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***Full Length Research Paper***

# Environmental and dietary factors affecting the progression of type 2 diabetic retinopathy in Aljabal Algharby, Libya

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**ABSTRACT**

The purpose of the paper is to study the role of some Environmental and Dietary Factors affecting the progression of Type 2 Diabetic Retinopathy in Aljabal Algharby, Libya. A prospective non-comparative study was conducted from September 2012 to July 2013 at the Ophthalmology Department in Gharian Central Teaching hospital, Gharian, Aljabal Algharbi, Libya. Thirty cases with medical history of uncontrolled Type 2 diabetes lasting more than 10 years and no other systemic diseases were collected. Complete ophthalmic clinical examination including dilated fundus examination and laboratory investigations as Random Blood Glaucose (RBG) level and Glycosylated Hemoglobin (HgA1c) besides Complete Blood Count (CBC) were carried out to all cases. The cohort included 30 cases 15 males (50%) and 15 females (50%). Their mean age was 55.29 ± 2.46 years (range, 48 years to 66 years: males; 53.39 ± 3.03 years and females; 56.67 ± 3.75 years). The duration of Type 2 diabetes mellitus ranged from 10 years up to 16 years with a mean 13.17 ± 2.16 years. All the cases were diagnosed with either normal or mild non-prolifrative stage of diabetic retinopathy. Thirty cases (100%) were having Random Blood Glucose (RBG) above 200 mg/ml and +ve Glycosylated Hemoglobin (HgA1c) results above 7% indicating the uncontrolled state of diabetes. Twenty six cases (86.7%) gave a history of regular intake of Virgin Olive Oil (VOO) in their diet. Twenty three cases (76.7%) had Secondary Polycythemia with a mean Red Blood Cells (RBC) Count 6.2 ± 0.5 million cells/mcL associated with a mean Hemoglobin (Hg) level 13.73 ± 1.32 g/dl in their blood picture which correlated with history of prolonged living at high altitude. In conclusion, the regular dietary intake of Virgin Olive Oil (VOO) which is a main component of the Mediterranean diet was proved to have a beneficial effect on the reduction of progression of type 2 diabetic retinopathy. On the other hand, the prolonged hypoxia exposure and associated Secondary Polycithemia may play a role in a process of tissue adaptation that results in a lower tissue response to the ischemic state responsible for type 2 diabetic retinopathy.

**Keywords:** Type 2 diabetic retinopathy, prolonged hypoxia, virgin olive oil.

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## INTRODUCTION

The International Diabetes Federation (IDF) published their Diabetes Atlas in 2006 and demonstrated that diabetes affects 246 million people worldwide and the latest version in 2011 estimates the number with diabetes to be 366 million people worldwide with a predicted rise to 552 million by 2030. It also estimates that 80% of people with diabetes live in low and middle income countries and the greatest number of people with diabetes is type 2 between 40 and 59 years of age (Scanlon et al., 2013).

Diabetic retinopathy (DR) is the most common microvascular complication of diabetes and remains one of the leading causes of blindness worldwide among adults aged 20 to 74 years. DR is characterized by gradual progressive retinal vasculopathy leading to endothelial cell dysfunction, breakdown of the blood–retinal barrier, ischemia-induced retinal neovascularization, and expansion of extracellular matrix

resulting in the outgrowth of fibrovascular tissue at vitreoretinal interface. Strong evidence indicates that chronic low-grade inflammation is implicated in the pathogenesis of DR. In addition, recent studies proved that neurodegeneration and impaired visual function are initiated early after the onset of diabetes and progress independently of the vascular lesions. The two most important visual complications of DR are diabetic macular edema (DME) and proliferative diabetic retinopathy (PDR) (Abu El-Asrar, 2013).

The retinal blood vessels are the only directly observable vascular system in the human body and also supply some of the most oxygen-demanding tissue, the photoreceptors of the retina (Morris et al., 2006). The function of the retina is sensitive to oxygen tension so that any change in the perfusion pressure of the eye affects the retina and the eye is able to auto regulate its hemodynamics although, systemic hypoxemia (lung or heart disease) or a vascular disease in the retina can cause retinal hypoxia (Arjamaa and Nikinmaa, 2006).

Tissue oxygenation in general and hypoxia in particular are important regulators of retinal physiology and pathophysiology. Also, reduced oxygen tension and hypoxia-inducible transcription factors along with some of their target genes are critically involved in retinal development, and especially in the generation of a normal retinal vasculature (Grimm and Willmann, 2012).

Meanwhile, although retinal hypoxia at sea level accounts for the developed world's largest cause of blindness, diabetic retinopathy investigation of retinal response to hypobaric hypoxia in healthy subjects may open new avenues for treatment of this debilitating disease (Morris et al., 2006).

