administered by the physician. This control subsequently reverses the transient visual fluctuations, which translates to the reversal, management and control of index myopia, with a favorable visual outcome. Most times, and depending on the type of diabetes, combination of drug therapy with modification in basic life style and risk factors are very paramount in the management plan for index myopia. However in type 1 diabetes, or in the failure of oral anti hyperglycemic drug in the control of type 2 DM, insulin could be used for treatment.

5.4. Counseling and Education:

Counseling and education are very important elements in the explanation and handling of the patients' general burden and specific ocular peculiarities associated with DM. They play a key role in dousing the anxiety during hyperglycemic induced myopia. The importance of counseling, especially on the essence of keeping to anti hyperglycemic drugs as prescribed, dieting, weight reduction programs and regular exercises cannot be over emphasized. They explain the effects of possible fluctuations in vision and eventual outcome, even after reversal; especially if patients do not keep to medications and diet. Patients with induced myopia could benefit enormously from counseling and education on the agents, risk factors or conditions inducing the myopia, and the nature or directions of the changes

occurring in the eye. They enlighten the patients on the timeline of the induced myopia, whether temporary or long standing; its reversal and prevention [28]. Counseling further touches on the sudden fluctuations in vision, its transient changes and its tentativeness. Patients should be counseled on possible future reoccurrence of induced myopia and the appropriate measures to be taken. The need for regular Patients' education on the importance of keeping to clinical appointments with the Physicians and Optometrists is crucial. This goes a long way in checking the possible fluctuations in blood sugar and vision respectively, as well as maintaining normalcy. Consistency with prescription drugs as prescribed and directed by the experts, judicious and strict adherence to drug adjustments, modification of dietary patterns and weight reduction plans could be achieved through counseling.

5.5. Clinical Judgment and Decision on Tentative Concave Correction:

The question of issuing a spectacle prescription during index myopia should not be encouraged. The eye care practitioner may delay prescribing spectacles until the refractive error stabilizes, which generally occurs when the patient's hyperglycemia is better controlled, otherwise there might be a distrust of medical care [15]. However, in certain circumstances or special situations a tentative spectacle prescription with adjustments may be issued in transient myopic change, and further modifications in the prescription may be needed when the refraction returns to normalcy or stabilizes [15]. This should be at the discretion of the eye care practitioner after extensive counseling and explanation to the patient, on the possible fluctuations and eventual outcome after reversal, which may be temporary. The justification for such issuance should also be guided by the patient's insistence on the spectacle acquisition, probable job demand, visual discomfort, social standing, acceptance of the legal and ethical implications and acceptance of overall cost implication. This decision also calls for regular patient's counseling due to possible future outcome.

6.0. THE CONTROVERSY ON THE DIRECTION OF THE REFRACTVE SHIFT IN HYPERGLYCEMIA (MYOPIA OR HYPEROPIA)

Several authors have come out with varying opinions on the actual direction of refractive shift in hyperglycemia in DM. Both myopic and hyperopic shifts have been reported and the underlying mechanism responsible remains to be established. The summaries of the results of various studies published in the scientific literature, describing acute refractive error changes with induced changes in blood glucose levels is shown in Table 2 [52]. There is alteration of the refractive systems, in form of index myopia and hyperopia. However, some authors are of the opinion that the controversy in the literature with regards to this underlying mechanism in refractive changes during hyperglycemia and the overall refractive outcome, could be explained by the balance between changes in the shape or the refractive index of the lens, which eventually determines myopia or hyperopia. If the change in the shape of the lens is small, hyperopia will predominate, due to a decrease in the refractive index of the lens. Alternatively, if the change in the shape of the lens is large in comparison to the decrease in the refractive index of the lens, the overall refractive error will result in myopia [45].

Index myopia and hyperopia are induced or acquired refractive errors which occur due to sudden changes in the refractive index of the intraocular lens. Investigators have observed both myopic [16] and hyperopic [17] refractive shifts in diabetic patients, which have been related to changing plasma glucose concentration. Also, the nature of fluctuation depends on the status of the underlying DM. If undiagnosed, or in a state of hyperglycemia, it could become more myopic [13], and if under intensive hyperglycemic control, it could be more hyperopic [13]. Duke-Elder concluded that hyperopia is less common than myopia and that the refractive power of the eye tends to vary directly as the sugar content of the blood; that is, there is a tendency towards hyperopia with decreased sugar or intensive glucose control, and towards myopia with elevated blood sugar [13].

Transient refractive changes, due to a variation in blood glucose, are well-known complications of DM. Both myopic shifts [13] and hyperopic shifts [86], have been reported in patients with DM after several days or weeks of hyperglycemia. There is little doubt that these transient changes in refraction are associated with variations in blood glucose levels, but the nature of the relationship between the two parameters remains in doubt. Both hypermetropic and myopic refractive shifts could occur from morphological changes in the cornea, crystalline lens, axial length or retinal thickness. The last two possibilities have been investigated previously, and no change in either axial length or retinal thickness was found with changing blood glucose concentration in 28 eyes [15]. A more recent work suggested that, at least in the majority of cases, when therapy is instituted to control hyperglycemia, and blood glucose falls, the refraction first changes in the hyperopic direction on the timescale of a few days or weeks and then gradually returns to their baseline values on the timescale of a few weeks or months [89].