On the other hand, some dietary habits are important determinants of individual cardiovascular and metabolic risk (Buscemi et al., 2013). Numerous health benefits have been attributed to the 'Mediterranean diet' over the last decades, including foods that were common in the Mediterranean regions (especially Crete) in the 1970s, with a frequent and abundant intake of fruit, vegetables, fish, olive oil and perhaps wine, has been reported to be associated with wide-ranging benefits including improved glucose metabolism and decreased risk of type 2 diabetes, obesity and Cardio Vascular Diseases (CVD) (Bellisle, 2009).

## Objective of the study

The aim of this work is to study the role of some Environmental and Dietary Factors on the Progression of Type 2 Diabetic Retinopathy in Aljabal Algharby, Libya.

## PATIENTS AND METHODS

### Study group

A prospective non-comparative study was carried out at Aljabal Algharbi, one of the Libyan provinces, located south west to the Libyan capital Tripoli and Gharian is considered as the largest sub province. The area is located about 1500 m above the sea level in Nafoussa heights and is rich in olive agriculture with Virgin Olive Oil (VOO) representing an essential component of the diet in this area. A clinical observation aroused the attention of ophthalmic practitioners working at Ophthalmology Department in Gharian Central Teaching Hospital, Gharian, Libya that was a considerable decrease in the incidence of prolifrative diabetic retinopathy among patients with type 2 diabetes mellitus despite the uncontrolled state of diabetes in many of them.

The necessary approval from ethics committee was obtained and a study was conducted from September 2012 to July 2013 at the Ophthalmology Department in Gharian Central Teaching hospital, Gharian, Aljabal Algharbi, Libya to investigate the effect of regular dietary intake of Virgin Olive Oil (VOO) and prolonged hypoxia exposure on progression of diabetic retinopathy in patients with uncontrolled Type 2 diabetic retinopathy. The study included thirty cases with normal or mild non proliferative diabetic retinopathy changes in their eyes despite living at high altitude and suffering from uncontrolled Type 2 diabetes mellitus (DM) for more than 10 years.

### Inclusion criteria

All patients included in the study were inhabitant or living at high altitude area and had a medical history of uncontrolled Type 2 diabetes mellitus (DM) lasting more than 10 years while ophthalmic examination of their eyes revealed normal or mild non proliferative diabetic retinopathy changes.

### Exclusion criteria

All patients with irrelevant medical history as regard to the control and duration of diabetes mellitus or any medical history of other systemic diseases except the uncontrolled Type 2 diabetes mellitus were excluded from the study. Also, patients with eye diseases that obscure fundus examination or eyes suffering from proliferative diabetic retinopathy changes were excluded. Only one patient from the same family was included in the study to eliminate the genetic factors from the results of the cohort and any patient giving history of living out side the high altitude area for more than one year in the last five years was omitted from the study.

### Clinical history

A thorough history was taken for each patient, focusing on:

(I) Diabetes Mellitus with special concern to the duration and medical control;
(II) Living at high altitude and its duration;
(III) Regular intake of Virgin Olive Oil (VOO) in the diet;
(IV) Eye diseases.

### Clinical examination and investigations

All patients were subjected to complete ophthalmic clinical examination including Visual Acuity (VA), Intra Ocular Tension (IOT), and dilated fundus examination with indirect ophthalmoscope, direct ophthalmoscope, slit lamp with +90 Diopter Lens, and Fundus Fluorescein Angiography (FFA).

Double masked ophthalmic examination sessions were performed to all patients where each patient was examined by two doctors separately and each examiner doctor provide a provisional

diagnosis as regard to the diabetic retinopathy stage of the patient and the final result was recorded after reviewing both examination records. The stage of diabetic retinopathy was assessed based on the recommendations of the Early Treatment Diabetic Retinopathy Study (ETDRS, 1985).

Laboratory investigations as Random Blood Glucose (RBG) level and Glycosylated Hemoglobin (HgA1c) to assure the diagnosis of both Type 2 diabetes and to confirm the uncontrolled state of diabetes mellitus were done in all the cases. The results were analyzed according to recommendations of United Kingdom Prospective Diabetes Study (UKPDS, 1998) Group.

Also, to assure Secondary Polycythemia resulting from prolonged hypoxia exposure Complete Blood Count (CBC) was carried out to all cases with a main concern to the Red Blood Cell (RBC) count (considered positive if above 6.2 million cells/mcL in males and above 5.6 million cells/mcL in females) and Hemoglobin (Hg) level (considered positive if above13 g/dL in men and above12 g/dL in women). According to the World Health Organization (WHO) definition, a hemoglobin level <13 g/dL in men and <12 g/dL in women were used to define anemia (WHO, 2007).

#### Statistical analysis

The patients in this study were collected at random. Statistical analysis of the present study was done, using the SPSS (statistical package for social sciences) version 12 on Windows XP. For quantitative data, the mean and standard deviation were calculated.