However, there was a significant correlation between the maximum hyperopic change in an eye and the daily rate of plasma glucose reduction over the first seven days of treatment, but not with the daily rate of plasma glucose reduction over the first three days [15]. The time lag could be attributed to the presence of the blood-ocular barriers. An explanation for the finding that more myopic eyes at base line had a larger maximum hyperopic change, is that myopic eye have a larger volume with elongated axial length and dysfunctional blood-ocular barrier; and the changes in the composition of the intra ocular fluid and the differences in osmotic pressure would be greater in myopic eyes than in eyes having hyperopia as a baseline refractive error [15].

Table 2. Conflicting results presented in the literature comparing acute refractive changes in the eye to changing blood glucose levels.

Author	Year	No of subjects	Key findings
Huggert	1954	23	Myopia before and hyperopia after the onset of treatment.
Gwinup et al.	1976	10	Myopia after induced hyperglycemia.
Fledelius	1987	72	Myopia and hyperopia (before and after the onset of treatment).
Saito et al.	1993	5	Hyperopia after the onset of treatment.
Furushima et al	1999	7	Myopia after induced hyperglycemia in non-diabetic subjects.
Steffes	1999	1	Myopia after induced hypoglycemia.
Okamoto et al	2000	14	Hyperopia after the onset of treatment.
Guisti	2003	20	Myopia after the onset of treatment.
Sonmez et al	2005	18	Hyperopia after the onset of treatment.

Source: Huntjens, B. & O'Donnell, C. (2006) [52].

7.0. IMPLICATIONS OF INDEX MYOPIA TO THE OPTOMETRISTS

Sudden refractive fluctuations are well-recognized features of hyperglycemia, and are phenomena that often embarrass optometrists, and other eye care practitioners.

The Ophthalmologists and Optometrists should always take DM into consideration in blur vision. The fact remains that DM is a common and often under-diagnosed disease that can cause blur vision, especially in adult patients [90].

In a complaint of a bilateral unexpected rapid change of vision, or sudden change in the spectacle prescription of a patient, the Optometrists are challenged, through their professional training to suspect the possibility of undiagnosed diabetes as the cause [52].

The eye care practitioner may postpone prescribing spectacles until the refractive error stabilizes in a suspected diabetes. This generally occurs when the patient's diabetes is better controlled, considering that refractive changes associated with diabetes can be both acute (transient) and chronic (sustained) [52].

Due to possible influence of fluctuating blood glucose, and the response of the crystalline lens to refractive error changes, as a result of untreated hyperglycemia; great concerns and caution should be applied by the Optometrists when carrying out eye examinations on diabetic patients [52].

It is appropriate for the eye care practitioners to enquire about blood glucose when carrying out eye examinations on diabetic patients. If uncharacteristically high or low at the time of refraction, it may be wise to repeat the refraction prior to prescribing; as well as advising patients about the possible implications for diabetic retinopathy and other oculo-visual complications associated with the disease [52].

Understanding how blood glucose can potentially affect the ocular parameters that contribute to the refractive power of the eye, would help the eye care practitioners establish a relationship between expected visual signs and symptoms, and periods of altering diabetic metabolic control. This will aid in appropriate patients advise [52].

Eye care practitioners understand several undesirable symptoms associated with acute hypoglycemia, and those associated with prolonged hypoglycemia which include more severe symptoms like visual disturbances, restlessness, irritability, inability to concentrate, mental confusion, and personality changes among others. Hyperglycemia however, often goes unnoticed by diabetic patients [91].

8.0. CONCLUSION

Index myopia is a sign of undiagnosed hyperglycemia in DM, and one of the wide range of visual complications in the anterior segment of the eye. It occurs due to increased refractive index of the intraocular lens caused by the osmotic gradient between the aqueous humor and the intraocular lens in hyperglycemia; mostly when there is poor metabolic control. This is a clinical concern to the optometrists due to the discrepancies in clinical refraction and the need for further modifications in the spectacle prescriptions. Early detection of signs and symptoms of DM, understanding the pathogenesis, taking a good history, conducting basic preliminary examinations, skilled ophthalmoscopy, differential diagnosis, laboratory and diagnostic investigations, good clinical skill and judgment are the keys to the prevention and diagnosis of index myopia. The outcome determines the medical or Ophthalmological/Optometric treatment plan, with Inter-specialty referrals and collaboration in its management. Given the current oral hypoglycemic drugs, diet and counselling, a reversal in index myopia could be easily achieved.

Ethical Approval

Ethical approval and clearance for this work was obtained from the Health Research and Ethics Committee of Government House Clinic, Umuahia, Abia state, Nigeria.

Consent: NA

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