## RESULTS

The results were analyzed using the SPSS (statistical package for social sciences) version 12 on Windows XP. Quantitative data were calculated as the mean and standard deviation. And a review was carried out to stand on the effect of prolonged hypoxia exposure and regular dietary intake of Virgin olive oil on the progression of Type 2 diabetic retinopathy.

Thirty cases, 15 males (50%) and 15 females (50%), were included in the cohort. The mean age was 55.29 ± 2.46 years (range, 48 years to 66 years: males; 53.39 ± 3.03 years and females; 56.67 ± 3.75 years).

The duration of Type 2 diabetes mellitus (DM) ranged from 10 years up to 16 years with a mean 13.17 ± 2.16 years. All the cases were diagnosed with either normal or mild non-prolifrative stage of diabetic retinopathy (DR). Thirty cases (100%) were having Random Blood Glucose (RBG) Level above 200 mg/ml and +ve Glycosylated Hemoglobin (HgA1c) results above 7% indicating the uncontrolled state of diabetes mellitus (DM). Twenty six cases (86.7%) gave a history of regular intake of Virgin Olive Oil (VOO) in their diet and twenty three cases (76.7%) had Secondary Polycythemia with their mean Red Blood Cells (RBC) Count 6.2 ± 0.5 million cells/mcL associated with increased Hemoglobin levels (Hg) in their blood picture with a mean Hemoglobin (Hg) level 13.73 ± 1.32 g/dl which correlated with history of prolonged living at high altitude (Figure 1).

It was significant that regular dietary intake of Virgin Olive Oil has a beneficial effect on the reduction of progression of type 2 diabetic retinopathy. Also,

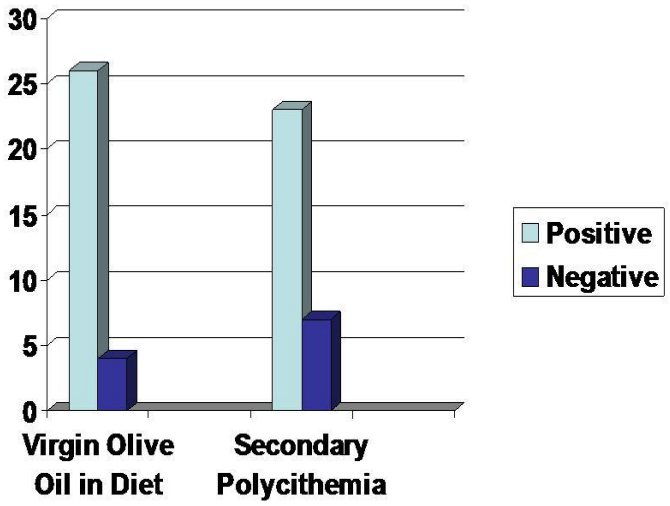


**Figure 1**. Illustration that from a total of thirty cases (100%) with uncontrolled Diabetes Mellitus (DM) and no or mild non-proliferative Diabetic Retinopathy (DR), twenty six cases (86.7%) had positive results of regular dietary intake of Virgin Olive Oil (VOO), twenty three cases (76.7%) proved positive results to have Secondary Polycithemia as a result from prolonged hypoxia exposure.

Secondary Polycithemia from prolonged hypoxia exposure may results in a lower tissue response to the ischemic state responsible for type 2 diabetic retinopathy.

## DISCUSSION

In this study, we investigated the role of some Environmental and Dietary Factors on the Progression of Type 2 Diabetic Retinopathy in Aljabal Algharby, Libya. The cohort included 15 males (50%) and 15 females (50%), all were inhabitant of aljabal algharby province, Libya, their mean age was 55.29 ± 2.46 years and the duration of diabetes 10 years up to 16 years with a mean 13.17 ± 2.16 years. All cases have history of uncontrolled diabetes that was proved from their medical history, Random Blood Glucose (RBG) Level above 200 mg/ml, and the presence of Glycosylated Hemoglobin (HgA1c) results above 7% in their blood analysis. All of the cases were subjected to clinical ophthalmic examinations and their fundus examination revealed normal or mild non-prolifrative stage of diabetic retinopathy which was not correlated with the duration and the state of uncontrolled diabetes mellitus.

Virgin Olive oil as an essential component of the 'Mediterranean diet' was proved to be present in the routine diet of twenty six cases (86.7%) in the study. The value of virgin olive oil was investigated by many authors as Perona et al. who reported an evidence about the beneficial effects of dietary virgin olive oil on blood pressure and Low density Lipoproteins (LDL) oxidation in type 2 diabetics and added that it is likely that the components responsible for the observed effects are the

monounsaturated fatty acids and the presence of antioxidants in the oil (Perona et al., 2009). Perona et al. also reported in another study that long-term Virgin Olive Oil (VOO) consumption modifies the fatty acid composition of plasma membrane, which influences the association of G proteins and PKCalpha with the lipid bilayer. These combined effects probably account for the positive effects of VOO on glycemic homeostasis (Perona et al., 2007).

Virgin olive oil (VOO) was not only valuable as a nutritional supplementation but it was also proved to play a role in improving the effect of aspirin on retinal vascular pattern in experimental diabetes mellitus as reported by De La Cruz et al. who mentioned that daily oral administration of VOO to diabetic rats may be a natural way to increase the neuroprotective effect of aspirin in diabetic animals (De La Cruz et al., 2010).

Virgin olive oil (VOO) seems to have a similar effect to Fibrates which are widely prescribed lipid-lowering drugs in the treatment of dyslipidemia and their main clinical effects, mediated by peroxisome proliferative activated receptor alpha activation, lead to a moderate reduction in total cholesterol and low-density lipoprotein cholesterol levels, besides a marked reduction in triglycerides and an increase in high-density lipoprotein cholesterol. A result that was confirmed by the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study which demonstrated that long-term lipid-lowering therapy with fenofibrate reduced the progression of Diabetic Retinopathy (DR) and the need for laser treatment in patients with type 2 diabetes although the mechanism of this effect does not seem to be related to plasma concentration of lipids (Keech et al., 2007).

On the other hand, the state of prolonged hypoxia was proved in twenty three cases (76.7%) all of them had secondary polycythemia with increased hemoglobin levels in the laboratory results of their blood picture which correlated with the history of prolonged living at high altitude. An observation that required more attention as despite not only the obvious role of diabetes mellitus in tissue hypoxia which is responsible for the production of diabetic retinopathy that was investigated by many authors as Grimm and Willmann who stated that when hypoxia is ill-timed, reduced oxygen tension may be associated with the development of retinal pathologies, including retinopathy of prematurity, diabetic retinopathy, glaucoma, age-related macular degeneration, or high altitude retinopathy as reduced oxygen tension activates a hypoxic response that culminates in an increased expression of vascular endothelial growth factor which causes pathological neovascularization of the delicate neuronal retina, a process that may ultimately lead to loss of vision (Grimm and Willmann, 2012). But also, the effect of high altitude that might share in aggravating the hypoxic state of the retina and may result in high altitude retinopathy as described by Morris et al. in a study about the eye at altitude (Morris et al., 2006). The incidence of diabetic retinopathy in our cases was much decreased.

A clinical observation that leads to an important question that is if an individual was already living at high altitude and his tissues were adapted to the low oxygen level what will be the expected reaction of his retina if he became diabetic or in another words does his retinal tissue withstand the hypoxic effect induced by diabetes because it is already adapted to hypoxia and in this case there will not be much release of vascular endothelial growth factor or it will react vigorously to this superadded hypoxic state. The answer to this question was a matter of controversy as while some investigators reported an increase in the incidence of macular affection and diabetic retinopathy and nephropathy among diabetic patients living at high altitude (Sayarlioglu et al., 2005; Pavlidis et al., 2005; Leal et al., 2008; Fischer et al., 2012).

Other investigators reported a beneficial effect of the state of hypoxia as Grimm and Willmann who stated that in contrast, preconditioning by well-defined and controlled short-term hypoxia is not devastating for the retina but instead induces a molecular response that provides protection to neuronal cells and that detailed investigation of hypoxic mechanisms during development and adulthood may thus reveal factors, which may be targeted by therapeutic approaches to save and preserve vision in patients (Grimm and Willmann, 2012). Averous et al. (2006) also reported a resolution of diabetic macular edema following high altitude exercise.

Secondary polycithemia as a direct effect from prolonged hypoxia exposure seems also to play a role in the reduction of Diabetic Retinopathy progression which correlates with the result of Bahar et al. who studied the association between diabetic retinopathy and hemoglobin level and reported that the level of hemoglobin in Diabetes Mellitus (DM) patients with Diabetic Retinopathy (DR) was lower than those without DR and added that the prevalence of anemia was higher in patients with more advanced DR (Bahar et al., 2013).

## Conclusion

The regular dietary intake of Virgin Olive Oil which is a main component of the Mediterranean diet was proved to have a beneficial effect on the reduction of progression of type 2 diabetic retinopathy. On the other hand, the prolonged hypoxia exposure may play a role in a process of tissue adaptation that results in a lower tissue response to the ischemic state responsible for type 2 diabetic retinopathy which may also result in a reduction of progression of type 2 diabetic retinopathy, an observation that sure needs more research and may in some way change the strategy in the treatment of diabetic retinopathy with oxygenating drugs and vasodilators as according to this hypothesis this will be like adding oil to fire.

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